Acute Pediatric Neurology

Thomas Sejersen
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Editors

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We would like to dedicate this book to all our patients and their families. They gave us the opportunities to acquire our knowledge and experience that cumulated to the production of this book.

Preface

A substantial proportion of admissions to pediatric emergency departments, urgent care clinics, hospital wards, and pediatric intensive care units have pediatric neurological causes (20–30 %), or are accompanied by neurological issues. This illustrates that neurological diseases account for a large volume of pediatric emergencies, and many severe and critical pediatric cases. There is thus a great need for care providers to have access to updated literature aiding in diagnosis and management of emergencies related to pediatric neurology. However, we could not find such a book in the present day publications. Although there are very good books in acute pediatrics, they do not cover the topics of acute pediatric neurology in sufficient details. Considering the importance of pediatric neurology both in volume and in severity of pediatric emergencies, it was therefore a surprise for us to find the lack of an updated book dedicated to this field. This issue became more pressing to both of us when we encountered frequent requests for neurological consultations from general pediatricians and pediatric intensivists. These health providers frequently expressed an urgent need for a reference book that covers comprehensive topics of pediatric neurological issues that can be used as a rapid guide for the care of children in acute settings.

Having previously had a very pleasant and productive collaboration in developing care guidelines for neuromuscular diseases, we (Thomas Sejersen and Ching Wang) decided to team up again to edit this book on acute pediatric neurology. It is our hope that we can to some extent fill this gap with the present multi-authored book. This book is intended to be a practical guide, covering major pediatric neurological diseases of relevance in the acute settings. The first part of the book, Chaps. 1, 2, 3, 4, 5, 6, 7, covers major acute neurological symptoms, and differential diagnoses to consider. These should help clinicians to recognize various neurological conditions presented, perform essential neurological examination, and formulate some differential diagnoses in preparation for further diagnostic workup. The second part of the book, Chaps. 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, is intended to give practical advice on managements including diagnostic assessments and therapeutic interventions on the common and important acute pediatric neurological

conditions. Although each chapter will have much of its own individual characteristic, they will all have three key elements: (1) description of presenting symptoms, (2) recommended assessments, and (3) recommended interventions. Most chapters have at least one European and one North American author. With this we hope to cover some of the differences that may exist in diagnosis and management in Europe and North America. We hope that this book will reach a wide readership including pediatricians, pediatric neurologists, neurologists, pediatric intensivists, and neonatologists. Should this book be well received, we hope that possible mistakes will be corrected in a second edition to follow. This will also allow us to keep updating and adding valuable new information on managements in acute pediatric neurology.

We want to use this opportunity to thank all the authors who contributed to the chapters in this book. They generously shared their precious experience in their field of expertise and worked with us patiently through the several revisions of the manuscripts. We also want to thank the developmental editors Barbara Lopez-Lucio and Joanna Bolesworth who helped compiling the chapters and keeping track on the production timelines, and the entire production team from Springer who produced this book in a pleasant and readable format. Lastly, we want to thank Drs. Darryl De Vivo and Lieven Lagae for their mentoring and encouragement and critical reading of the chapters.

Stockholm, Sweden — Thomas Sejersen
TX, USA — Ching H. Wang

Foreword I

In times of nonstop and everywhere availability of web-"knowledge", it seems strange to advocate a classic textbook on pediatric neurology and especially on acute problems in clinical pediatric neurology. Most of our fellows (those who actually see the patients in the emergency ward) know very well where to find the adequate dosage for treating an ongoing seizure, but sometimes lack the background scientific knowledge about long-lasting seizures and status epilepticus. Our classical teaching is very good in describing the most common neurological diseases, but not too much emphasis is put on the acute aspects of these diseases. In this respect, it is indeed time for a good and reliable textbook on acute aspects in pediatric neurology. Looking at my (full) bookcase, I find only one book on "neurologic emergencies in infancy and childhood" (eds. J.M. Pellock, E.C.Myer), published back in 1993! It is one of the few textbooks I have actually read from page 1 to page 408 (I admit) and I still consult it in late night situations when I get nervous about an acute neurological problem in a child on the ward. But now, I get even more nervous realizing that I continue to turn to a 20-year-old textbook…

The book you are holding in your hands, *Acute Pediatric Neurology*, therefore certainly fills a gap and a need. The book deals with almost all acute neurological problems in childhood and is written by experts in the field. What I like best in most chapters is the theoretical and pathophysiological background of these acute neurological situations. This is what we need to fully understand our treatment paradigms. It remains the only way to prevent the art of medicine of becoming a web-based cookbook business. In addition, lots of flowcharts and tables give advice on what diagnostic tests to run and which treatments are the most adequate. The editors and authors have to be congratulated with this textbook! I am sure it will be used in many teaching opportunities and in everyday clinical situations, but my advice is to simply start reading it now! It will give you a good and reassuring feeling, either because you will continue to fool yourself with "I already know this" or because (as in my case), you will silently admit a lot of things have changed in the last 20 years and you badly needed this magnificent update.

Leuven, Belgium — Lieven Lagae

Foreword II

It is hard to imagine anything more frightening to a parent than an acutely ill child with new-onset neurological symptoms. The presenting symptoms might include sudden loss of consciousness or memory, confusion or disorientation, fever and neck stiffness, acute-onset headache with early morning vomiting, a new-onset seizure or limb paralysis, acute loss of vision, dizziness, or vertigo.

Furthermore, it is hard to imagine anything more challenging to the physician than evaluating this acutely ill child, noting the key presenting signs, formulating a differential diagnosis, and initiating an appropriate management plan.

This textbook edited by Professors Thomas Sejersen and Ching Wang successfully prepares the clinician for the challenges presented by these common acute pediatric neurological disorders. It is required reading for any physician or nurse practitioner who may be responsible for the evaluation and the management of an acutely ill child with such a neurological complaint. These children may be seen in the doctor's office, in a walk-in clinic, or in the emergency room. As a result, the family physician, general practitioner, pediatrician, emergency medicine physician, and pediatric house staff need to be prepared to make the initial decisions when evaluating these acutely ill children; and, when immediately available, the child neurologist should be consulted and directly involved in formulating the diagnosis, evaluation, and treatment plan.

The textbook is organized in an orderly and logical fashion with the first part addressing the acute symptomatic presentation, and the second part focusing on the urgent management of these many different conditions. Some of the disorders are acutely disabling, but transient, whereas others are life-threatening, such as bacterial meningitis and intracranial hypertension. Professors Sejersen and Wang share their considerable professional talent and expertise as senior child neurologists. Both editors are internationally recognized for their expertise in pediatric neuromuscular diseases. Each also has broad experience in the field of child neurology. To complement their collective clinical skills, the editors have assembled an international group of experts from eight different countries as authors of the 19 chapters. The end result is a modern, up-to-date description of the presentation and the

management of the most common acute neurological disorders presenting in childhood. I suspect that you will enjoy reading their lucid, informative chapters as much as I have.

New York, USA Darryl C. De Vivo, MD

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Part I
Acute Neurological Symptoms

Chapter 1
Unconsciousness, Coma, and Death by Neurological Criteria

Tommy Stödberg, Claes G. Frostell, and Björn A. Larsson

Abstract Acute clinical situations involving unconsciousness, coma, and death by neurological criteria evoke strong concerns in pediatric practice and signal the need for a structured diagnostic and therapeutic approach. We the authors have in this chapter attempted to review and define relevant terminology including giving references to basic sources of information. In the first part, etiological factors and diagnostic as well as initial therapeutic strategies are pointed out to be of use when a pediatric patient with unconsciousness or coma is encountered. Prognostic aspects and rehabilitation are touched upon but not to any detail, as the chapter is more focused on the initial stages (first days) of illness. The advantage of a team-based and multi-professional way to work clinically is pointed out. In the second part, the pathophysiological and legal basis for a correct procedure for defining death by neurological criteria has been presented in detail. Necessary and supportive diagnostic steps including practical requirements are dealt with. Aspects of supporting a family in a time of crisis are also reviewed.

Keywords Coma • Unconsciousness • Death by neurological criteria • Brain death • Trauma • Meningitis • Encephalitis • Intoxication • Children • Neonate

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1.1 Introduction

The terms unconsciousness, coma, and death by neurological criteria (brain death) embrace some of the most feared and challenging clinical situations in acute pediatric medicine, for parents as well as caregivers. A two-track approach has to be simultaneously set up, in which both rapid and adequate supportive as well as symptomatic care have to be instituted while an aggressive push to better diagnostic accuracy is pursued. In practical terms the optimal situation would be to bring the child to a PICU where the intensivist collaborates closely with a pediatric neurologist. We shall herein define each condition, summarize background data on epidemiology and etiology, and give an outline how to rationally move ahead towards symptomatic and etiologic diagnosis as a basis for choice of therapeutic strategy. Treatment itself is not within the scope of this chapter but is touched upon since it is closely associated with the diagnostic procedures in the acute management.

The discussion on death by neurological criteria contains terms that the medical profession alone cannot define. Obviously legal issues such as autonomy and the definition of death are in focus here, which will require close interaction between the medicinal and legal professions. What is agreed upon must then secure acceptance from the society in general. There are some national differences in the legal requirements and practices. As an example, in Great Britain it is enough to diagnose cessation of brain stem function in order to declare death by neurological criteria. However in most countries cessation of function of the whole brain (including the brain stem) needs to be demonstrated.

1.2 Unconsciousness, Coma

1.2.1 Consciousness

The unconscious patient arriving in the emergency room constitutes a classic diagnostic and therapeutic challenge in medicine. In a clinical medical context, consciousness could be viewed as having two major aspects: the level of wakefulness, i.e., alertness, and the content or quality of consciousness, i.e., the awareness of self and environment including various overlapping cognitive brain functions such as attention, perception, and memory. Wakefulness has its neurobiological substrate in the ascending reticular activating system (ARAS) in the pons and midbrain projecting to the thalamus and the cerebral cortex. Awareness depends on complex cortical networks and their subcortical connections and are not fully understood [1, 2].

1.2.2 Impairment of Consciousness

Impairment of consciousness is a basic and dramatic symptom of disturbed cerebral function involving altered awareness of self and environment in

Table 1.1 Disorders of consciousness [3, 4]

	Arousal	Sleep/wake cycles	Awareness	Motor function	Respiratory function
Death by neurological criteria (brain death)	Absent	Absent	Absent	Absent or spinal reflexes only	Absent
Coma	Absent	Absent	Absent	Nonpurposeful, reflexive	Variable
Vegetative state	Present	Present	Absent	Nonpurposeful	Present
Minimally conscious state	Present	Present	Present, limited	Purposeful, limited, and intermittent	Present
Locked-in syndrome[a]	Present	Present	Present	Quadriplegia, eye movement preserved	Present

[a]Locked-in syndrome is not a disorder of consciousness but an important differential diagnosis

Table 1.2 The Glasgow Coma Scale

Adult/standard	Score	Pediatric (<4–5 years) [6]
Eye opening		
Spontaneous	4	Spontaneous
To speech	3	To speech
To pain	2	To pain
None	1	None
Best verbal response		
Oriented	5	Coos, babbles (age appropriate)
Confused	4	Irritable, cries
Inappropriate words	3	Cries to pain
Incomprehensible sounds	2	Moans to pain
None	1	None
Best motor response		
Obeys commands	6	Spontaneous movements
Localizes pain[a]	5	Withdraws to touch
Withdraws to pain[b]	4	Withdraws to pain[b]
Abnormal flexion[a]	3	Abnormal flexion[a]
Extensor response[a]	2	Extensor response[a]
None[a]	1	None[a]

[a]Test by supraocular pressure
[b]Test by nail bed pressure

combination with varying levels of wakefulness. Terms used to describe such conditions are multiple (stupor, somnolence, obtundation, lethargy), usually not well defined and should be avoided. More structured attempts have been made to define the concepts of coma, vegetative state, and minimally conscious state (Table 1.1). In addition the level of consciousness can be described by means of validated scales. The most widely used of these scales, the Glasgow Coma Scale (GCS) [5], was developed to assess impairment of consciousness in adults with traumatic brain injury, to detect deterioration in these patients and as an early prognostic tool. Later the GCS has been used also in nontraumatic etiologies and in children [6, 7] (Table 1.2). Alternative scales have been developed and compared to the GCS [8, 9].

1.2.3 Coma

The term coma—in its strictest sense—means a total absence of awareness and wakefulness [10]. The comatose patient lies with eyes closed, does not speak and has no voluntary movements. In response to strong stimuli, i.e., pain, there can be abnormal reflex motor responses but EEG shows no arousal reaction and no sleep/wake cycles. Coma also implies a certain duration of the state, at least 1 h. Coma can be caused by a relatively localized disruption of the ARAS. On the other hand, if the cause is cortical, the disruption has to be extensive and bilateral.

1.2.4 The Vegetative State

In the vegetative state the patient has some level of wakefulness illustrated by arousal reactions and sleep/wake cycles on the EEG but shows no signs of awareness (i.e., no purposeful movements, no pursuit eye movements, no communication) [3, 11]. The preservation of hypothalamic and brainstem functions implied by the ability to be aroused also allows for prolonged survival (persistent vegetative state—PVS).

1.2.5 Minimally Conscious State

In the minimally conscious state, purposeful behavior, as an expression of awareness, occurs inconsistently but is reproducible or sustained enough to be differentiated from reflexive behavior [4]. Misdiagnosis of states of impaired consciousness, false positives, and false negatives is probably common [12, 13]. The locked-in syndrome, with anarthria and quadriplegia but fully preserved consciousness, has to be distinguished from states of impaired consciousness.

1.2.6 Epidemiology, Etiology, and Outcome

Population-based studies are few and reliable incidence figures of coma are lacking. Different case definitions and outcome measures have been used. The five-point Glasgow Outcome Scale (GOS) [14] (Table 1.3) has been widely used in both traumatic and nontraumatic coma, and there are other outcome scales more adapted to younger children, like the Pediatric Cerebral Performance Category Scale [15].

The incidence of 30/100.000 children per year was found in a sole British study of coma due to nontraumatic etiologies with peak incidence during infancy [16].

Table 1.3 The Glasgow Outcome Scale [14]

1.	Death
2.	Persistent vegetative state
3.	Severe disability: conscious but disabled
4.	Moderate disability: disabled but independent
5.	Good recovery: normal daily activities, no or minor deficits

Children with a GCS score of ≤12 for at least 6 h were included, thus probably overestimating the incidence of actual coma in a stricter meaning. Of these, 38 % of cases were caused by infection. Intoxication and epilepsy represented 10 % each, complications of congenital malformations 8 %, accidents (nontraumatic) 7 %, and metabolic conditions 5 %. In 14.5 % of cases etiology was unknown. Overall mortality was 45 %, with 35 % (66 % of survivors) having a complete recovery and 20 % had mild to profound sequelae. Outcome depended on etiology. In the accident (smoke inhalation, burns, strangulation, drowning), congenital malformations and infection categories mortality was 84 %, 73 %, and 60 %, respectively. Among survivors late outcome was poorer for infants than for older children [17].

To summarize, the potential nontraumatic causes of coma are varied (Table 1.4), and the outcome spans from complete recovery to severe handicap or death. Prognosis is highly dependent on etiology. Prompt management including etiological treatment, if available, can be lifesaving.

Traumatic brain injury (TBI) is the leading cause of death in children >1 year. In older children motor vehicle-/traffic-related accidents predominate and in younger children falls [18]. In infants <1 year inflicted TBI (non-accidental head injury—NAHI) is the leading cause of severe TBI, carries a high mortality, and should always be suspected in infants with encephalopathy or seizures of unknown etiology. The battered child is a manifold more common event than official statistics may state [19]. In some countries (Sweden and others) caregivers are mandated by law to pursue, document, and act upon a suspicion of child abuse.

Epidemiological data on TBI varies because of differences in methodology and case definition. In a comparison of studies from Europe, United States, Australia, and Asia, the annual overall incidence of hospitalization due to TBI was 103–344/100.000 [20]. Mortality was 15–38/100.000 corresponding to 2,4–11 % of cases ("case mortality rate"). Of severe TBI, 50–64 % had unfavorable outcome on the Glasgow Outcome Scale including deaths, persistent vegetative state (PVS), and severe disability.

Overall TBI is 1.5–2 times more common in males than in females. Children and older adults (>65 years) are more afflicted by TBI. Severe TBI averages 10 % of hospitalized TBI with a rough mortality rate of 50 %. There are no data on incidence of TBI-related coma, but an estimate from severe TBI (defined as GCS score ≤8) would give an approximate figure of 10–35/100.000 which is in the same range as nontraumatic coma. In adults an early GCS score of ≤8 is a reliable predictor of poor outcome. In children a GCS score of ≤5 might be the critical cutoff [21].

Table 1.4 Etiologies of nontraumatic coma

Infection
CNS infection: meningitis, encephalitis, abscess
Systemic infection: sepsis
Inflammation
Postinfectious/postimmunization: ADEM, AHLE, ANE, HSE, other
Antibody-related encephalitis: Anti-NMDAR, anti-VGKC, Hashimoto, other
CNS vasculitis: primary (PACNS) and secondary
Rheumatic disorder: SLE, HLH, MAS, other
Stroke
Ischemia
Hemorrhage
Sinovenous thrombosis
Hypoxia-ischemia
Cardiac failure, cardiac arrest, shock
Respiratory failure
Near drowning, strangulation, smoke inhalation
Metabolic
Diabetic ketoacidosis, hypoglycemia
Electrolyte and fluid disturbances
Endocrine disorder
Hepatic encephalopathy
Renal encephalopathy
Inborn errors of metabolism: organic acidemias, amino acidemias, urea cycle defects, mitochondrial disease, fatty acid oxidation and carnitine defects, carbohydrate disorders, other
Intoxication: accidental, deliberate, Münchhausen by proxy, medication adverse reaction
Neoplasia
Infiltration, edema, mass effect, hydrocephalus, herniation
Epilepsy
Epileptic seizure, status epilepticus, NCSE
FIRES, other
Other
Hypertensive encephalopathy, PRES, congenital malformation (hydrocephalus), dissociative (conversion) disorder

ADEM acute disseminated encephalomyelitis, *AHLE* acute hemorrhagic leukoencephalopathy, *ANE* acute necrotizing encephalopathy, *HSE* hemorrhagic shock and encephalopathy, *NMDAR* *N*-Methyl-D-aspartate receptor, *VGKC* voltage-gated potassium channel, *PACNS* primary angiitis of the CNS, *HLH* hemophagocytic lymphohistiocytosis, *MAS* macrophage activation syndrome, *NCSE* nonconvulsive status epilepticus, *FIRES* febrile infection-related epilepsy syndrome, *PRES* posterior reversible encephalopathy syndrome

1.2.7 Diagnosis and Assessment of Coma and Other States of Impaired Consciousness

In the emergency setting the management of the comatose patient should be rapid and structured and include simultaneous diagnostic and therapeutic measures. Several papers have been published on this subject and similar algorithms are

Table 1.5 Acute management of the comatose child

1.	*Vital functions*: Airway, breathing, circulation. Treat ongoing epileptic seizure
2.	*Basic metabolic homeostasis*: bedside blood glucose, arterial blood gases (pO_2, pCO_2, pH, HCO_3^-, BE), lactate, electrolytes, correct abnormalities, monitor. Further blood sampling
3.	*General physical examination*
4.	*Neurological examination*
	Level of unconsciousness, GCS
	Spontaneous movements, muscle tone, posturing, tendon, and plantar reflexes
	Brain stem reflexes and respiration pattern
	Other: fontanelle, meningism, fundoscopy…
5.	*Computed tomography*: Neurosurgery? Monitor for and treat increased ICP?
6.	*Further workup and treatment*
	Expanded blood chemistry, infection (cultures, PCR), toxicology
	Lumbar puncture
	MRI
	EEG, cEEG
	Metabolic investigations
	Consider: Antibiotics/antivirals? Immunological treatment (steroids, IVIG, plasmapheresis)? Antidote? Stroke treatment? Treatment of nonconvulsive seizures? Treatment for metabolic crisis? Normalize body temperature

suggested [22–24]. Table 1.5 summarizes the steps in the acute management proposed here. Also many hospital emergency departments work according to Advanced Pediatric Life Support (APLS)-based protocols [25]. When possible, the patient should be transferred to a pediatric intensive care unit—PICU.

While the patient is assessed and treated, a member of the team should take a first medical history from parents or other available sources as soon as possible. Are there any previous or present illnesses? Medications? Ongoing infection? Preceding trauma or intoxication? Seizures? Hereditary conditions in the family? Did the present condition develop suddenly (cardiac arrhythmia, seizure, intracranial hemorrhage) or slowly, progressively (infection, inflammation, metabolic causes)? Other symptoms than decreased consciousness? In the younger child signs and symptoms can be unspecific and difficult to interpret.

1.2.7.1 Assessment and Stabilization of Vital Functions and Basic Metabolic Homeostasis

At first secure vital functions (ABC: airway, breathing, circulation). Auscultate heart and lungs. Monitor blood oxygenation, blood pressure, heart rate, respiratory rate, and pattern, as well as body temperature. Free airway and optimal oxygenation, ventilation, and circulation constitute the basis for further management. Establish IV access. Treat ongoing epileptic seizures. Endotracheal intubation, mechanical ventilation, and circulatory support (saline solution IV and inotropics) might be needed. Hypertension can be seen as a compensatory mechanism to maintain cerebral perfusion in cases of ischemia or increased intracranial pressure (ICP). Do not

normalize systemic blood pressure until this has been considered. Blood glucose, arterial blood gases (pO_2, pCO_2, pH, HCO_3^-, BE), lactate, and electrolytes should be analyzed beside if possible. Correct metabolic abnormalities. Take blood samples for complete blood count, C-reactive protein (CRP), liver, coagulation, renal, and thyroid function tests. If sepsis cannot be ruled out, secure bacterial cultures.

1.2.7.2 General Physical Examination

If not already done at this stage, do a brief general examination including inspection of the head, scalp, and skin for signs of trauma, cyanosis, jaundice, anemia, pigmentation abnormalities, and rashes. If trauma and cervical spine injury are suspected, the neck must be stabilized and not manipulated until further investigated. The abdomen should be palpated for signs of peritonitis or hepatosplenomegaly.

1.2.7.3 Neurological Examination

The neurological examination should assess:

1. The level of unconsciousness according to a validated scale.
2. Spontaneous movements, muscle tone, posturing, tendon, and plantar (Babinski's sign) reflexes.
3. The brain stem reflexes and respiration pattern.
4. Others, e.g., check the fontanelle in infants, signs of meningeal irritation, and fundoscopy.

The aim is to answer a few crucial questions. Is the patient unconscious and, if so, how deep? Are there signs of increased ICP and/or herniation? Any signs of a focal structural CNS lesion (requiring immediate treatment?) or other topographic or etiologic clues?

First, the Glasgow Coma Scale can be used to assess and describe the level of unconsciousness.

Spontaneous movements, muscle tone, posturing, tendon, and plantar (Babinski's sign) reflexes can give information about the level and localization of CNS dysfunction. Asymmetric findings suggest unilateral structural lesions. Decorticate posturing with flexion of the arms and extension of the legs is thought to be caused by bilateral lesions above the midbrain. Decerebrate posturing with extension and internal rotation of arms and legs suggests lesions affecting the pons and/or midbrain. Lesions below the pons (medulla oblongata or spinal cord) cause flaccid paresis.

Examination of the brain stem reflexes and respiration pattern is essential to detect brain stem dysfunction and herniation syndromes. The pupillary light reflex, the oculocephalic reflex (Doll's eyes test), the corneal reflex, and the gag and cough reflexes can help determine the level and degree of brainstem dysfunction (Table 1.6). In death by neurological criteria, none of these reflexes are present.

The uncal herniation syndrome is usually due to a unilateral mass lesion or swelling pushing the uncus of the ipsilateral temporal lobe through the tentorium.

Table 1.6 Brainstem reflexes and respiration in coma [22, 24]

	Examination	Normal response	Brainstem nucleus localization	Interpretation
Pupils	Response to light	Direct and consensual constriction	Midbrain	Brisk response: brainstem intact Unresponsive: midbrain-upper pons dysfunction Unilateral dilated: n.III dysfunction (uncal herniation?)
Oculocephalic (Doll´s eye)	Turn head side to side	Conjugate eye deviation in opposite direction to head	Pons	Full deviation with saccades: normal forebrain control Full deviation, no saccades: diencephalon dysfunction, brainstem intact Minimal deviation: midbrain-upper pons dysfunction No deviation: lower pons dysfunction
Corneal	Stimulation of cornea	Eyelid closure	Pons	No response: lower brainstem dysfunction
Cough	Stimulation of carina	Cough	Medulla	No response: lower brainstem dysfunction
Gag	Stimulation of soft palate	Symmetric elevation of soft palate	Medulla	No response: lower brainstem dysfunction
Respiratory pattern	Observed before mechanical ventilation or heavy sedation	Normal breathing	Respiratory centers in pons and medulla	Normal: brainstem intact Cheyne-Stokes: diencephalon dysfunction Hyperventilation: midbrain-upper pons dysfunction Ataxic, shallow: lower pons dysfunction Gasping, slow, irregular, arrest: medulla dysfunction

This compresses the ipsilateral oculomotor nerve causing a dilated and nonreactive ipsilateral pupil and in the end also oculomotor paresis with the eye turned outward and downward. Uncal herniation can also cause ipsilateral hemiparesis due to compression of the contralateral cerebral peduncle. Uncal herniation should always be suspected from a unilateral dilated pupil.

Central herniation is usually caused by diffuse brain edema or obstructive hydrocephalus with significantly increased ICP that pushes the diencephalon (thalamus and hypothalamus) down through the tentorium and the cerebellar tonsils down through the foramen magnum. In progressive central herniation, the CNS

Table 1.7 Herniation syndromes [22]

Uncal	Unilateral fixed dilated pupil
	Unilateral ptosis
	Minimal deviation of eyes on oculocephalic testing
	Hemiparesis
Diencephalic[a]	Small or midpoint pupils reactive to light
	Full deviation of eyes on oculocephalic testing
	Flexor response to supraocular pain and decorticate posturing
	Hypertonia and hyperreflexia with extensor plantars
	Cheyne-Stokes respiration
Midbrain-upper pontine	Midpoint pupils, fixed to light
	Minimal deviation of eyes on oculocephalic testing
	Extensor response to supraocular pain and decerebrate posturing
	Hyperventilation
Lower pontine	Midpoint pupils, fixed to light
	No response on oculocephalic testing
	No response to supraocular pain or flexion of legs only
	Flaccidity with extensor plantars
	Shallow or ataxic respiration
Medullary	Pupils dilated and fixed to light
	Slow, irregular, gasping or arrested respiration

[a]May be mimicked by drugs, toxins, metabolic disturbance and ictal/postictal epileptic conditions

dysfunction spreads in a rostrocaudal direction from the diencephalon through the midbrain and pons to the medulla. Diencephalic, midbrain-upper pons and lower pons-medulla stages can be distinguished from examining the brain stem reflexes, posturing, and respiration pattern (Table 1.7).

Increased ICP. In a patient with depressed consciousness one should always assume that ICP is increased until indicated otherwise. Signs of increased ICP include headache and nausea, depressed consciousness in itself, herniation signs, tense fontanelle (infants), setting-sun phenomenon, systemic hypertension, and bradycardia. In subacute or chronic increase of ICP, fundoscopy may reveal papilledema, but normal fundoscopy does not exclude increased ICP! Signs of increased ICP and/or herniation require immediate measures to reverse the progression towards severe brain injury or death. This can include reduction of ICP through pharmacological interventions or neurosurgery.

Others. Meningism (neck stiffness, Kernig's sign, Brudzinski's sign) suggests meningeal irritation with infectious meningitis being the most common cause. Nonconvulsive epileptic seizures are common in critically ill and comatose patients [26] and can be suspected from subtle signs like nystagmus and tonic eye deviation.

1.2.7.4 Acute Neuroimaging

After completing the neurological examination, the next procedure to consider is neuroimaging. Despite its drawbacks with radiation exposure and a lower

sensitivity than MRI, in the emergency setting computed tomography (CT) is usually the first choice due to its wide availability and short acquisition time. CT has sufficient sensitivity for structural abnormalities that might need immediate intervention like intracranial hemorrhage, tumor, hydrocephalus, cerebral edema, midline shift, and herniation. CT should be done in all children with depressed consciousness of unknown cause and in all patients where a structural lesion is suspected (usually due to asymmetric or focal signs or symptoms). If stroke is suspected computed tomography angiography (CTA) is of additional value. Based on CT findings, acute neurosurgery (ventriculostomy with ICP monitoring or decompression of a mass lesion) or other specific treatments based on diagnosis might be required at this point

1.2.7.5 Further Emergency Workup

Depending on the evaluation this far additional investigations may be warranted. This could include expanded blood chemistry, toxicology screening in blood and urine, and search for infectious agents (cultures and PCR) from different sites and body fluids. Fever should be treated. If intoxication is suggested, consider gastric lavage, charcoal, and antidotes. In addition consider lumbar puncture, MRI, EEG, and metabolic workup.

Lumbar puncture (LP) is warranted in patients with suspected infection or inflammation of the nervous system. Cerebrospinal fluid is analyzed for cell count/cytology, biochemistry, and microbe detection (microscopy, cultures, PCR, antibodies), and the ICP is measured. The risk of provoking herniation by performing LP must be considered in patients with depressed consciousness and/or asymmetric/focal signs or symptoms. LP should then be deferred and a CT done. Likewise, an impaired coagulation (especially platelet count $<40–50 \times 10^9$/L) could be a contraindication to LP. If the suspicion of a CNS infection is high, start antibiotics and antivirals (aciclovir) without delay. If the CT does not show a focal mass lesion or impending herniation and if the suspicion of infection/inflammation remains, LP can usually be done safely after stabilizing and observing the patient for a couple of hours. Note that a normal CT does not exclude increased ICP and risk of herniation.

Magnetic Resonance Imaging (MRI). If CT is normal or ambiguous and the cause of coma is still unknown or insufficiently characterized, MRI of the head should be sought as soon as available and the patient is stable enough to tolerate the longer acquisition time. MRI has higher sensitivity and specificity for most etiologies and more specifically has added value in detecting ischemia, infection, inflammation/demyelination, metabolic disorders, traumatic diffuse axonal injury, and posterior fossa pathology. MRI is an important tool to characterize and date lesions in inflicted TBI in abused infants. MR angiography (MRA) and MR venography (MRV) are used to assess stroke and sinovenous thrombosis respectively.

Electroencephalogram (EEG) is used for several purposes in the acute setting. EEG is needed to detect, in order to treat, nonconvulsive status epilepticus as the

cause of coma. Electrographic, but clinically silent, seizures are common in critically ill and often heavily sedated patients in intensive care, independent of etiology [26]. Therefore continuous EEG (cEEG) monitoring, if available, is preferred at least initially to ensure good sensitivity. Most would agree that electrographic nonconvulsive seizures should be ambitiously treated in the critically ill child, but details are under debate and more research needed.

In addition to detecting epileptic seizure activity, EEG visualizes cortical electric activity and thus reflects the level of unconsciousness (or anesthesia). Different patterns of slowing and absence of faster activity characterizes encephalopathy (disturbance of cerebral function) but is nonspecific in relation to etiology. Focal slowing suggests a structural lesion. Discontinuous or isoelectric EEG has a negative predictive value but must be interpreted with caution. Certain EEG findings suggest specific etiologies but the specificity is low. cEEG is used to monitor depth of anesthesia in the treatment of status epilepticus and in severe traumatic brain injury.

Metabolic workup is warranted if coma is suspected to be caused by a decompensated metabolic disease—metabolic crisis (Table 1.3). Clues to an underlying metabolic disorder could be laboratory findings (acidosis, increased lactate, hyperammonemia, hypoglycemia), certain MRI findings, recurrent encephalopathy, and psychomotor delay. First-line investigations include organic and amino acids in urine and in plasma amino acids, free fatty acids, acylcarnitines, and total and free carnitine. Treatment protocols for metabolic crisis with unknown diagnosis involve stopping feeds, administering glucose infusion and cofactors, and removing toxic metabolites.

1.2.8 Outcome Prediction

The questions concerning whether ones child will die, acquire lifelong disability, or completely recover are intensely present for parents (and other relatives) of a comatose child. An attitude of not knowing is the basis in the acute situation. To what extent a parent would benefit from a general "map" of the situation, describing different influencing factors and possible outcomes is highly individual, but this could make a traumatic situation more comprehensible if conveyed in a sensitive manner. When something is known beyond reasonable doubt, it should be communicated to the parents.

In addition to the psychological aspects, there is also a medical need to know as a basis for rational decisions about therapy, withdrawal of life support, and rehabilitation. Our ability to predict outcome for a child in coma is limited. Clinical, electrophysiologic, radiologic, and biochemical data provide a basis [22–24], but generally data are weaker for children than for adults.

A Glasgow Coma Scale score of ≤8 for adults and possibly ≤5 for children [21] carries a poor prognosis, and especially the motor response component has strong predictive value. The duration of coma affects outcome as does etiology. Multiple other clinical variables have correlated with poor outcome in different studies.

Among electrophysiologic measures somatosensory-evoked potentials (SSEPs) and EEG are the most used. Normal SSEPs predict good neurologic outcome, whereas bilaterally absent SSEPs predict poor outcome. Isoelectric or burst-suppression pattern on the EEG has a negative predictive value, especially when repeated. Other electrophysiologic tests studied include motor-evoked potentials (MEP), brainstem auditory-evoked potentials (BAEP), and event-related potentials (ERP).

Neuroimaging (CT, MRI) findings correlating with poor outcome include brain stem lesions, diffuse axonal injury, and global hypoxia-ischemia. There are some studies on the potential of magnetic resonance spectroscopy (MRS) as a prognostic tool.

Biochemical markers in blood and cerebrospinal fluid like neuron-specific enolase (NSE), s100B, and glial fibrillary acidic protein (GFAp) are sensitive to brain damage, but their specificity and predictive power are at present insufficient.

To conclude clinical variables and complementary tests, provide a basis for predicting outcome, but no combination of these have been shown to have absolute predictive power. In relation to the individual child, data has to be treated with caution until the prognosis is unequivocal. The balance between being prematurely gloomy and engaging in futile treatments is difficult but essential in managing the critically ill child in coma.

1.3 Diagnosis of Death by Neurological Criteria in Infants and Children and an Outline of How to Manage the Clinical Situation

1.3.1 Background

Defining death has important medical, legal, and ethical issues. Traditionally, death has been determined by the cessation of respiration and circulation (heart beat). With progress in resuscitation, technical advances, and the possibility of organ donation as an immediate consequence of death, a need for a better definition of death arose. In 1959 Mollaret and Goulon described coma dépassé (irreversible coma) in patients without brain function [27]. This led to an ethical discussion on whether these patients could be considered dead or not. In 1968 a definition of irreversible coma was presented, “the Harvard Criteria,” where the necessary criteria to define coma dépassé were described [28]. The first European country to accept death by neurological criteria as a legal definition of death was Finland in 1971. In 1976 the Medical Conference of Royal Colleges in the United Kingdom published a statement on death by neurological criteria. Here the apnea test was introduced as function of the brain stem [29]. In the United Kingdom a total lack of brain stem function was accepted as an indicator for diagnosing death by neurological criteria [29].

The Uniform Determination of Death Act (UDDA) was accepted in the United States in 1981 (the whole brain death criterion). Today total infarction of the whole brain is commonly accepted as death even if the body's metabolic processes are functioning and advanced life support temporarily upholds vital functions. The guidelines listed above apply to adults. In 1987 guidelines for the determination of death by neurological criteria in children were presented [30]. These guidelines are now revised and described in more detail below [31].

1.3.2 Epidemiology

In adults death by neurological criteria is most commonly the result of traumatic brain injury and subarachnoid hemorrhage. The most common cause for death by neurological criteria in children is motor vehicle accidents, shaken baby syndrome, and abuse. Other causes are sudden infant death syndrome (SIDS), near drowning, and severe infections involving the CNS [32]. In one report, including 590 infants and children in the United States, head injury represented a third of all causes of death by neurological criteria [33]. Further data from North America demonstrates that the majority of children declared dead by neurological criteria are between 11 and 18 years of age and that only 55 % of these cases (all children dead by neurological criteria) became organ donors. Furthermore, from 1993 to 2003 the number of pediatric donors dead by neurological criteria decreased by 22 % [34].

1.3.3 Death by Neurological Criteria

Death by neurological criteria is a clinical diagnosis defined as irreversible cessation of all functions of the entire brain, including the brainstem, with a known irreversible cause of coma. Coma, absence of brain stem reflexes, and the presence of apnea are the clinical criteria confirming death by neurological criteria. The declaration of death by neurological criteria in children does not differ from adults in any significant way. The most important differences are the age-related periods of observation.

When diagnosing death by neurological criteria, it is of importance to review the patient's medical history, to differentiate the cause of coma from other reversible causes, and to conclude that the condition is irreversible. Possible misdiagnosis of death by neurological criteria can be the locked-in syndrome, hypothermia, and drug intoxication. When death by neurological criteria is diagnosed, further life support will be withdrawn. It is important to recognize that severe brain damage is not the same as death by neurological criteria. The only organ that cannot be replaced or supported technically is the brain. However, today's technical advances makes it is possible to sustain and uphold vital functions for a prolonged period of

time despite the irreparably damaged brain and brain stem, thus making organ donation possible.

Children who are comatose as the result of a massive brain injury are generally diagnosed dead by neurological criteria within 2 days of hospitalization. Within 2 days following this declaration, intensive care is typically withdrawn or organ donation is carried out [34].

1.3.4 Guidelines for the Determination of Death by Neurological Criteria in Infants and Children

In "Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations-executive summary" [31], the authors revise the 1987 pediatric brain death guidelines [30].

In the citation below [31] it is stated that:

> Prerequisites for initiating an evaluation of brain death. Hypotension, hypothermia and metabolic disturbances should be treated and corrected and medications that can interfere with the neurological examination and apnea testing should be discontinued allowing for adequate clearance before proceeding with these evaluations.
>
> Number of examinations, examiners and observation periods. Two examinations including apnea testing with each examination separated by an observation period are required. Examinations should be carried out by different attending physicians. Apnea testing may be performed by the same physician. An observation period of 24 hours for term newborns (37 weeks gestational age) to 30 days of age and 12 hours for infants and children (>30 days to 18 years) is recommended.
>
> The first examination determines that the child has met the accepted neurological examination criteria for a diagnosis of brain death. The second examination confirms brain death on an unchanged and irreversible condition.
>
> Assessment of neurological function after cardiopulmonary resuscitation or other severe acute brain injuries should be deferred for 24 hours or longer if there are concerns or inconsistencies in the examination.
>
> Apnea testing to support the diagnosis of brain death must be performed safely and requires documentation of an arterial $PaCO_2$ of 20 mm Hg above the baseline and resulting in a $PaCO_2 \geq 60$ mm Hg with no respiratory effort during the testing period. If the apnea test cannot be safely completed, an ancillary study should be performed.
>
> Ancillary studies (electroencephalogram and radionuclide cerebral blood flow) are generally not required to establish brain death and are not a substitute for the neurological examination, but may be recommended for local legal purposes.
>
> Ancillary studies may be used to assist clinicians in diagnosing brain death (i) when components of the examination or apnea testing cannot be completed safely due to the underlying medical condition of the patient; (ii) if there is uncertainty about the results of the neurological examination; (iii) if a medication effect may be present; or (iv) to reduce the inter-examination observation period.
>
> When ancillary studies are used, a second clinical examination and apnea test should be carried out, and components that can be completed must remain consistent with death by neurological criteria. In this instance, the observation interval may be shortened, and the second neurological examination and apnea test (or all components that are able to be completed safely) can be performed at any time thereafter.

After the above-mentioned criteria are fulfilled, a declaration of death can be issued. The guidelines above, with some alterations, are generally accepted as human death by medical and legal communities. However, there are religious and philosophical considerations regarding these criteria which are not always wholly accepted. This fact should be taken into consideration when discussing death and donation with parents who have strong religious beliefs [35–39].

1.3.5 Special Concerns Regarding Term Neonates and Young Infants

Colleagues in the already cited task force (Committee for Determination of Brain Death in Infants and Children) continue with stating that the determination of brain death in infants and children is a clinical diagnosis. However due to lack of sufficient data, recommendations for preterm infants (less than 37 weeks gestational age) were not included in the guidelines [31], for reasons commented upon below.

In neonates and infants the diagnosis of death using neurological criteria is more complicated to determine than in adults. The brain continues to develop during the first 2 years of life. During particular phases of development, there may be periods of vulnerability and different responses to injury [40]. Infants and young children have increased resistance to brain damage and may unexpectedly recover substantial CNS function from a clinical situation that an adult would not. The infant cranium is not a rigid structure (up to 1.5 years when the sutures close) and allows for some expansion from brain swelling, which in turn decreases the risk of brainstem incarceration.

In preterm and term neonates, the cranial nerve response is not completely matured. The pupillary light reflex is absent before gestational week 29–30. The lesser amount of pigmentation and the smaller pupil make it more problematic to assess the pupillary light reflex. In intubated patients and in neonates with swollen features, it may be difficult to assess ocular motility.

Ancillary methods, such as assessing cerebral blood flow (CBF) with four-vessel cerebral angiography, are the golden standard in adults. Because of significant physiological and cerebrovascular differences in neonates and young infants, four-vessel cerebral angiography may not be conclusive.

Ashwal [41] reports data on 30 newborns that underwent EEG and radionuclide perfusion investigations. The results showed that one third of the infants with electro-cerebral silence (ECS) had evidence of CBF and that 58 % of those with no CBF had evidence of EEG activity. CBF data indicated that CBF was absent in 72 % of the brain-dead newborns. These findings accentuate the limitations of both CBF and EEG investigations for confirmation of death by neurological criteria in neonates [41].

If EEG and/or CBF investigations are not conclusive, the patient cannot be pronounced dead. It is then recommended that death by neurological criteria should be determined clinically and based on repeated examinations rather than relying exclusively on ancillary studies [31].

1.3.6 Support of the Family, Breaking Bad News

The discussion concerning death and a potential donation is not simple in adults and for several reasons more complicated in children. A caring presence combined with detailed and truthful information builds trust. Withholding information or being falsely positive may lead to distrust and anger [42]. Parents require repeated information. Once it is decided that diagnosing death by neurological criteria is necessary there is no rush. There is time to summarize the course of events and to demonstrate X-ray findings, electroencephalogram results, etc. The information given has to be understood and this may take some time.

It might be helpful to let the parents participate during the diagnostic procedures [43, 44]. Furthermore, the parents must be prepared that once their child is declared dead, all support (including ventilator support) will be withdrawn or, if discussed and decided, donation will be carried out.

Even after death has occurred, the need to stay with their child is described by parents. Memories, that later can bring comfort will be created by providing opportunities for the parents to be present during difficult procedures and at the time of death.

It is our experience that before intensive care is withdrawn, it can be helpful to promote some kind of gathering around the patient. Perhaps a ceremonial led by a religious authorized person (priest, imam, rabbi, etc.) or just a name giving or remembrance ceremony where parents and relatives can participate.

Parents need to be prepared for the scenario when intensive care is withdrawn. It is therefore helpful to describe this procedure; in which order intensive care is withdrawn and how comfort will be provided for the child. Furthermore, it is recommended to discuss how the parents would like this moment in time to be and to express that we are very sensitive to the family's wishes. At an appropriate time we provide general information concerning burial and postmortem procedures. We also inform them on planned follow up meetings.

1.3.7 On Organ Donation

We typically discuss this issue when other questions are resolved. We present the opportunity of donation to the parents and that we would like them to discuss this with an experienced member from the transplantation team. In this way the palliative treatment and the question of eventual organ donation is kept separate.

1.4 Conclusions

The early stages of unconsciousness and coma can be managed with the application of adequate and rehearsed clinical algorithms as outlined here. The two-track approach (immediate supportive care AND diagnostic forward progress), as well as the multi-professional and team aspects of this work, have herein been emphasized. When severe illness is present which then deteriorates towards permanent brain damage, a more challenging multidimensional clinical situation must be faced. As stated above, even the worst diagnosis of death by neurological criteria in a child need not be a point of total despair to all. In modern medicine we should then, with little hesitation, move ahead towards exploring the still open possibility of organ donation. We maintain this cannot be carried out without a carefully prepared organization, in which proper designation of roles and tasks have been assigned well ahead of the appearance of a child that has moved to the point of death by neurological criteria. When the donation option is not available and the outcome poor, the care givers need to be able to guide the family through to acceptance and closure.

It is of great importance that the various criteria to be applied in these states are firmly established, their signs known and communicated within the whole organization that care for children, and then respected throughout the chain of care. A general acceptance in the local society must be established. If not, endless and painful exchange of opinionated care and poor decision-making threaten to cancel rational activity in a desperate situation. This may in turn result in legal controversy and fruitless battles.

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Chapter 2
Seizures

James J. Riviello Jr. and Rod C. Scott

Abstract Seizures occur from excessive cortical excitation and their clinical manifestations vary depending upon the cortical areas involved. Seizures may occur in a patient with underlying epilepsy or result from an acute central nervous system (CNS) insult. This chapter defines the various terms used in describing seizures, the classification, the pathophysiology, and the various clinical manifestations of seizures. We will also describe the diagnostic studies needed for seizures, especially the electroencephalogram (EEG). The treatment of seizures and status epilepticus is reviewed in Chap. 10.

Keywords Seizures • Status epilepticus • Seizure classification

2.1 Introduction

Seizures represent a neurologic event whose clinical manifestations result from excessive CNS excitation [1]. The underlying neurophysiology of this excessive excitation is a transient hypersynchronous neuronal discharge. Seizures usually have a short duration, lasting less than several minutes. A prolonged seizure is referred to as status epilepticus (SE), and SE is more likely to occur in the critically ill. Epilepsy is defined as a condition in which there are recurrent, unprovoked seizures [2, 3].

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Table 2.1 Immediate seizure management goals

(1) Recognize the seizure May require CEEG monitoring in some patients
(2) Maintain the vital signs by ensuring the ABCs: airway, breathing, and circulation
(3) Treat the Seizure, if duration > 5 min Certain circumstances require immediate treatment
(4) Identify and treat the precipitating cause, if known
(5) Determine if an AED is needed to prevent subsequent seizure activity

AED antiepileptic drug, *CEEG* continuous EEG

The patient with epilepsy has a lowered seizure threshold, and certain factors, such as intercurrent illness or sleep deprivation, may precipitate a seizure. With a first seizure, it is important to determine if the seizure results from an acute CNS insult or it is the initial presentation of epilepsy. An acute CNS insult is more likely if the first seizure occurs during an illness, for which a specific treatment may be needed.

Seizures may occur with epilepsy or may result from an acute primary CNS insult, such as stroke, intracranial hemorrhage, or traumatic brain injury, or from a systemic disorder with secondary effects on the CNS, such as hypoglycemia, hypoxemia, or hypotension. A focal neurologic deficit is more suggestive of a primary intracranial insult, whereas global (diffuse) CNS dysfunction suggests a secondary CNS insult, such as hypoglycemia. However, focal dysfunction may occur even with global CNS dysfunction.

Subclinical seizures, also called electrographic seizures or nonconvulsive seizures, occur without obvious clinical manifestations, and EEG recording is needed to identify them. Subclinical seizures are common in a critically ill patient with an acute brain injury [4] or in a patient with epilepsy. There is a growing body of evidence that subclinical or electrographic seizures increase the risk of brain injury when they occur in conjunction with an acute CNS insult [5, 6]. The term uncoupling describes the situation when clinical seizures are controlled after the administration of an antiepileptic drug (AED) yet the electrographic seizures persist, as the clinical manifestations are "uncoupled" from the electrographic seizure. Whether clinical or subclinical, seizures represent a potential neurologic emergency, since they signify a CNS disturbance. Nonconvulsive seizures may cause altered awareness, which may be difficult to detect in the critically ill patients.

There are five immediate management goals when a patient presents with a seizure (Table 2.1). The first is to recognize the episode as a seizure. The second is to maintain the vital signs by ensuring the airway, breathing, and circulation, the ABCs. The third is to immediately treat the seizure, especially if prolonged, and the fourth is to identify and treat the precipitating cause, if possible. The last is to determine the AED needed to prevent subsequent seizure activity. Especially in regard to recognizing a seizure, it is important to know that the clinical manifestations of a seizure may vary.

The classification of seizures and the epilepsy syndromes guides management. There are three major classification systems: (1) seizure duration; (2) seizure onset,

Table 2.2 Stages of status epilepticus [7, 8]

Incipient stage (0–5 min)
Early stage (5–30 min)
Special circumstances of the early stage: situations that need immediate seizure control
Transition stage
Late stage (established) (30–60 min)
Refractory stage (>60 min)
Postictal stage

either focal or generalized; and (3) seizure etiology. The duration of seizure is important because aggressive treatment is needed for prolonged seizures. Status epilepticus, defined as a prolonged seizure lasting greater than 30 min or serial seizures without return of consciousness for 30 min, is a medical emergency and requires immediate termination. Although 30 min is the duration used to define status epilepticus, an operational definition recommends AED treatment after 5 min for a continuous seizure or serial seizures without a return of consciousness [1]. The staging of SE also guides treatment [7, 8] (Table 2.2).

The International League Against Epilepsy (ILAE) has developed an international classification of epileptic seizures which classifies seizures according to the clinical manifestations and the epilepsy syndromes associated with a constellation of signs and symptoms [2, 3]. Seizures are divided into focal or generalized according to their cortical onset. This is important because the origin in the cortex and its spread, especially how much cortex is ultimately involved, determines the clinical manifestations of the seizure. The AEDs used to prevent seizure recurrence typically have specific efficacies for either a focal or a generalized seizure. A focal seizure is defined as one whose initial clinical manifestations indicate activation of only a focal area, or one part of the cortex, or in other words, the initial activation of a focal group of neurons. A generalized seizure is one with "more than minimal involvement of both cerebral hemispheres," or in other words the initial activation of neurons throughout both hemispheres. A generalized seizure may not simultaneously involve every neuron.

The third system classifies seizures and epilepsy by their etiology, dividing them into symptomatic, cryptogenic, and idiopathic [2, 3]. A symptomatic seizure is one for which the exact cause is identified. A cryptogenic seizure is one in which an underlying specific etiology is presumed, because the neurologic state is abnormal but is not yet identified. The idiopathic seizure is one in which etiology is not known, either arises spontaneously or from an obscure unknown cause. Many of the seizures identified as idiopathic have been associated with a genetic disorder or a channelopathy. A patient presenting with a new-onset seizure or status epilepticus from a specific cause would be classified as having an acute symptomatic seizure. If a past known CNS insult had caused epilepsy, then this a remote symptomatic seizure. However, a patient with epilepsy may have a seizure precipitated by an acute illness. This is referred to as a remote symptomatic seizure with an acute precipitant [9] or an acute or chronic seizure [10].

The new classification system replaces symptomatic, cryptogenic, and idiopathic with genetic, structural/metabolic, and unknown [3]. The distinction between complex partial and simple partial seizures is also eliminated. However, these terms are still in common clinical use.

2.2 Introduction to Seizure Pathophysiology

Two levels of seizure pathophysiology are important for understanding treatment. The first is at the level of the neuronal membrane and the second is at the level of physiologic disturbances occurring in the patient.

2.2.1 Pathophysiology at the Cellular Level

Seizures result from inherent neuronal membrane instability caused by excessive CNS excitation, inadequate CNS inhibition, or a combination of the two. Simplistically, a seizure starts when CNS excitation outweighs CNS inhibition which results in prolonged membrane depolarization and ends when the CNS inhibitory systems outweigh the excitatory systems. The neuronal cell membrane is semipermeable with an intracellular to extracellular gradient maintained by osmolar differences across the membrane. The resting membrane potential (RMP) is approximately −70 uV across the membrane with ion flux across the membrane determining its discharge pattern [11]. Normally, the extracellular sodium concentration and intracellular potassium concentration are high, with the reverse for the intracellular space (low Na^+, high K^+), with this gradient maintained by a Na-K exchange pump. Cell depolarization results in sodium ion influx which lowers the RMP and causes depolarization. If depolarization is excessive, an epileptic discharge is generated. There is a high extracellular chloride ion concentration at rest. After depolarization, a chloride ion influx repolarizes the cell and reestablishes the RMP. Maintaining the RMP is dependent on the Na-K ATP pump. Acute neurologic insults, such as hypoxia, ischemia, or hypoglycemia, result in failure of the Na-K membrane pump, with the inability to restore the RMP and excessive depolarization. An excess of excitatory neurotransmitters results in excitotoxicity. Calcium and magnesium inhibit sodium influx. So excessive Na influx occurs with hypocalcemia or hypomagnesemia, resulting in increased excitability.

Understanding membrane physiology allows us to understand the relationship between electrolyte disorders and acute seizures [12] and why seizures occur with specific electrolyte disorders. CNS depression with encephalopathy is generally seen in disorders of sodium and osmolality, although increased CNS excitability may result in seizures. Hypercalcemia and hypermagnesemia produce CNS depression, whereas hypocalcemia and hypomagnesemia increase CNS excitability and

cause seizures. Disorders of potassium rarely produce seizures. In the experimental model excessive excitation itself may cause neuronal injury and cell death, referred to as excitotoxic injury.

As described above, seizures spontaneously stop when the inhibitory systems outweigh the excitatory systems. Therefore, mechanistically, a seizure develops into status epilepticus when there is a failure of the inhibitory factors [1]. In addition, status epilepticus may be more difficult to control as the duration increases and may not respond to the conventional AEDs. A rapid modification in the properties of $GABA_A$ receptors [13] through mechanisms such as altered receptor trafficking (see below) likely contributes to the reduction in inhibition.

2.2.2 Pathophysiology at the Patient Level

Lothman outlined the alterations in systemic and brain metabolism occurring with a prolonged seizure [8]: there is a decreased brain oxygen tension, with a mismatch between the sustained increase in oxygen and glucose utilization and a fall in cerebral blood flow, followed by depletion of brain glucose and oxygen. In the early stages of a seizure, brain compensatory mechanisms may protect against neuronal injury. However, as the seizure progresses, these compensatory mechanisms may become exhausted, which dramatically increase the risk of neuronal injury. This point defines the transition stage from early to late (established) SE. During all stages, the ability to compensate requires adequate airway and good breathing, circulation, and cerebral blood flow (CBF). During the early stages, blood pressure (BP) and blood lactate and glucose increase, and pH decreases [8]. The BP increases as a result of autoregulation, which increases the CBF to match the increased cerebral glucose and oxygen utilization in order to prevent neuronal exhaustion. Brain tissue oxygenation is preserved, but brain glucose stores slowly decrease. The transition stage marks the progression of the early stage to the late stage. In the late stage, BP may decrease to normal and hypotension, respiratory compromise, leading to hypercarbia, hypoxemia, decreased pH, lactate and glucose, and hyperthermia occurs. Brain parenchyma oxygen and glucose decrease, while cerebral glucose and oxygen utilization remains elevated, and CBF may decrease. Convulsive and nonconvulsive seizures increase intracranial pressure, potentially aggravating already compromised CNS compensatory mechanisms [14]. In all stages, compensatory mechanisms require adequate airway, breathing, circulation, and cerebral blood flow.

A time-dependent efficacy of treatment occurs in experimental models of SE. This decreased benzodiazepine response occurs rapidly after the onset of SE in young animals with ages corresponding to a human toddler [15]. Diazepam and the other benzodiazepines enhance the function of a subset of benzodiazepine-sensitive $GABA_A$ receptors. The surface expression of these receptors declines during SE resulting from activity-dependent trafficking of subunits of $GABA_A$ receptors [12].

Table 2.3 Seizure types

Generalized seizures
Tonic-clonic (any combination)
Absence
Typical
Atypical
Absence with special features:
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Focal seizures
Unknown
Epileptic spasms

2.3 Presenting Acute Symptoms

The classification of the seizure starts with the seizure semiology, defined as the study of signs and symptom with seizure types divided into either focal or generalized seizures. There are as many different types of status epilepticus as there are seizure types (Table 2.3). There are three types of focal seizures, also known as partial seizures or localization-related seizures. The simple focal (partial) seizure has its clinical manifestation without altered awareness, the complex focal (partial) seizure has its clinical manifestations with altered awareness, and the focal (partial) seizure with secondary generalization starts with a focal manifestation and then evolves into a generalized tonic-clonic seizure. A simple focal (partial) seizure is really an aura, and when prolonged, is referred to as epilepsia partialis continua. The clinical manifestations of a focal seizure depend upon the origin of the discharge and the cortex involved as it propagates. The seizure semiology of the focal seizure is different in the infant. Rather than the generalized tonic-clonic seizure, the most frequent seizure types in infants are astatic, behavioral arrest, clonic, epileptic spasms, tonic seizure, and the versive seizure [16].

Generalized seizures typically have no focal features and consist of the following seizure types [2, 3]. The absence seizure or the atypical absence seizure has altered awareness, usually with eye blinking. The tonic-clonic seizure starts with initial tonic activity (a sustained posture), followed by clonic movements, or the "jerking." The myoclonic seizure differs from a clonic seizure by the duration of the movement (<100 ms). A tonic seizure occurs with mostly a sustained posture, whereas an atonic seizure consists of a loss of muscle tone, resulting in a decrease in muscle activity (may be limp). The atypical absence seizure, the tonic, and the atonic seizures typically with a neurologic disorder associated with a developmental disability or mental retardation.

Seizures and SE are also classified by semiology as convulsive or nonconvulsive, as this is what is clinically observed: whether there are convulsive movements or

only altered awareness. This scheme is more applicable in the acute setting with a critically ill child with recurrent seizures or status epilepticus. Convulsive SE (CSE) is relatively easy to identify because of the overt convulsions, whereas nonconvulsive seizures or nonconvulsive SE (NCSE) may have no outward convulsive movements, and EEG is needed to identify the electrographic seizure activity. In a study of NCSE, subtle motor activity and ocular movement abnormalities were present in 75 and 50 %, respectively, in patients with NCSE [17]. Nonconvulsive seizures or SE must also be considered in a patient with known epilepsy who presents with altered awareness.

The presence of nonconvulsive seizures or nonconvulsive status epilepticus is especially important in the patient with an acute brain injury, since electrographic seizures themselves may add to the neurological insult. In many neurological ICUs, continuous EEG monitoring is considered mandatory. Patients with CSE treated with anticonvulsants may cease their convulsive movements, yet remain in nonconvulsive status epilepticus, manifesting itself as continued altered awareness.

2.4 Diagnosis and Differential Diagnosis

The treatment of a seizure or SE starts with attention to the ABCs. The anticonvulsant treatment of status epilepticus is detailed in Chap. 10. Diagnostic studies to identify the precipitating cause must be considered as part of the treatment sequence, as an AED may control seizure activity but does not treat the underlying cause. Failure to treat the underlying cause may result in refractory SE. The appropriate diagnostic studies are done after the patient has been stabilized, and these are determined by the history, examination, and age, with a greater need to exclude treatable causes in the youngest children. Seizure classification guides management since an acute symptomatic seizure demands a complete work up to identify etiology, whereas in the patient with remote symptomatic seizures, or symptomatic epilepsy, a complete evaluation may not be needed, and the evaluation is determined by the specific history. Acute symptomatic SE is more likely in younger children. It is especially important to determine if the child has had a preceding history of seizures, or epilepsy, or if the seizure has occurred in the setting of an acute illness, even if just a nonspecific upper respiratory tract infection, and if there are any preceding psychiatric symptoms, movement disorders, or family history of autoimmune disorders. These symptoms suggest an acute autoimmune disorder (NMDA receptor encephalitis). Seizures may have an acute precipitant in a patient with epilepsy. This is referred to as remote symptomatic epilepsy with an acute precipitant or acute on remote epilepsy. In the American Academy of Neurology (AAN) practice parameter for the diagnostic assessment of the child with status epilepticus, a retrospective study, remote symptomatic SE with an acute precipitant occurred in 1 % of patient [9], whereas in the prospective North London status epilepticus surveillance study, an acute on remote cause occurred in 16 % [10].

Serum glucose should be rapidly checked to exclude hypoglycemia. CBC may be helpful for infection, although leukocytosis occurs from SE itself. Electrolytes, calcium, phosphorus, and magnesium values may be helpful in children with vomiting and diarrhea [9]. Low AED levels may be associated with SE [9]. Serum studies may be needed if there is suspicion for a specific toxin [9]. The AAN practice parameter [9] reported the following abnormalities in children undergoing acute evaluation: abnormal electrolytes (6 %), positive blood cultures (2.5 %), CNS infection (2.8 %), low AED levels (32 %,) ingestion (3.6 %), inborn error of metabolism (4.2 %), epileptiform abnormalities (43 %), and neuroimaging abnormalities (8 %). In the prospective study of new-onset SE, electrolyte abnormalities were found in 1.4 %, CNS infection in 9 %, and toxins in 1.4 % [18]. In a prospective study of new-onset seizures presenting with SE, in the acute symptomatic cases, the cause was CNS infection in 55 %, vascular in 21 %, and toxin, trauma, and electrolytes disturbances occurred in 8 % each [18]. In remote symptomatic cases, 31 % had inborn errors of metabolism, 30 % had cerebral dysgenesis, 15 % had a remote vascular cause, and a remote infection, chromosomal abnormality, or mesial temporal sclerosis occurred in 8 % each.

2.5 Assessment

In a recent review, Freilich and colleagues recommend that electrolytes, EEG, and CT/MRI are always done for new-onset SE, and if the clinical suspicion exists, urine toxicology, genetic or metabolic testing, and lumbar puncture should also be considered. For refractory SE or persistent encephalopathy, continuous EEG is recommended. For SE in a known patient with epilepsy, AED levels are always recommended, electrolytes, EEG, and CT/MRI need to be considered, and video EEG should be done when there is persistent SE or encephalopathy [19]. Lumbar puncture to exclude meningitis must be considered in the febrile child, but is not absolutely necessary in every child, depending upon the clinical situation and the ability to clinically assess the older child. If there is concern for increased intracranial pressure or a structural lesion, LP is deferred until neuroimaging is done, but antibiotics should be given prior to LP, ultimately relying on cell count and bacterial cultures. CSF pleocytosis may occur without infection, due to either an inflammatory process or breakdown in the blood-brain barrier.

Neuroimaging is indicated for new-onset SE, especially without a defined cause, or a prior history of epilepsy. The AAN practice parameter for neuroimaging in seizures recommended an emergent (scan immediately) scan for new-onset SE, or in a known epileptic not responding to treatment [20]. The child needs to be stabilized before the scan. A higher incidence of life-threatening lesions (hemorrhage, brain swelling, mass effect) occurs with a first-time seizure or in a child with epilepsy and new focal deficits, persistent altered mental status, with or without intoxication, fever, recent trauma, persistent headache, cancer, or on

Table 2.4 Conditions with a high risk for clinically significant findings on neuroimaging

New focal deficits, persistent altered awareness, persistent headaches
Sickle cell disease
Hemorrhagic disorders, anticoagulation
Cerebral vascular disease
Malignancy
HIV infection
Hydrocephalus
Travel to area endemic for cysticercosis
Closed head injury

anticoagulation [20, 21] (Table 2.4). Although MRI is more sensitive but is rarely available for emergent studies, a CAT scan will adequately identify life-threatening conditions. In our study of new-onset afebrile seizures, two criteria were associated with a high risk for a clinically significant finding: a predisposing condition and a focal seizure in a patient less than 33 months of age. Only 38/475 (8 %) had clinically significant findings and only 3 of these needed immediate intervention [21]. In the AAN practice parameter, neuroimaging abnormalities were present in 8 % [8], and with new-onset seizures presenting with SE, a diagnosis was made by neuroimaging (CT, MRI) in 30 %, with management changed in 24 % [28/143]and 20 % of cranial CAT scans were abnormal, with 14 (10 %) showing acute abnormalities, and 14 (10 %) showing chronic abnormalities [18].

An EEG is not usually needed at treatment onset for CSE, unless there is a strong suspicion for pseudoseizures or pseudostatus epilepticus, which occurs in children but is more common in adults. Lorazepam is frequently administered as first-line treatment for CSE. However, if the convulsive movements stop but there is no clinical improvement, with ongoing altered awareness, an EEG is needed to exclude NCSE. In an adult study, NCSE occurred in 14 % of patients treated for CGSE [22]. In a study in children, NCSE occurred in 5/19 following control of CSE; in 2 of these, NCSE occurred after treatment of CSE and in 3, NCSE occurred after treatment of refractory status epilepticus (RSE) [23]. In a study of all ages, NCSE was detected in 8 % of all comatose patients [24]; in children, NCSE only was detected in 2/19 children following an hypoxic-ischemic insult (Fig. 2.1) [23]. Figure 2.2 is an example of focal NCSE following a convulsive seizure with persistent altered awareness.

The indications for emergency EEG include unexplained altered awareness (to exclude NCSE); neuromuscular paralysis for SE, which eliminates the convulsive movements by neuromuscular blockade; continuous IV therapy for refractory SE, or when there is no improvement or return to baseline mental status after controlling overt convulsive movements (to exclude NCSE or nonconvulsive seizures) [25]. The EEG is useful whenever the diagnosis is in doubt, especially for pseudoseizures [26]. In a study in children, 6 of 29 children admitted with CSE had pseudostatus epilepticus [27]. There has been an increased use of continuous EEG monitoring in the critically ill patient to detect NCSE and nonconvulsive seizures as their treatment may decrease the risk of secondary brain injury.

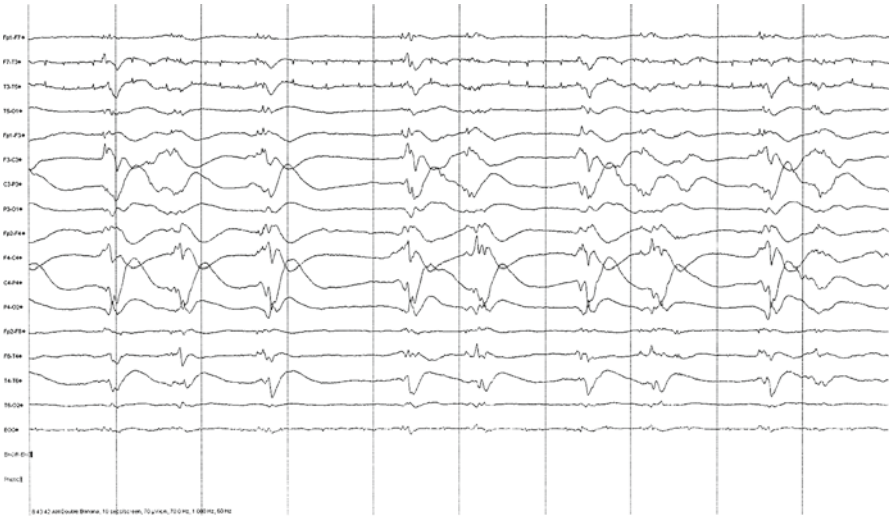

Fig. 2.1 Generalized nonconvulsive status epilepticus. EEG of generalized nonconvulsive status epilepticus. Child was comatose following a cardiac arrest. Generalized spike and slow wave discharges with a bicentral predominance

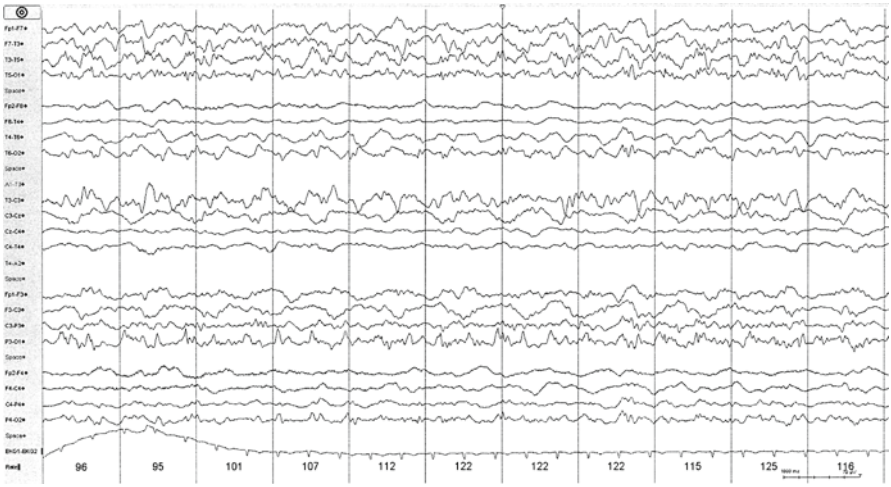

Fig. 2.2 Focal nonconvulsive status epilepticus. Child had a convulsive seizure followed by persistent altered awareness. Recurrent spikes and sharp waves in the posterior region bilaterally, left greater than right

Continuous EEG monitoring may also detect clinical activity that mimics seizure activity, which occurs frequently in this population, and unless continuous EEG monitoring is done, AEDs may be used to treat these movements. In a study of 100 children in coma, non-epileptic events were confused with seizures in 17, whereas documented epileptic seizures occurred in only 7 children [28]. In another

study of 100 children, changes were made in AED treatment in 43 children and non-epileptic events were detected in 21 children [29]. Continuous EEG monitoring is also useful in the management of refractory seizures and when the patient undergoes therapeutic neuromuscular blockade. Patients with epilepsy or with seizures immediately before the continuous EEG are at a higher risk for ongoing seizure activity [30].

Refractory Status Epilepticus (RSE): The SE is considered refractory when seizures continue despite treatment with the first two AEDs used. There are two recent reviews of the etiologies that cause RSE. The CSF examination is important in this group as unusual infections or inflammatory and autoimmune disorders may be the cause [31, 32].

2.6 Special Consideration

Some pediatric epilepsy syndromes classified under "epileptic encephalopathy (EE)" may not present with CSE, but often have brief, frequent seizures, and/or frequent abnormal epileptiform activity on EEG. It is hypothesized that the encephalopathic features (cognitive impairment, behavior problems, physical problems such as ataxia) are a direct consequence of the epileptic electrical phenomenon, and suppression of epileptic activity may improve seizure and developmental outcome [3] Although this hypothesis is still debated, there is general consensus amongst clinicians that some of these syndromes warrant early effective treatment.

West syndrome is one of the most recognized of the EEs, and often presents between 3 and 7 months of age. It is characterized by the triad of epileptic spasms (infantile spasms), psychomotor regression, and the characteristic hypsarrhythmia pattern on EEG [33]. The spasms are symmetric, brief generalized seizures (>100 ms to 1–2 s), involving flexion and/or extension of axial muscles and the extremities. Asymmetric spasms often indicate underlying structural brain pathology. Typically, the spasms occur in clusters and on awakening from sleep. The psychomotor regression usually follows onset of epileptic spasms, and visual agnosia (loss of eye contact) is often the first sign of regression. Children with symptomatic etiology of WS may have psychomotor impairment prior to the onset of the spasms.

The prognosis of WS is determined mostly by the underlying etiology. The majority of children with WS have congenital (e.g., tuberous sclerosis, genetic defects) or acquired (e.g., hypoxic-ischemic insult, brain infection) structural brain abnormalities, or neuro-metabolic disorders (e.g., pyridoxine dependency, organic aciduria) and generally have a poor prognosis (Pellock et al. 2010). They often have persistent seizures, profound cognitive impairment, and the epilepsy evolves into Lennox-Gastaut syndrome in 20–50 %. About 15 % children with WS have no identifiable etiology and tend to have a better psychomotor outcome.

2.7 Conclusion

This chapter reviews the definitions, basic concepts, and various clinical manifestations of seizures and status epilepticus as they relate to acute neurological disorders in children. It is especially important to identify the precipitating cause. Understanding the pathophysiology of seizures and reviewing the results of diagnostic studies, especially the electroencephalogram (EEG), set the stage for antiepileptic drug treatment.

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Chapter 3
Acute Headache

Jens Böhmer and Alyssa A. LeBel

Abstract Headache is a common childhood complaint that is rarely caused by a serious etiology. The diagnosis of a benign headache is primarily based on careful history taking and clinical examination. Unnecessary investigations are often prescribed in the absence of clear indications. However, acute presentation of a child with severe headache needs to be taken seriously as undiagnosed conditions such as meningitis and subarachnoid hemorrhage can lead to serious neurological impairment. Overuse of analgesics, a frequent problem in adults with chronic headaches, is also likely to cause recurrent headaches in children and adolescents.

Keywords Headache • Migraine • Tension-type headache • Secondary headache

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3.1 Introduction

3.1.1 Epidemiology

Headache in children is a common complaint; still studies reveal significant differences in the epidemiology in childhood populations, with prevalence rates between 5 and 40 % in the general pediatric population. The prevalence rises during adolescence and reaches 80 % at the time of transfer from pediatric care. Before puberty, no sex differences exist but in later adolescence females predominate, especially with regard to migraine.

Visits to the emergency department with the chief complaint of headache account for less than 2 % of all visits. When comparing children with adults in the setting of visits in the emergency department, primary headaches are less common in the pediatric population. Of those seeking help in the emergency department, the vast majority has upper respiratory tract infections, such as viral URI, otitis, or streptococcal pharyngitis (ca 60 %); another 20 % have migraine or another primary headache, mostly tension-type headache. Viral meningitis accounts for less than 10 % and 5–10 % present without a clear diagnosis [1].

3.1.2 Pathophysiology

The brain itself (and the meninges with the exception of the basal dura mater) is insensitive to pain—the most pain-sensitive intracranial structures are blood vessels. Vasodilatation, inflammation, and displacement (e.g., by traction or pressure) cause pain.

3.1.3 Anatomy

Pain-sensitive structures commonly causing headache are found both intra- and extracranially.

3.1.3.1 Intracranial, Supratentorial

Vessels are innervated by the trigeminal nerve ($V_{1,2,3}$): the dura is innervated by V_1 referring pain to the eye and forehead. V_2&$_3$ innervate the middle cerebral artery, referring pain to the temples.

3.1.3.2 Intracranial, Infratentorial

Vessels are innervated by the first three cervical nerves, referring pain from structures of the posterior fossa to the neck and occiput. Part of the posterior fossa is innervated by the glossopharyngeal and vagal nerves that project pain to the ear and throat.

3.1.3.3 Extracranial

Scalp arteries, muscles (neck extensors, masseter/temporal muscle, frontal muscle, extraorbital muscles), and the periosteum of the sinuses are sensitive to pain.

3.1.4 Ophthalmology

Generally, ophthalmologic diseases are rarely the cause of headache. The exclusion of refractive errors is simple and recommended though. Latent squint is a treatable reason for headache and should not be missed. Optic nerve neuritis comes with an afferent pupillary defect, and retrobulbar pain worsens with extraocular movements. Glaucoma is a very rare entity in childhood that can present with focal ocular as well as abdominal pain or generalized headache.

The development of papilledema as a consequence of raised intracranial pressure takes time (approximately 1 week); therefore, the role of performing fundoscopy in the setting of the emergency department remains unclear. In the evaluation of headache in the outpatient clinic, an ophthalmologic examination with fundoscopy definitely is indicated. See also Chap. 5.

3.1.5 Neuroradiology

The value of neuroimaging is low in evaluating headache in children without warning signs. In the absence of signs of raised intracranial pressure, magnetic resonance imaging (MRI) is generally preferred, but computed tomography (CT) might be the tool of choice in an emergency setting. A CT with simple sedation is easier to perform than an MRI that usually requires general anesthesia until the age of 7. CT is not useful in evaluating the posterior fossa (e.g., Chiari I malformation). Be aware not to prolong the queues to the MRI even further with a scan that you already know is not going to reveal any pathology.

3.1.6 Seizures and Headache

Seizures and headaches (especially migraine) are a common comorbidity. A seizure can trigger a migraine attack and vice versa. Especially after a generalized tonic-clonic seizure, headache can occur.

A headache attack can be the only manifestation of a seizure, which makes epilepsy a (rare) differential diagnosis of periodic headache. Most commonly, a patient with known epilepsy has either post-seizure headache or headache as a seizure equivalent.

3.2 Presenting Acute Symptoms

When a child presents with headache, it is helpful first to search for signs that may indicate a more serious underlying condition. Be alert for the presence of the "Red Flags" (Box 3.1) as warning signs [2].

Box 3.1. "Red Flags"

- Inability of the patient to easily describe the quality of the pain she is suffering.
- General or neurological examination reveals a possible pathology (e.g., paresis, ataxia, diplopia, dysphagia, severely altered consciousness, nuchal rigidity).
- Headache that is maximal from the onset is unlikely migraine, and uncommon catastrophic conditions, such as seen with subarachnoid/intracerebral hemorrhage or acute hydrocephalus, need to be excluded.
- Chronic, progressive headache, especially when accompanied by a decline in school performance or free time activity.
- Children less than 6 years with headache as their main symptom.
- Occipital headache.
- Orthostatic headache.
- Headache that wakes the child at night or that is present at awakening and that is accompanied by nausea or vomiting.
- Headache that worsens by Valsalva maneuver (coughing, defecation).
- Papilledema: must be evaluated by neuroradiology.
- Preexisting conditions (ventriculoperitoneal shunt, phacomatosis, hypercoagulopathy, malignancy, immunocompromised patient, sickle-cell disease).

3.3 Diagnosis and Differential Diagnoses

3.3.1 Classification

Headaches are divided into primary and secondary headaches. Primary headaches are those that do not result from a specific other underlying cause (infectious, toxic, structural). Secondary headache are headaches due to an underlying disorder. Classical and usually benign examples of the latter category include headache after trauma or respiratory tract infection, but all dangerous headaches such as those due to meningitis, intracranial hemorrhage, or malignancy also belong to this heterogeneous group. The primary headaches are quite common but do still not often receive the attention they deserve, given the fact that patients and doctors generally focus on the exclusion of serious conditions associated with secondary headaches [3].

All headaches are classified by the International Headache Society, which provides diagnostic criteria for all types of headache in their International Headache Classification [4].

These classifications provide limited clinical benefit for the pediatrician, partially due the fact that the young patients have difficulties describing their symptoms but mostly because children's headache rarely completely fit into only one of the rather rigid categories. Different types of headaches commonly occur or emerge over time [5].

Of the primary headaches, migraine and tension-type headache are the ones of daily importance for the clinician, and their diagnostic criteria are specified below. Migraine without aura accounts for more than 80 % of pediatric (and adult) migraine; the remaining 20 % include migraine with aura and rare forms such as hemiplegic and basilar migraine (see Chap. 12). Rare entities of pediatric primary headaches are cluster headache, which occurs in children over 10 years with bursts of headache of intensive pain around or behind one eye and spreading ipsilaterally to the face. Typical features are ipsilateral autonomic dysfunction, restlessness, and a positive response to inhaled oxygen. Further examples are hemicrania continua, benign exertional headache, and headache during sexual intercourse.

3.3.2 Primary Headaches

3.3.2.1 Diagnostic Criteria for Migraine Without Aura in Children and Adolescents

A. At least five attacks fulfilling criteria B–D
B. Headache attacks (untreated or unsuccessfully treated) lasting 1–72 h
C. Headache having at least two of the following characteristics:

1. Unilateral location (may be bilateral, frontotemporal, but not occipital)
2. Pulsating quality

3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity

D. During the headache, at least one of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia, which may be inferred from behavior

E. Not attributed to another disease

3.3.2.2 Diagnostic Criteria for Migraine with Aura in Children and Adolescents

A. At least two attacks fulfilling criteria B–D.
B. Aura consisting of at least one of the following, but no motor weakness:

1. Fully reversible visual symptoms, including positive features (e.g., flickering lights, spots, or lines) and/or negative features (e.g., loss of vision)
2. Fully reversible sensory symptoms, including positive features (e.g., pins and needles) and/or negative features (e.g., numbness)
3. Fully reversible dysphasic speech disturbances

C. At least two of the following:

1. Homonymous visual symptoms and/or unilateral sensory symptoms.
2. At least one aura symptom develops gradually over >5 min and/or different aura symptoms occur in succession over >5 min.
3. Each symptom lasts >5 min and <60 min.

D. Headache begins during the aura or follows the aura within 60 min.
E. Not attributable to another disorder.

3.3.2.3 Diagnostic Criteria for Tension-Type Headache in Children and Adolescents

A. At least 10 episodes fulfilling the criteria B–D
B. Headache lasting from 30 min to 7 days
C. Headache has at least two of the following characteristics:

1. Bilateral location
2. Pressing/tightening (nonpulsating) quality
3. Mild to moderate intensity
4. Not aggravated by routine physical activity such as walking or climbing stairs

D. Both of the following

1. No nausea or vomiting (anorexia may occur)
2. No more than one of photophobia or phonophobia

E. Not attributed to another disorder

3.3.3 Secondary Headaches

3.3.3.1 Respiratory Tract Infection

The first episode of acute headache that leads to a hospital visit is most commonly due to viral infection of the upper respiratory tract (viral URI, otitis, sinusitis, or streptococcal pharyngitis) in pediatric patients (as opposed to adults where subarachnoid hemorrhage is more frequent). *Sinusitis* is clinically diagnosed and clearly overestimated as a reason of headache. Local signs are present. Some cases (severe headache, signs of systemic infection, suspicion of local spreading) may require imaging.

3.3.3.2 Meningitis/Encephalitis

Viral meningitis is one of the more common causes of headache in the pediatric population, though not a dangerous one. *Bacterial meningitis* with its overwhelming course is usually not difficult to diagnose and presents with signs of acute illness, high fever, nuchal rigidity, photophobia, and laboratory signs of severe infection. Since headache can precede fever and systemic illness by hours, it is important to follow the course of a patient with a suspected benign headache attack: if the pain does not improve after taking adequate doses of analgesics and/or sleep, imaging/lumbar puncture might be indicated. Confusion, low-grade fever, focal seizures, and especially agitation are the hallmarks of *encephalitis*, with herpes virus being the most concerning agent. Besides lumbar puncture and empiric treatment with Acyclovir, an acute EEG can be very useful. See also Chaps. 13 and 16.

3.3.3.3 Lyme Disease

The infection with tick-borne *Borrelia burgdorferi* can lead to chronic daily headache, often accompanied by low-grade fever and general malaise. Facial palsy is another common symptom. The risk is higher in endemic areas, in summer and autumn, and especially if the tick bite (that, unfortunately, is not always detected or remembered) was on the head, which puts children at risk. It does not have to be preceded by erythema chronica migrans and is diagnosed by the evidence of serum and intrathecal antibodies against *Borrelia*. See also Chap. 13.

3.3.3.4 Traumatic Headache

Initial loss of consciousness, neurological signs, vomiting, and progression of symptoms regardless of the initial trauma warrant imaging. Minor head trauma is a common trigger of migraine attacks. See also Chap. 19.

3.3.3.5 Neoplasm

Fear or suspicion of a central nervous system (CNS) tumor as a cause of headache is a frequent reason to worry in parents. Although CNS tumors do go with headache in approximately 50 % of the cases, absence of "Red Flags" (see Box 3.1) can exclude a brain tumor in almost all children presenting with acute headache. However, it must also be noted that childhood brain tumors may be midline processes presenting without focal neurological signs.

3.3.3.6 Hypertension

It is medical malpractice not to obtain the blood pressure in any patient with headache. Idiopathic hypertension is extremely unusual in children, but secondary causes such as renal artery stenosis or pheochromocytoma need to be ruled out.

3.3.3.7 Post Lumbar Puncture Headache

Headache after a lumbar puncture is still a common complaint due to the use of traumatic needles (incidence of headache 20–40 % versus atraumatic needles, incidence 3 %). *Post lumbar puncture headache* is the consequence of leakage of CSF, arises within a week after the puncture (commonly between 24 and 48 h), has an orthostatic character, usually resolves within 7 days, and is treated with simple analgesics (rarely, epidural blood patch).

3.3.3.8 Pseudotumor Cerebri

The diagnosis of pseudotumor cerebri (PTC) (also somewhat misleadingly called idiopathic intracranial hypertension [IIH]) is one of exclusions in a patient with chronic headache, bilateral papilledema (in almost all cases), and cerebral spinal fluid (CSF) opening pressure of >25 mm H_2O (20–25 cm H_2O representing a grey area). Other conditions, such as CNS infection, have to be ruled out. A cranial MRI reveals no pathologic findings but can show hints of IIH such as slit ventricles, the empty sella sign, or irregularities in the course of the optic nerve. Associated symptoms are visual disturbances (e.g., field defects or diplopia); the most common comorbidity is obesity. The headache is often posterior; in smaller children fatigue and irritability may predominate. Spinal taps usually bring relief. PTC has mostly been associated with impaired cerebral venous drainage, often due to medications (e.g., cortisol), dietary supplements (e.g., vitamin A), or systemic, especially endocrinologic, diseases. Sinus venous thrombosis is the most dangerous cause. See also Chap. 11.

3.3.3.9 Hydrocephalus

Resulting from an impaired circulation and/or absorption of CSF, hydrocephalus after infancy is very rare and usually acquired as the result of trauma or intracranial neoplasm. Pediatric brain tumors are most likely infratentorial, which makes them prone to disturb CSF flow quickly, within days or weeks. The typical features are progressive morning headache and vomiting, the latter often relieving the former. Papilledema might be present as well as lateral rectal nerve palsy or dysphagia. In its most severe form, Cushing's triad of elevated systemic blood pressure, bradycardia, and irregular breathing patterns is present as a sign of raised intracranial pressure, urging prompt treatment. See also Chap. 11.

3.3.3.10 Shunt Dysfunction

In an existing hydrocephalus that is treated with a ventriculoperitoneal (rarely, ventriculoatrial) shunt, new-onset headache regardless of location or severity requires the exclusion of shunt dysfunction. Depending on the clinical severity, the algorithm might be to start with ultrasound of the stomach to look for the existence of a pseudocyst, X-rays of the shunt to rule out catheter discontinuation, and finally cranial CT. Typically, wide ventricles are present, but in cases of decreased compliance of the brain (stiff brain syndrome), this sign might be absent. Examination of the shunt might show discontinuation, the skull should be palpated for fluid pads, and the valve (if present) should be checked by pressing: if no quick refilling is present, obstruction is likely. Especially in patients with MMC and hydrocephalus that complain about headache and/or other symptoms, UTI should be ruled out as the source of symptoms. See also Chap. 11.

3.3.3.11 Chiari Malformations

Representing a group of hindbrain herniation syndromes, these congenital malformations are distinct etiologies and not a sequence. *Chiari I* is the displacement of the cerebellar tonsils below the foramen magnum. It is one of the most common incidental findings in times of routine MRIs and is rarely symptomatic. Of note, a cranial CT cannot rule out its presence if suspected, due to CT's limitations when imaging the posterior fossa. They can lead to CSF flow obstruction causing occipital headache that can be constant or come in attacks of sometimes only some minutes. Associated symptoms are neck pain, ataxia, and obstructive sleep apnea syndrome; exacerbation during upper respiratory tract infection is seen. The evaluation can be expanded by cine-MRI to visualize CSF flow, and sometimes neurosurgery is needed if oral analgesics fail. Most children born with a myelomeningocele also have the *Chiari II* malformation and hydrocephalus, thus headache in this

population is mostly related to shunt dysfunction. This malformation is much more complex with larger parts of the hindbrain herniating through the foramen magnum. The very rare cases of *Chiari III* (displacement of parts of the hindbrain into a cervical MMC) and *Chiari IV* (hypoplasia of the cerebellum) lack clinical significance.

3.3.3.12 Vascular Dissection

Sudden onset of unilateral head or neck pain, lateralizing neurological signs (particularly Horner's syndrome) in combination with stigmata of a connective tissue disorder (such as fibromuscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome) and/or a recent trauma (especially whiplash or chiropractic maneuvers), raises concerns about this entity that can occur in the supply zone of the carotid or the vertebral artery.

3.3.3.13 Temporomandibular Joint Disorders

A rare disorder in children, this entity is characterized by unilateral or at least asymmetrical focal pain on the side of the head. Palpation reveals tenderness of the joint. Psychosocial factors play a role, and dental abnormalities (malocclusion, bruxism, or prior trauma) need to be considered.

3.3.3.14 Stroke/Intracranial Hemorrhage

With an incidence of 3.5–6 per 100.000/year, stroke is relatively uncommon in the pediatric population. Headache can be one of the presenting symptoms but objective neurological signs guide the diagnosis. Stroke-like episodes that show infarctions not bound to vascular borders raise suspicion of mitochondrial diseases, such as MELAS. Bleeding, such as subarachnoid or intracerebral hemorrhage (possibly from an aneurysm), can have headache as its sole symptom. See also Chap. 15.

3.3.3.15 Poisons

Carbon monoxide poisoning is a potentially life-threatening condition, mostly caused by defective gas heaters or cookers in badly ventilated environments. Severe cases come with general signs such as confusion and respiratory distress followed by coma, but in milder cases, headache might be the only symptom. Since carbon monoxide binds to hemoglobin with a much higher affinity than oxygen, the emergency treatment consists of high-flow oxygen; hyperbaric treatment can be an option in severe cases.

Lead poisoning as a course of headache should be excluded in cases of chronic headache in the presence of symptoms such as decline in attention, fatigue, and anemia in children at risk, e.g., living in an old house with plumbed drainage.

3.3.3.16 Obstructive Sleep Apnea Syndrome/Obesity

Obesity is the leading cause of obstructive sleep apnea syndrome (OSAS), but muscular hypotonia, e.g., in patients with Down syndrome, may increase the risk in children. The history of snoring in combination with daytime fatigue should raise suspicion, and polysomnography is recommended.

3.3.3.17 Night Hypoventilation

Weakness or dysfunction of respiratory muscles, typically in a child with neuromuscular disease, frequently presents as morning headache due to nighttime hypoventilation. Even patients with cystic fibrosis are prone to headache, possibly due to hypercapnia.

3.3.3.18 Systemic Disorders

Systemic lupus erythematosus, sarcoidosis, vasculitis, thyroid and parathyroid disorders, HIV/AIDS, sickle-cell disease, malaria, and many more diseases that do not primarily affect the central nervous system may have headache as one of their symptoms, although most probably not the only or leading one. They endorse the importance of an accurate history and examination in all patients.

3.4 Assessment

3.4.1 Medical History

Have in mind that commonly patients and parents are mostly worried about malignancy as the reason for the headache—reassurance is very important once warning signs for CNS tumor have been ruled out.

The goal of the medical history is to discern the headache pattern of the patient: Chronic versus periodic, disabling versus tolerable, progressive versus nonprogressive. To ask the child about the intensity of the headache (e.g., using the visual analogue scale VAS) does not help to discriminate benign from malignant forms of headache. It is more important to find out whether the child is still

able to participate in daily activities. An important part of taking the history can be to let the young child draw a picture of her type of headache.

Migraine patients most commonly have a first generation relative suffering from headache as well, but asking about it can be challenging, since some people cease having migraines in adulthood, some never understood their attacks actually were migraine, and some simply take so much medicine that they transformed from typical migraine into a constant daily headache.

Typical questions to be included when interviewing a patient with headache:

3.4.1.1 When Has the Headache Started?

Headache that has been present for more than 2 months is very likely a primary headache. Most headaches due to serious intracranial pathology have lasted for less than 2 months.

3.4.1.2 What Is the Course of an Attack?

Brief sensations of headache pain, lasting for seconds, may be experienced by patients with migraines. Sharp and brief electrical sensations may also be a feature of cranial neuralgia. Severe headache that lasts several minutes may be a sign of abnormal CSF flow dynamics, as in Chiari I malformation. Migraine attacks are shorter in children than in adults but usually not less than 30 min and generally 2–4 h. Tension-type headache may be daily and persistent, with fluctuations in intensity.

3.4.1.3 What Is the Quality and Localization of the Headache, and Does It Fit into a Pattern of the Primary Headaches?

Throbbing, pulsatile, moderate to severe headache located uni- or bilateral frontal, frontotemporal, or temporal is typical for migraine. Dull, constant, non-disabling bilateral headache could be tension-type headache. Shooting or radiating headache from the neck suggests cervical radiculopathy. Occipital headache, a constricting quality, or the inability to describe and localize the pain may indicate a secondary generator of headache.

3.4.1.4 Are There Any Associated Symptoms?

Phono- and photophobia, nausea, and vomiting occur in both benign and malignant cases, but nausea particularly indicates migraine rather than tension-type headache.

3.4.1.5 Are There Prodromal Symptoms?

They may present as mood changes, hunger attacks, hypo- or hyperactivity, paleness, yawning, or simply the feeling that a headache attack is about to start. All of these symptoms are seen in patients with migraine.

3.4.1.6 Is There an Aura?

Aura is a neurological deficit before a pending migraine headache (seldom, only aura without associated headache), most commonly of the visual system (visual field deficit, flickering), but all systems (sensory, motor, hearing) can be affected, typically unilateral. Rare forms include "Alice-in-wonderland" or confusional aura.

3.4.1.7 Does the Child Miss School?

The number of missed days both gives an idea about how severe the attacks are and helps to determine the need for prophylactic treatment. Sometimes the question about missed free time activities, rather than school days, reveals the true extent of the impact that the headache has on the life of the patient. Chronic headaches may be associated with disability in all aspects of daily life.

3.4.1.8 Does the Child Wake Up with Headache?

This is not uncommon in tension-type headache or during migraine attacks. If the child wakes up because of the headache, it is a warning sign of a possible secondary generator.

3.4.1.9 Does the Child Drink Enough?

This question also aims to exclude caffeine-dependent headache, not only seen in coffee addicts but mainly in those consuming large amounts of caffeine-containing sodas. A relatively small amount of caffeine, in moderation, may be useful symptomatically.

3.4.1.10 Does the Child Take Analgesics?

Which analgesics, which dosage, how often, how fast in the attack are they taken? More than 10 days with simple analgesics or 6 days with migraine-specific

medication per month suggests medication-overuse headache. The typical patient still has his or her regular migraine attacks, and also a constant low-grade headache that is partially relieved by the medication, but returning before scheduled for next dose of analgesics.

3.4.1.11 Does the Child Have an Explanation for His/Her Headache or See a Pattern of It?

Children before the age of 10 rarely see the connection between cause and effect, but adolescents often know what triggers their attacks and how to prevent them. Common triggers for headache are internal cycles (menstruation, changed sleeping behavior) and different foods (cheese, chocolate) but stress in school, leisure time, and family conflict remain the most significant triggers. Migraine tends to occur during periods of letdown and calm, for example, during the holidays.

3.4.2 Physical Examination

- Vital signs
- Complete physical and neurological examination (mental state, nuchal rigidity, coordination, balance, pupillary reflexes, eye movements, visual field, facial symmetry, gag reflex, motor and sensory system, tendon reflexes) including testing for the mobility of the cervical spine, muscular trigger points of the head and neck, and palpation of the temporomandibular joint
- Growth percentiles including head circumference
- Blood pressure

3.5 Treatment

The mainstay of headache treatment in pediatrics is mild analgesics, such as acetaminophen and NSAIDs. Overcautiousness is not useful; early and adequate administration is more important than the choice of which drug is given. No first-line analgesics have proven to be superior to any other, and local or personal preferences may guide treatment. Treatment of pediatric headache remains unsatisfying; many children are not treated lege artis. A severe underlying disorder cannot be completely masked by simple analgesics; neither do objective neurological findings disappear. For treatment of headaches, see also Chap. 12.

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Chapter 4
Acute Disturbance of Motor Function

Thomas Sejersen and Ching H. Wang

Abstract Acute motor dysfunction results from loss of function in any part of the neural axis connecting motor neurons in the brain with different levels of the motor unit (spinal motor neurons, peripheral nerves, neuromuscular junctions, and skeletal muscle). The motor dysfunction may present with symptoms of muscle hypotonia, paralysis, spasticity, or as "movement disorder." When diagnosing the cause of an acute motor dysfunction, it is helpful to combine information on (1) the type of motor dysfunction (e.g., presence and distribution of paralysis, ataxia, involuntary movements), (2) identification of the anatomical level of the deficit (supraspinal, spinal cord, peripheral motor nerve, neuromuscular junction, skeletal muscle, musculoskeletal system), and (3) the underlying pathogenic cause of the dysfunction (e.g., infection, inflammation, metabolic, compression, hereditary). In the initial acute situation, be observant on urgent situations necessitating immediate diagnostic work-up and interventions.

Keywords Neuropathy • Myopathy • Myasthenia • Floppy infant • Paralysis • Motor dysfunction

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4.1 Introduction

Acute motor dysfunction results from loss of function in any part of the neural axis connecting motor neurons in the brain with different levels of the motor unit (spinal motor neurons, peripheral nerves, neuromuscular junctions, and skeletal muscle). Total loss of function for one or more muscles defines paralysis and may go with or without simultaneous sensory loss of the affected area. This occurs in a wide range of diseases and may present as intermittent, relapsing, progressive, acute/subacute, or as a highly urgent emergency. When diagnosing the cause of an acute motor dysfunction, it is helpful to combine information on (1) the type of motor dysfunction, (2) anatomical level of the deficit, and (3) the underlying pathogenic cause of the dysfunction [1].

The motor dysfunction may present with symptoms of muscle hypotonia, paralysis, or spasticity. Alternatively the symptoms may belong to different diagnosis commonly referred to as "movement disorders" (e.g., ataxia, dyskinesia, dystonia, athetosis, myoclonus, and tics; see Chap. 18). The identification of the anatomical level of the deficit includes both information on which muscles are affected and identification of the level of lesion (e.g., brain, spinal cord, motor nerve, neuromuscular junction, muscle; see Tables 4.1, 4.2, 4.3, 4.4, 4.5, and 4.6). The underlying causes to consider include genetic neuromuscular disorders, autoimmune conditions, infections, toxic/metabolic conditions, trauma, compression, hypoxia, vascular events, seizures, and psychosomatic (conversion) disorder. Other causes of motor disturbance include systemic illness, fatigue, catatonia, and pain. Careful history taking and physical examination can help to identify appropriate further investigations to perform and from this to arrive at a diagnosis of the underlying cause of the acute motor dysfunction.

4.2 Clinical Examination of Acute Motor Disturbance

Observations of the child's movement pattern prior to any examinations may give important information on severity and anatomical level affected and also serve as a base for specific tests of the motor function. In this initial observation, watch for extent and distribution of weakness, muscle wasting, and involuntary movements (e.g., fasciculations, twitches, tremor, and other involuntary movements). It is also important to make quick functional assessments of the ability of the child to walk, walk on heels and toes, run, and jump (both legs and one leg at a time) and to define if the motor dysfunction is characterized by muscle weakness, ataxia, spasticity, or other movement disorder (see also Chap. 18). Some further clinical tests that aid in the diagnostic work-up are discussed below.

Table 4.1 Acute disturbance of motor function at the supraspinal level

Condition	Typical symptom/finding	Initial diagnostic aid
Brain infection, postinfectious (meningitis, encephalitis, ADEM, multiple sclerosis)	Motor dysfunction typically accompanied by brain symptoms (See Chaps. 14 and 17). MS may initially present solely with motor disturbance (paralysis, ataxia, spasms)	LP with CSF analysis, bacterial culture, virus isolation, serology, brain MRI. See Chaps. 14 and 17
Toxic/metabolic	See Chap. 9	Blood gas. Toxicology screens. For acute neurometabolic crisis, see Chap. 9
Traumatic brain injury	Acute motor dysfunction typically accompanied by other CNS dysfunctions	Neuroradiology, ICP. See Chap. 12
Hypoxic/ischemic insult (near drowning, CO poisoning)	See Chap. 8	Blood gas, EEG, neuroradiology (MRI with spectroscopy). CO poisoning: carboxyhemoglobin. See Chap. 8
Tumor	Focal weakness/paralysis. May be accompanied by other brain symptoms. See Chap. 11	Neuroradiology. See also Chap. 11
Congenital brain malformation		
Chiari malformation: cerebellar tonsils displaced downward through foramen magnum	Headache, fatigue, muscle weakness in the head and face, difficulty swallowing, dizziness, nausea, impaired coordination, and, in severe cases, paralysis (of hands)	MRI of brain (and spinal cord)
Vascular events (stroke, transient ischemic attack, vasculitis) [6, 7, 16]	See Chap. 16	Neuroradiology, hypercoagulability panel, echocardiogram. See Chap. 16, Fig. 1
Seizures (e.g., Todd's paralysis, i.e., focal weakness in part of body after seizure)	Transient weakness in, e.g., hand, arm, or leg after (partial) seizure. May also affect speech, vision, or gaze. Usually subsides within 48 h	Blood glucose, electrolytes, EEG, neuroradiology, blood gas, toxic screens. See Chap. 2
Alternating hemiplegia [17, 18]	Diagnostic criteria: (1) onset before 18 months of age, (2) repeated episodes of hemiplegia, (3) episodes of bilateral hemiplegia/quadriplegia, (4) other paroxysmal attacks (tonic/dystonic attacks, nystagmus, strabismus, dyspnea), (5) immediate disappearance of symptoms upon sleep, (6) developmental delay, (7) not attributable to other known cause	Clinical diagnosis. brain MRI to exclude structural/vascular/metabolic Brain disorder. Metabolic screening to exclude mitochondrial disorders, CSF/blood glucose to exclude glucose transporter defects, thyroid panel to exclude periodic paralysis with thyrotoxicosis, video EEG to exclude epilepsy
Conversion disorder	Motor symptoms may present as, e.g., paralysis, impaired balance, gait problems, swallowing difficulties, dystonia, tremor, myoclonus, or other movement disorder	Clinical assessment, neurological findings inconsistent with symptom. See Chap. 7

Table 4.2 Acute disturbance of motor function at the level of the spinal cord

Condition	Typical symptom/finding	Initial diagnostic aid
Infectious/postinfectious (epidural abscess, osteomyelitis, transverse myelitis [19], neuromyelitis optica [20], poliomyelitis, West Nile virus)	Progressive weakness in lower/all extremities, paresthesia, sensory loss, bladder/bowel incontinence, midline back pain, malaise. See Chaps. 14 and 17	Spine MRI, LP with CSF analysis, bacterial culture, enterovirus PCR/immunodiagnostics, s-NMO IgG elevated in neuromyelitis optica. See also Chaps. 14 and 17
Trauma	Acute weakness in lower/all extremeties, pareshesis, sensory loss, bladder/bowel incontinence, pain, malaise	Spine X-ray and CT or MRI
Tumor	See Chap. 12	Spine CT or MRI
Motor neuron disease (spinal muscular atrophy)	Generalized (symmetrical) muscle weakness with spared sensation. Fasciculations may occur (tongue). Decreased muscle tone and peripheral reflexes	Genetic testing smn1 gene (EMG)
Spinal cord malformation (dysraphism): spina bifida, diastematomyelia, spinal dermal sinus, spinal lipoma, tethered cord, syringomyelia	Chronic pain, abnormal sensation, paralysis, loss of urinary/bowel control, foot and spinal deformities. Signs of the disorder usually develop slowly, but sudden onset may occur	Spine CT or MRI
Foramen magnum stenosis (e.g., achondroplasia)	Apnea, paralysis (quadriplegia), muscle hypotonia	Brain and spine CT or MRI. Sleep study (polysomnography)

Table 4.3 Acute disturbance of motor function at the level of the peripheral motor nerve

Condition	Typical symptom/finding	Initial diagnostic aid
Autoimmune (AIDP, CIDP)	Frequently history of preceding infection. Initial abnormal sensation and motor function in feet/legs.	Neurophysiology (nerve conduction study): conduction slowing/block
Guillain–Barré syndrome [9–11]	Muscle weakness may progress to involve facial muscles and respiratory muscles resulting in respiratory failure. See Sect. 4.4.2.3	LP with CSF analysis: elevated CSF protein, normal/slightly elevated lymphocytes
Hereditary neuropathies	Distal symmetric muscle weakness with/without abnormal sensation. Rarely acute presentation. Pes cavus, family history common	Nerve conduction study of motor and sensory nerves demonstrates reduced nerve conduction speed (myelin damage) or reduced nerve conduction strength (axonal damage). Genetic testing
Facial palsy (congenital 8 %, Bell's palsy 42 %, infection (neuroborreliosis—Lyme disease) 13 %, trauma 21 %, leukemia/tumor 2 %, hypertension, otitis media, mastoiditis)	Dysfunction of cranial nerve VII (facial nerve) resulting in paresis of muscles on affected side. Lyme disease frequent cause in areas endemic for Borrelia	Cranial nerve examination, eye closure (secure corneal lubrication), blood pressure, Borrelia serology spinal fluid + serum, serology herpes zoster, EBV, CMV, blood count, otoscopy, oral and parotid exam
Toxic/metabolic (chemotherapy, deficiency vitamin B12)	Initially paresthesia and sensory loss in a stocking distribution with later appearance of muscle weakness	Neurophysiology (nerve conduction study), vit B12 in blood, indirect markers homocysteine, methylmalonic acid, and holotranscobalamin
Trauma		
Brachial plexus injury	Obstetric brachial plexus palsy occurs in less than 1 % of live births and may result in pain, loss of sensation, or paralysis/weakness	Neurophysiology (EMG, nerve conduction study), MRI
Focal nerve compression (e.g., following awkward positioning in deep sleep)	Flaccid paralysis in muscle(s) supplied by affected nerve (e.g., radial nerve, common ulnar nerve). Sensory loss, decreased reflexes	Nerve conduction study
Critical illness polyneuropathy [21–23]	CIP is a frequent complication of critical illness, often together with CIM. It presents as flaccid weakness, usually symmetrical and sometimes severe, prolonged weaning from mechanical ventilation, muscle wasting	EMG, nerve conduction study

Table 4.4 Acute disturbance of motor function at the level of the neuromuscular junction

Condition	Typical symptom/finding	Initial diagnostic aid
Infection: infant botulism [13]	Symptoms typically start 18–36 h after toxin ingestion. Constipation, muscle weakness, drooping eyelids, ophthalmoplegia, swallowing difficulty, drooling	Botulinum toxin in stool
	Hypotonia and weak reflexes	EMG with repetitive nerve stimulation (decrement), single-fiber EMG
Autoimmune: myasthenia gravis (MG) [12]	Transient neonatal MG: generalized muscle weakness, hypotonia, poor suck, respiratory difficulty	Anti-ACh receptor antibodies, anti-MuSK antibodies, EMG with repetitive nerve stimulation (decrement), single-fiber EMG
Hereditary congenital myasthenia	Generalized weakness, hypotonia, drooping eyelids, ophthalmoplegia, and delays in motor skills (crawling, sitting, and walking). Babies may have poor head control and difficulty feeding	EMG with repetitive nerve stimulation (decrement), single-fiber EMG, genetic testing
Snake venom (neurotoxins, mostly found in elapid snake species)	Presynaptic neurotoxins (e.g., Elapids, Viperids): progressive paralysis with onset >1 h after bite, postsynaptic neurotoxins (many elapids, e.g., cobra); flaccid paralysis reversible with antivenom therapy	History and clinical examination. Blood pressure, neurological assessment. ECG if general condition affected
	Dendrotoxins and fasciculins (e.g., mamba, rattlesnakes): spasms, fasciculations, tetany often in <1 h from bite	Hemoglobin, complete blood count, serum creatine kinase, blood gas, coagulation status (INT, aPTT, D-dimer), s-creatinine. Repeated tests over 24 h

Table 4.5 Acute disturbance of motor function at the level of the skeletal muscle

Condition	Typical symptom/finding	Initial diagnostic aid
Virus infection (coxsackie, influenza [24], parainfluenza, EBV, adenovirus, Dengue fever, Lassa fever)	Myalgia, muscle weakness. General malaise, fever, headache. Catarrhal symptoms	Serology tests, virus isolation, PCR
Brucellosis (zoonosis)	Brucellosis: history of exposure to infected animals or food. Fatigue, undulating fever, weakness, excessive sweating, myalgia, abdominal pain, arthralgia	Brucella antibodies/culture/PCR
Rickettsia (typhus, Q fever, Rocky Mountain spotted fever, Mediterranean spotted fever, African tick-bite fever)	Transmitted by mites. Skin lesions/rash, fever, headache, myalgia	Typical clinical presentation, immunoassays, PCR
Trichinosis (roundworm Trichinella spiralis)	Intake of undercooked pork, fish, or wild game. Diarrhea, facial edema, splinter hemorrhage under nails, myalgia	Exposure history, typical clinical presentation, lab: blood count (eosinophilia, serum creatine kinase elevation, immunoassays)
Tetanus (neurotoxin tetanospasmin from Clostridium tetani)	Insufficient protection tetanus vaccination? Muscle spasms of jaw, trismus, frequent 1st symptom. Swallowing difficulty, myalgia, and stiffness in neck, shoulders, back. Progressive spasms and convulsions potentially life threatening	Clinical diagnosis, spatula test (involuntary spasm of jaw upon touching posterior pharyngeal wall)
Dermatomyositis/polymyositis [25]	Symmetrical weakness, fatigue, malaise, weight loss, mild fever, myalgia, pain in chest/abdomen, palpitations. In dermatomyositis violet/dusky red rash most easily detected in face, eyelids, around nails	Serum creatine kinase elevated, autoantibodies, muscle biopsy, muscle MRI
Metabolic (hypothyroidism, vitamin D deficiency)	Vitamin D deficiency has been associated with muscle weakness and pain in both adults and children	25-OH-vitamin D in blood
	Hypothyroidism may present as constipation, muscle weakness, hypotonia, poor growth, poor mental development, delayed development	Thyroid panel

(continued)

Table 4.5 (continued)

Condition	Typical symptom/finding	Initial diagnostic aid
Hereditary muscle diseases: myopathies and muscular dystrophies [26, 27]	Delayed motor milestones. Muscle weakness with decreased distal reflexes. Contractures. Rarely presents acutely. See Chaps. 10 and 15	Serum creatine kinase (CK) elevated in muscular dystrophies (commonly >10× normal value), p-lactate (frequently elevated in mitochondrial myopathy, repeated tests recommended), genetic testing, neurophysiology (EMG), muscle biopsy. See Chaps. 10 and 15
Malignant hyperthermia [14, 15]	Masseter contraction early warning sign. Other early signs: unexplained tachycardia, elevated end-tidal CO2 concentration, and muscle rigidity. Hyperthermia is late sign. Urgent condition, see Sect. 4.4.2.5	Typical clinical presentation. Raised CK, myoglobin, K, and P levels in blood. Metabolic/respiratory acidosis
Hypokalemic periodic paralysis	Hereditary autosomal dominant hypokalemic periodic paralysis: family history common. Attacks of weakness, lasting hours to days, provoked by, e.g., exercise, carbohydrate-rich meal, or sudden temperature changes	s-K low during attack of paralysis. CMAP (exercise EMG) Hereditary hypokalemic periodic paralysis: Mutation analysis of *SCN4A* and *CACNA1S* genes
	Acquired hypokalemic paralysis may be caused by frequent diarrheas	s-K, s-electrolytes, blood gas, ECG
Hyperkalemic periodic paralysis	Hereditary autosomal dominant hyperkalemic periodic paralysis: family history common. Exacerbate by K intake or cold. Weakness and myotonia	Serum potassium, electrolytes, blood gas, ECG. Mutation analysis of *SCN4A*
Critical illness myopathy (CIM) [21–23]	CIM is a frequent complication of critical illness, often together with CIP. It presents as flaccid weakness, usually symmetrical and sometimes severe; prolonged weaning from mechanical ventilation; muscle wasting	EMG, nerve conduction study, muscle biopsy (loss of myosin)
Drug-induced myopathy [28]: Corticosteroid-induced myopathy Colchicine, chloroquine, lipid-lowering drugs (e.g., statins), diuretics, D-penicillamine (myasthenic syndrome)	Symmetrical weakness, often severe. Myalgia and muscle atrophy	Muscle strength reduced, often markedly. Tenderness on palpation

Table 4.6 Acute disturbance of motor function, other musculoskeletal causes

Condition	Typical symptom/finding	Initial diagnostic aid
Infection/postinfectious		
Septic joints Autoimmune arthritis Osteomyelitis	Local pain, malaise, weakness in muscles in affected area	Ultrasound/X-ray/MRI/scint, arthrocentesis, bacterial culture, CRP, SR, blood count, autoantibody tests
Trauma/sports injury		
Fracture	History of trauma. Pain, swelling, obvious deformity	X-ray, ultrasound, MRI, clinical exam
Elbow dislocation	Common dislocation in children under age 5 years (Nursemaid's elbow) pain, reduced movement of affected arm	Clinical examination (inability to rotate arm and flexing elbow fully)
Compartment syndrome	Abnormal sensation, (severe) pain, swelling, reduced strength, pallor Muscle compartment tense on palpation	Compartment syndrome: serum creatine kinase, urine-myoglobin, compartment pressure measurement
Deep vein thrombosis	Commonly in leg. Pain, swelling, tenderness. Red, warm skin	Ultrasound, venography, MRI
Snake venom (hemotoxic procoagulant or myotoxic venom)	Hemotoxins (e.g., most vipers) cause hemolysis and disrupted blood clotting. Commonly severe pain in wound site, followed by swelling and discoloration. General symptoms with vomiting, dyspnea, dizziness, affected circulation	Hemotoxins: D-dimer elevated, fibrinogen very low, prolonged prothrombin time, APTT, and clotting time. Assess renal function
	Myotoxins (e.g., rattlesnakes): rhabdomyolysis with muscle pain, tenderness, and paralysis	Myotoxins: serum creatine kinase, s-myoglobin, and u-myoglobin highly elevated. Assess renal function
Tumor		
Osteosarcoma, Rhabdomyosarcoma	Palpable tumor mass, pain, abnormal sensitivity, and muscle weakness if nerve compression. Osteosarcomas may cause bone pain, limping, and fracture	X-ray, MRI, CT scan, biopsy

4.2.1 Muscle Strength Grading

The Medical Research Council (MRC) scale for muscle strength is a clinically easy and useful way to grade muscle weakness. The strength of each tested muscle is graded as follows:

0—no voluntary movement is observed.
1—only a trace/flicker of movement or fasciculation is observed.
2—movement is observed only if resistance of gravity is removed (i.e., cannot move against gravity).
3—movement against gravity with no further added resistance can be observed.
4—movement against gravity and some added resistance can be observed.
5—movement occurs against gravity and full resistance of tester (= normal strength).

This confrontational muscle strength testing is only reliable in patients who understand and cooperate with the exam. Patients with psychosomatic complaints often exhibit segmental weakness that is not consistent with neuroanatomical distribution.

4.2.2 Test of Muscle Tone

Examine resistance of limbs to passive movement and range of movement of peripheral joints (e.g., wrist). Abnormal muscle tone may present as:

Flaccidity: Absence of muscle tone. Extremities feel "heavy," offer no resistance to passive movement, and will immediately drop after releasing grip of arm or leg.
Hypotonia: Decreased muscle tone, usually accompanied by muscle weakness. For test of muscle tone in the newborn or infant, see Sect. 4.2.1.
Hypertonia: Increased muscle tone. Sign of lesion of premotor cortex, basal ganglia, or descending pathways. Chronic upper motor neuron damage results in increased muscle tone, whereas lower motor neuron damage results in decreased muscle tone.
Spasticity: Velocity-dependent increase in tonic stretch reflexes (muscle tone). See also below and Chap. 18 for testing for spasticity.
Rigidity: Simultaneous increase in muscle tone of agonist and antagonist muscles resulting in constant contraction resistant to passive movement.

4.2.3 Tendon Reflexes

A check of tendon reflexes provides information on the integrity of the reflex circuits involving spinal cord motor neurons, peripheral sensory and motor nerves, and the muscles innervated by the motor nerves. In general increased reflexes are seen

in conditions affecting the upper motor system prior to spinal motor neurons and decreased reflexes seen in conditions affecting the lower part of the motor system (motor neuron in spinal cord, peripheral nerves, neuromuscular junction, and skeletal muscle).

The main spinal nerve roots involved in most commonly tested reflexes are for biceps C5, biceps C6, brachioradialis C6, triceps C7, patellar L4, and Achilles tendon S1.

Tendon reflexes are commonly graded 0 (absent), 1 (trace), 2 (normal), 3 (brisk), 4 (nonsustained myoclonus = few repetitions), or 5 (sustained myoclonus).

4.2.4 Babinski Sign

The hallux dorsiflexes and the other toes fan out when the lateral side of the foot is stroked firmly with a blunt point from heel to toes. This is present in normal children up to approximately 6 months of age. In older children this may indicate pyramidal tract dysfunction (cortex, brain stem, or spinal cord).

4.2.5 Clonus

Clonus is a regular repetitive movement of a joint elicited by a sudden stretching of the muscle and maintaining the stretch, commonly tested at ankle. Sustained ankle clonus is a sign of pyramidal tract lesion.

4.2.6 Finger–Nose Test

Testing the ability to touch rapidly the tip of the nose with the tip of the forefinger, alternating between left and right hand, with and without aid of vision. This is often abnormal in cerebellar disease (ataxia) and tremor. Motor impersistence due to weakness can show target dysmetria or tremor in this test.

4.2.7 L'Hermitte Sign

Paresthesias, including tingling, buzzing, electrical shocks, partial numbness, and sharp pains, brought on by marked flexion or extension of the neck. This is a sign of compression of spinal cord.

4.2.8 Diadochokinesis

Diadochokinesis is the inability to carry out rapid alternating movements, e.g., pronation and supination of the forearm. Abnormal in paresis, extrapyramidal processes, and cerebellar diseases.

4.2.9 Gowers' Sign

Gowers' sign describes necessity to use the arms, by placing the hands on the knees, when rising from lying or sitting to standing position. It indicates weakness of proximal leg muscles and truncal muscles, e.g., Duchenne muscular dystrophy. In the more severe levels, the patients need to first use their hands to push on the floor before they place their hands on their legs to "walk up" their knee and thigh.

4.2.10 Spasticity Testing

Assessment of spasticity, i.e., increase in muscle tone due to hyperexcitability of the stretch reflex, includes identifying which muscles or muscle groups are overactive and determining the effect of spasticity on all aspects of patient function. In spasticity there is resistance when trying to move an arm or leg that increases as the speed of the movement is increased. Other useful signs are presence of sustained clonus at ankle, wrist, or other joints and increase in tendon reflexes. See Chap. 18, Sect. 18.4.2, for further details on assessment of spasticity.

4.3 Hypotonia of the Newborn or Infant

A child presenting with generalized muscle hypotonia, either in the neonatal period or later during the first year of life, is often referred to as a floppy infant. Hypotonia is characterized as a state of low muscle tone. It is related to, but not identical to, muscle weakness. The latter is characterized by decreased ability to perform voluntary movements. The floppy infant often has both hypotonia and weakness. The prognosis of infants with neonatal hypotonia is entirely dependent on the cause and varies immensely. It is therefore essential to evaluate the cause of hypotonia in order to outline further investigations and treatment [2–4]. Ethical aspects and prognosis are especially important to consider.

4.3.1 Presenting Symptoms

Clinical signs that are typically present in a floppy infant are:

- Head lag when pulled from lying to sitting position
- A tendency to "slip through" the examiner's hands in the shoulder suspension test, i.e., picking the child up holding it under the arms
- A "frog-legged" posture when lying on the back
- Inability to lift head and limbs against gravity in the "ventral suspension test," i.e., when lifting the infant with the examiner's hand under the chest and abdomen
- Positive "scarf sign," i.e., the elbow easily crosses the midline when in supine position pulling the hand across the chest
- Diminished resistance to passive movement of the limbs and increased range of movement of the peripheral joints

4.3.2 Diagnosis and Differential Diagnoses of the Hypotonic Infant

Significant hypotonia usually has an underlying cause, although in some cases no reason is identified and the hypotonia resolves spontaneously (benign congenital hypotonia). More than 400 disorders have been associated with hypotonia. Once the infant has been identified as hypotonic (see above), it is next helpful to determine whether the cause is central or peripheral.

Central origin of hypotonia is characterized by altered responsiveness/cognition, decreased Moro and grasp reflexes, ability to lift the extremities from the underlying table (no muscle weakness), and increased or decreased tendon reflexes (biceps, triceps, brachioradialis, knee and ankle jerk).

Common causes of hypotonia from brain and other systemic disorders include sepsis, cardiac failure, hypoxic–ischemic encephalopathy, syndromes (e.g., Down syndrome, Prader–Willi syndrome, neuronal migration disorders, gene mutation/duplication/deletion syndromes, and chromosomal aberrations; dysmorphic features may be a clue), vascular events (intracranial hemorrhagic or ischemic stroke), metabolic encephalopathy (e.g., hypoglycemia, hyperbilirubinemia, electrolyte disturbances, neurometabolic disorder; see also Chap. 9), drug side effects (iatrogenic, toxins), endocrine disorders(e.g., hypothyroidism), and trauma (e.g., spinal cord trauma from difficult assisted delivery at birth, frequently asymmetry of hypotonia).

Peripheral neuromuscular origin of hypotonia is characterized by normal level of responsiveness/cognition, inability to lift the extremities from the underlying table (i.e., weakness), and absence of deep tendon reflexes (biceps, triceps, brachioradialis, knee and ankle jerk).

Common neuromuscular disorders to be considered are spinal muscular atrophy (SMA) type I (very severe hypotonia and weakness but alert), neurogenic arthrogryposis multiplex congenita (fixed joint position at birth combined with weakness and hypotonia, varied etiologies), neonatal myasthenia gravis (known myasthenia in mother), congenital myotonic dystrophy, congenital muscular dystrophies, congenital myopathies (e.g., central core disease, nemaline myopathy, myotubular myopathy), or metabolic myopathies (e.g., mitochondrial myopathies). Other conditions to consider are botulism, connective tissue disorders (e.g., Marfan syndrome, Ehler–Danlos syndrome), and benign congenital hypotonia.

4.3.3 Assessments of the Hypotonic Infant

The following checkpoints for medical history, examination, and initial work-up can be helpful in order to identify the cause of the muscular hypotonia and possible associated features [2–4].

4.3.3.1 Medical History

Family history (affected parents or siblings, consanguinity, stillbirths, maternal disease) and pregnancy and delivery history (drug exposure, fetal movements, polyhydramniosis, perinatal asphyxia, Apgar scores, respiratory effort, ability to feed).

4.3.3.2 Physical Examination

Observe for level of responsiveness/cognition, seizures, level of spontaneous activity, character of cry (often weak with pronounced peripheral weakness in SMA, hoarse cry in hypothyroidism), dysmorphic features, sucking/feeding, breathing and thorax configuration, arthrogryposis, resistance to passive movements over joints, hepatosplenomegaly (in storage diseases like Pompe disease), cardiovascular examination, cranial nerve function, hypotonia and clinical pointers to floppiness (see above), fasciculations, facial weakness, high-arched palate, muscle power (antigravity movements), deep tendon reflexes, primary neonatal reflexes, and asymmetry of hypotonia.

4.3.3.3 Assessment

The initial work-up of the floppy infant depends upon the medical history and findings in the clinical evaluation.

Investigations for floppiness suspected to be of central origin should include glucose, electrolytes, blood gas (umbilical cord blood pH in neonates), complete blood count, bilirubin, septic screen including lumbar puncture, electroencephalography (EEG)/ambulatory EEG, ultrasound/computed tomography (CT)/magnetic resonance imaging (MRI), metabolic screening (serum-lactate, serum-ammonium, organic acids in urine, and plasma aminogram), infection (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus (TORCH)), karyotype (if dysmorphic features), array-comparative genomic hybridization (CGH), and specific genetic analyses (e.g., Prader–Willi syndrome).

Investigations for floppiness suspected to be of peripheral origin include serum muscle enzyme levels (creatine kinase), electromyography (EMG), nerve conduction velocity, muscle biopsy (e.g., congenital myopathy such as centronuclear myopathy or nemaline myopathy), specific genetic tests (e.g., DNA triplet (CTG) repeats for congenital myotonic dystrophy type 1 and SMN1 gene deletion for SMA) and EMG repetitive nerve stimulation (decrement), anti-ACh receptor antibodies in mother and infant, and/or trial of oral therapy of cholinesterase inhibitor if myasthenia is suspected. Administration of short-acting acetylcholinesterase inhibitor (e.g., edrophonium chloride) with assessment of repetitive nerve stimulation and motor function (selected muscles) can also be helpful, but is not very reliable in infants.

4.4 Acute Paralysis

Several motor disturbances present as true neurological emergencies and require immediate medical attention. We will list some of these urgent conditions in this section. In Sect. 4.5 we will include the diagnosis and treatment for other less urgent motor dysfunctions.

4.4.1 Presenting Symptoms

Acute loss of motor function is mostly flaccid [1, 5]. Flaccid paralysis is the term for loss of muscle strength and tone for one or more muscles, to be distinguished from other causes of motor dysfunction (e.g., spasticity, ataxia, other movement disorders covered in Chap. 17). It should be noted that the nature of weakness may change over time from flaccid in the acute phase to spastic at later stages (e.g., asphyxia or vascular brain events). The muscle weakness can be accompanied by sensory loss in the affected area if there is sensory damage as well as motor. Although paralysis is defined as a complete loss of strength in a limb or a muscle group, we here cover also noncomplete loss of muscle function.

4.4.2 Loss of Motor Function: Urgent Considerations

In the acute situation it may be helpful to keep in mind certain urgent situations before a more elaborate diagnostic work-up is initiated [1].

4.4.2.1 Cerebrovascular Insults

Stroke may present as paralysis of face, arm, and/or leg. It may be complete or partial and may be accompanied by loss of vision and speech [6, 7].

Subarachnoid hemorrhage typically presents with a sudden, severe, "worst ever" headache, with photophobia, loss of consciousness, and oculomotor nerve palsy.

Subdural hemorrhage sometimes follows relatively minor trauma and may be suggested by nausea, vomiting, confusion, diminishing Glasgow Coma Scale, localized weakness, loss of bowel function, and bladder weakness. Subarachnoid hemorrhage and intraventricular hemorrhage in particular are life threatening if they remain undiagnosed. See also Chap. 16.

Diagnosis: Urgent CT/MRI of brain

4.4.2.2 Spinal Cord Compression

Symptoms may include back pain, numbness or paresthesias, weakness or paralysis, bladder and/or bowel dysfunction, hyperreflexia, and loss of tone below level of suspected injury [8]. Saddle (perineal) anesthesia, bladder retention, and leg weakness are typical of cauda equina syndrome.

Diagnosis: MRI (or CT) of spine

4.4.2.3 Acute Inflammatory Demyelinating Polyneuropathy (Guillain–Barré Syndrome)

Acute inflammatory demyelinating polyneuropathy (AIDP) typically follows a viral or bacterial illness, commonly presenting as ascending paresthesia in hands and feet, followed by muscle weakness [9–11]. Symptoms usually start in the lower limbs. The muscle weakness (and paresthesia) is sometimes accompanied by pain, most commonly in legs and back. The muscle weakness may progress to involve respiratory muscles, resulting in acute respiratory failure necessitating intubation and respiratory support.

Diagnosis: Cerebral spinal fluid (CSF) shows increased protein with or without increased white blood cell (WBC) count. When WBC is increased it is predominantly lymphocytic. Nerve conduction study (demyelinating, absent F-wave) confirms diagnosis.

4.4.2.4 Acute Neuromuscular Junction Dysfunction: Myasthenic Crisis and Botulism

Myasthenic crisis is a life-threatening exacerbation of myasthenia gravis (MG) necessitating mechanical ventilation because of acute weakness of respiratory muscles [12]. Common presentations of MG include ptosis and diplopia caused by ocular muscle weakness. Generalized weakness with fatigability involving trunk and extremity muscles is noted in approximately 85 % of patients and may be the dominant complaint. Dysphonia and difficulty with chewing and/or swallowing due to bulbar muscle involvement may also be noted. MG crisis may be provoked by fever, infections, aspiration, thyroid disease, stress (emotional, trauma, surgery), or medications (e.g., high-dose corticosteroids and the antibiotics aminoglycosides, ciprofloxacin, clindamycin, erythromycin). See Chap. 14 for treatment.

Diagnosis: Neurophysiology (repetitive nerve stimulation, single-fiber EMG), serology for Anti-AChR, and Anti-MuSK antibodies.

Acute botulism shares many of the symptoms of severe myasthenia gravis. It is caused by infection by spores of Clostridium botulinum or ingestion of botulinum toxin [13]. In children, botulism is most commonly caused by colonization (infection) of the intestine. The major symptoms are feeding difficulties, drooling, general muscle weakness, and ventilatory failure. Constipation is also often seen and may precede the onset of neurologic abnormalities by several days. Loss of facial expression, ptosis, and extraocular muscle paralysis are other common features.

Diagnosis: C. botulinum culture of stool specimens, botulinum toxin analysis in serum.

4.4.2.5 Malignant Hyperthermia

Malignant hyperthermia is a life-threatening condition characterized by muscle rigidity, rhabdomyolysis, and increased oxidative metabolism [14, 15]. The latter results in very high temperature (late sign), increased heart rate and breathing rate, increased CO_2 production, increased O_2 consumption, and acidosis. The condition occurs when a person with malignant hyperthermia susceptibility is exposed to triggering factors, including most inhalation anesthetics (e.g., halothane, sevoflurane, desflurane, isoflurane, enflurane) or depolarizing muscle relaxants (succinylcholine, decamethonium, and suxamethonium). Susceptibility for malignant hyperthermia is often inherited as an autosomal dominant disorder. Six genes are linked to the condition, most commonly the ryanodine receptor gene (*RYR1*). Masseter contraction is an early clinical warning sign. Other early signs include unexplained tachycardia, elevated end-tidal CO_2 concentration, and muscle rigidity. See Chap. 15 for treatment.

Diagnosis: Clinical signs are outlined above. Check urine for myoglobin, blood for muscle enzyme CK, potassium (K) and phosphorus (P) levels, metabolic or respiratory acidosis, and kidney functions.

4.5 Acute Motor Dysfunction: Diagnosis and Differential Diagnoses

Once the more urgent conditions have been ruled out (see Sect. 4.3.2 above), it may be helpful to define the anatomic level of the dysfunction and from this reach a diagnosis or differential diagnoses for the underlying cause.

Acute paralysis or other motor dysfunction can be caused by a very wide range of disease states, affecting the brain, motor unit, or musculoskeletal system (Tables 4.1, 4.2, 4.3, 4.4, 4.5, and 4.6). Careful questioning of a patient who reports sudden motor loss can help determine the exact anatomy of the motor deficit, any accompanying features, and the likely pathophysiology. The anatomic description of the deficit helps localize the site of lesion.

Subacute or chronic damage to the brain involving upper motor neuron is typically characterized by increased muscle tone (hypertonia, spasticity, rigidity) and increased tendon reflexes. They are also often, but not always, accompanied by brain symptoms other than motor dysfunction. It should be kept in mind that brain lesions in the very acute stage may present as flaccid type of paralysis with decreased muscle tone, only later to develop increase in muscle tone.

Disturbed neuromuscular function reflects pathology at the level of the motor unit (the motor neuron residing in the anterior horn of the spinal cord, its extended motor nerve, the neuromuscular junction, or the muscle fiber). Conditions affecting the motor unit are characterized by decreased muscle tone and decreased tendon reflexes.

Most neuromuscular diseases develop gradually and do not present with acute onset of symptoms. The most common causes of an acutely developing muscle weakness, sometimes with urgent need to first secure respiratory function, are myasthenia and botulism (see Sect. 4.4.2.4 above), acute inflammatory demyelinating polyneuropathy (AIDP; Guillain–Barré syndrome: see Sect. 4.4.2.3 above), critical illness polyneuropathy, and critical illness myopathy. Other important causes to consider are anterior horn cell dysfunction (enterovirus infection—polio-like symptoms, or spinal muscular atrophy), neuromuscular transmission defects other than myasthenia (e.g., anticholinesterase pesticide poisoning), inflammatory muscle diseases, and muscle ion channel diseases.

4.5.1 Acute Motor Disturbance: Brain

A multitude of brain conditions may result in acute motor disturbance, including brain infections (see Chap. 14), inflammation (see Chap. 16), vascular events (see Chap. 16), toxic/metabolic conditions (see Chap. 9), trauma (see Chap. 19), hypoxia (see Chap. 8), tumors (see Chap. 12), malformations, seizures (see Chaps. 2 and 11), and conversion disorder (see Chap. 7). Be observant for

cerebrovascular conditions in need of urgent assessment and intervention (see Sect. 4.4.2.1). Table 4.1 [6, 7, 16–18] summarizes typical symptoms, findings, and diagnostic aids.

4.5.2 Acute Motor Disturbance: Spinal Cord

At the level of the spinal cord, conditions to consider as the cause of acute paralysis include infections (see Chap. 14), inflammation (see Chap. 17), trauma, tumors, vascular events (see Chap. 16), motor neuron disease, and malformations. Table 4.2 [19, 20] summarizes typical symptoms, findings, and diagnostic aids. Spinal cord compression constitutes an urgent condition in need of immediate care (see Sect. 4.4.2.2).

4.5.3 Acute Motor Disturbance: Peripheral Motor Nerve

Common causes for peripheral motor nerve dysfunction resulting in acute muscle weakness are infection, inflammation, trauma, compression (including tumor), toxic/metabolic conditions, and critical illness neuropathy. Hereditary neuropathies rarely present with acute symptoms, but can do so, e.g., due to increased vulnerability for toxic/metabolic causes of neuropathy.

Be observant for the need of urgent diagnosis and care of acute inflammatory demyelinating polyneuropathy (see Sect. 4.4.2.3). Typical symptoms, findings, and diagnostic aids are summarized in Table 4.3 [9–11, 21–23]. See also Chap. 15 for management of neuromuscular disorders.

4.5.4 Acute Motor Disturbance: Neuromuscular Junction

Neuromuscular junction dysfunction may arise from myasthenia gravis (autoimmune), botulism, or hereditary myasthenic syndromes. The diagnosis of neuromuscular junction disorders is frequently delayed, in particular if the suspicion is never raised. This may be the case if typical symptoms such as fatigability, fluctuations of weakness, ptosis, and ophthalmoplegia are not evident. It should be noted that neuromuscular junction dysfunction requires specific neurophysiological analysis using, repetitive nerve stimulation EMG. The diagnosis and early intervention is particularly important in urgent situations such as in botulism or myasthenic crisis (see Sect. 4.4.2.4). Typical symptoms and diagnostic aids are summarized in Table 4.4 [12, 13]. See also Chap. 15 for management of neuromuscular disorders.

4.5.5 Acute Motor Disturbance: Skeletal Muscle

Skeletal muscle diseases usually develop gradually without acute onset of symptoms. The most common causes of an acutely developing skeletal muscle disease are critical illness myopathy and acute myoglobinuria caused by rhabdomyolysis. In acute myoglobinuria it is important to assess renal functions as highly elevated levels of myoglobin may occlude the renal system and eventually lead to renal failure. Rare but urgent situations affecting skeletal muscle include malignant hyperthermia (see Sect. 4.4.4.5) and tetanus.

Other causes for skeletal muscle dysfunction include infection and inflammatory, metabolic, and hereditary conditions. See Table 4.5 [14, 15, 21–28] for typical findings and diagnostic aids. See also Chap. 10 for acute muscle weakness associated with myoglobinuria and Chap. 15 for management of neuromuscular disorders.

4.5.6 Acute Motor Disturbance: Musculoskeletal System

Musculoskeletal causes of acute motor dysfunction include infections and inflammation in joints and bones, trauma, tumors, deep vein thrombosis, snake venom, and compartment syndrome.

The typical symptoms, findings, and diagnostic aids are summarized in Table 4.6.

4.6 Conclusion

Acute motor dysfunction results from loss of function in any part of the neural axis connecting the brain motor neurons with the different levels of the motor unit (motor neuron, peripheral nerves, neuromuscular junction, and skeletal muscle itself). When diagnosing the cause of an acute motor dysfunction, it is helpful to combine information on (1) the type of motor dysfunction (e.g., presence and distribution of paralysis, ataxia, involuntary movements), (2) identification of the anatomical level of the deficit (supraspinal, spinal cord, peripheral motor nerve, neuromuscular junction, skeletal muscle, musculoskeletal system), and (3) the underlying pathogenic cause of the dysfunction (e.g., infection, inflammation, metabolic, compression, hereditary). In the initial acute situation, be observant on urgent situations such as cerebrovascular insults, spinal cord compression, acute inflammatory demyelinating polyneuropathy, botulism, myasthenic crisis, and malignant hyperthermia necessitating immediate diagnostic work-up and interventions.

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Chapter 5
Acute Disturbance of Vision

Kristina K. Teär Fahnehjelm and Douglas R. Fredrick

Abstract Vision loss in children may be of sudden onset or may be long standing but suddenly discovered. The neurologist must determine which children need urgent diagnostic neurologic or ophthalmic evaluation. Systematic assessment of visual acuity, eye movements, pupil response, visual fields, and optic nerve and fundus evaluation will enable the practitioner to refine the differential diagnosis and streamline evaluation and treatment. For parents, there are few conditions that are more anxiety provoking than the discovery that their child has poor vision in one or both eyes. Their concern is often in contrast to the child's seeming indifference to the poor vision or wandering eye. There are also patients without any obvious visual loss where eye examinations may help diagnose neurologic damage, like retinal hemorrhages, suggestive, for example, for shaken baby syndrome. In this chapter, we will provide the clinician with a systematic approach to the child with apparent sudden onset of poor vision, strabismus, or abnormal pupil.

Keywords Optic neuritis • Papilledema • Strabismus • Optic nerve hypoplasia • Optic atrophy • Retinal bleedings • Shaken baby syndrome

5.1 Pediatric Eye Exam

The clinician must be resourceful when examining children with an ocular or visual complaint. Knowing how to reconcile subjective complaints with objective findings is essential in determining whether further neurologic workup is indicated.

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Fig. 5.1 Testing visual acuity using forced choice preferential-looking test

5.1.1 Assessment of Visual Acuity

A newborn often fixates light but often will not fix and follow properly until the age of 2 months. The human face is the best fixation target, and it may be necessary to first use an auditory cue as well as place the face about 10–15 in. from the child's. After fixation is established, stop making noise and see if the child continues to follow the face. Remember children with cerebral pathology like periventricular leukomalacia or hypoxic ischemic encephalopathy may have delayed fixation due to cerebral visual impairment. Vision can be quantified in preverbal, preliterate children, by using preferential-looking tests, which are cardboard targets of vertically oriented black and white stripes of varying width and contrast. If a child can discern a pattern, they will make a saccadic eye movement toward the side with the stripes (Fig. 5.1). The movement is observed by the examiner. Progressively thinner stripes are presented until no saccade is made, indicating lack of perception. The spatial separation of the stripes is measured in cycles per degree and can be used to estimate visual acuity [1]. In preliterate but verbal children, visual acuity can be tested using matching strategies (HOTV cards) or easily recognizable figures (Lea) or child recognition charts (Fig. 5.2) [2]. The gold standard visual assessment is the use of Snellen full line visual acuity. Presentation of single optotypes can overestimate visual acuity, especially in the condition of amblyopia or cerebral visual impairment.

In addition to visual acuity, it is important to note fixation preference. In infants, notation must be made whether the child can not only fix and follow (F&F) but also is the vision central (not eccentric) steady (no nystagmus) and maintained. Young infants may have saccadic smooth pursuits. Children should see 20/40 (or 6/12) by 4 years of age. When testing vision, it is important to test both eyes open at first then, if possible, occlude each eye individually. It is imperative to make certain that

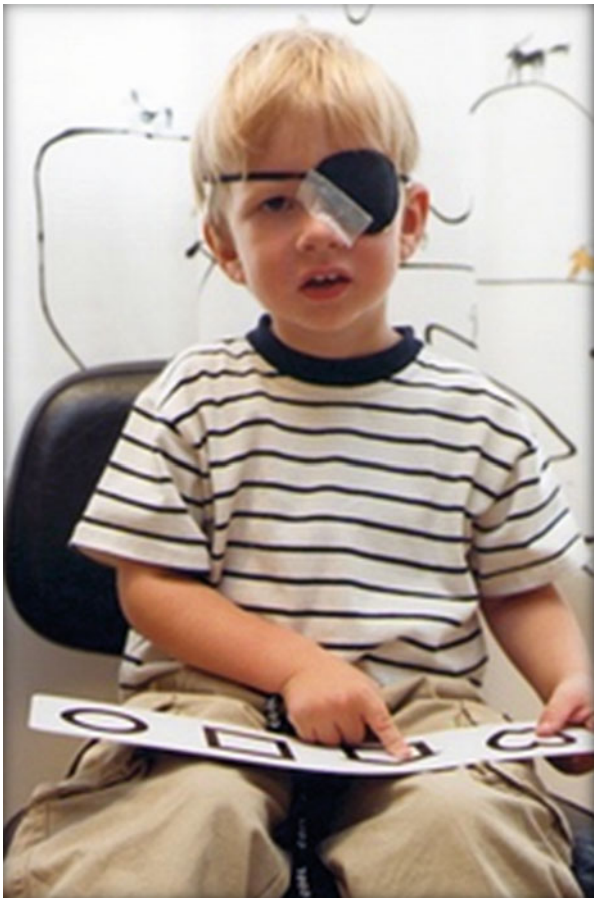

Fig. 5.2 Testing vision with matching figures (Lea test)

when occluding one eye, the child is not peaking around the patch. Also remember to check near vision acuity, which will be necessary for inpatients. Most patients with refractive error will have good near vision; those with optic nerve, cerebral, or retinal pathology will have poor vision, distance as well as near.

5.1.2 Color Vision Testing

A sensitive test of optic nerve dysfunction is desaturation or loss of color vision. This is particularly useful in cases of optic neuritis or optic nerve trauma where the fellow eye has normal color vision compared to the affected eye. Color vision test plates are sometimes available in primary care clinics, but if not available, the use of colored crayons or markers can be used for a quick assessment of color vision, desaturation, and asymmetry.

5.1.3 Visual Field Assessment

Obtaining an accurate visual field assessment can be difficult even in the most cooperative children. The key to obtaining accurate measurement is maintaining fixation, and for children less than 4 years old, two examiners will be required to do confrontation visual field assessment. With child seated in the parent's lap, one examiner sits in front of the child holding their attention straight ahead with an interesting toy or fixation device. The second examiner stands behind the child and surreptitiously introduces a toy into the child's peripheral vision. If the child makes a saccadic eye movement or turns their head toward the introduced object, that indicates full peripheral field. The technique will detect hemianopias but not subtle visual field defects. Older children of 6–7 years of age often can be examined with a Goldmann visual field machine, which allows the tester to constantly monitor visual fixation. A skilled technician can obtain an accurate visual field exam, but such skill is vanishing as automated devices to measure extent of visual fields cannot assure fixation in children who are easily distracted. Automated visual field examinations are limited by their high number of false negatives and positives, as well as fixation losses, and are often not secure until 8 or 9 years of age.

5.1.4 Pupil Exam

Like the visual field exam, an accurate pupillary assessment requires maintained fixation, preferably at a distant target to minimize constriction due to accommodation. A video screen or noise-making toy provides good fixation as pupils are examined for size, shape, symmetry, reaction to light, and reaction to accommodation. Pupils should react briskly to light, but this may be difficult to see in the infant with dark irises and poor cooperation. They should be equal in size in both dark and light. If pupils are asymmetric (*anisocoria*), it must be determined which pupil is pathologic, the small one or the large pupil. Anisocoria can be due to local abnormalities in the iris or the iris muscle or an abnormal innervation of the efferent visual pathways which allow normal contraction or dilatation. One should try to determine if there is any structural anomaly of the iris or unusual shape of the pupil. A magnifying glass/strong plus glass can be useful to assess if there is *iris coloboma* (Fig. 5.3) *or aniridia*. Aniridia can be associated with Wilms' tumor. An iris coloboma can be associated with coloboma in the ocular fundus and causes severe visual impairment (Fig. 5.4). It may also be associated with different multisystem syndromes such as CHARGE syndrome or cat eye syndrome [3]. There are also other conditions that can result in unusually shaped pupils. For example, chronic uveitis, which occurs most often in children with juvenile rheumatoid arthritis, can be associated with inflammation inside of the eye that leads to adhesions of the iris to the lens of the eye, which can lead to irregularly shaped pupils that react poorly to light. *Leukocoria*,

Fig. 5.3 Coloboma of the iris causing irregular pupil

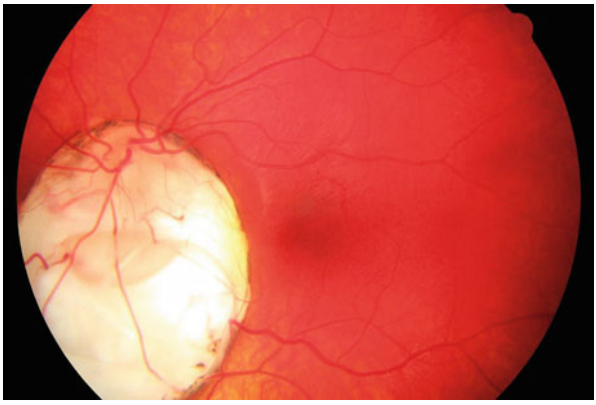

Fig. 5.4 Coloboma of the retina and choroid

Fig. 5.5 Cataracts causing leukocoria

a white pupil, may be caused by congenital cataract (Fig. 5.5) or fundus coloboma or associated with serious ocular pathology like retinoblastoma (Fig. 5.6). Children with leukocoria should be *immediately* referred to a pediatric ophthalmologist for further investigation and prompt intervention. Other causes of leukocoria include infections, retinopathy of prematurity, or other congenital malformations. If there is

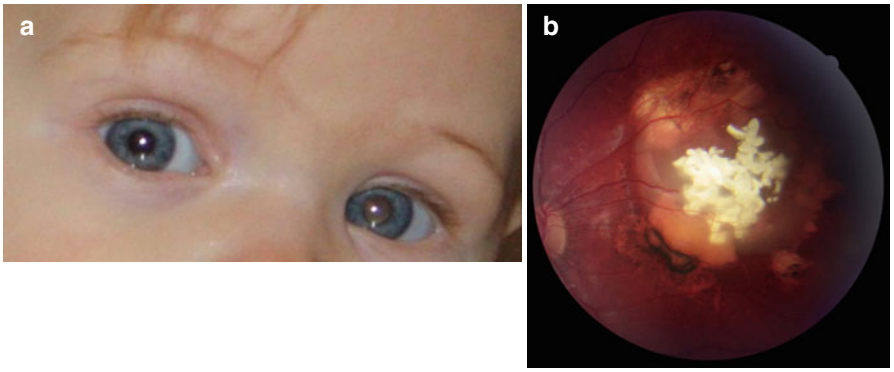

Fig. 5.6 (**a**) Leukocoria left eye. (**b**) White calcified retinoblastoma causing white pupil in photograph of child

no leukocoria or other structural abnormality but the pupils are unequal in size, then one should proceed with testing of pupillary reactions to direct or indirect light. *Physiological anisocoria* is likely when pupillary reactions of both eyes are the same in dim or bright light and the difference of pupil size is no more than 1.0 mm, provided that there is no ptosis or motility disturbances. This needs no further investigation. If the pupil is abnormally *big*, there may be a cranial nerve III paralysis or a so-called *tonic pupil.* Also drugs accidentally administered locally or inhaled or a traumatic dilated sphincter paralysis can be causative. If there is no reaction when examining the pupil reactions to light, a pharmacologically induced CN III paralysis (check for ptosis and motility disturbances) or an Adie's tonic pupil may be present. The difference in pupil size is greater in light. Pupillary disturbances are common in CN III paralysis. If there is a suspicion of CN III paralysis, there may be indication for acute neuroimaging. An abnormally small pupil may be present in *Horner syndrome* or uveitis with synechia. The difference is greater in dim light if a Horner syndrome, which signifies a lesion in the sympathetic pathway, is present. Check these patients for ptosis, for unilateral anhidrosis of the scalp, and for different colors of the iris (iris heterochromia). There are locally administered eye drops that can be helpful in diagnosis. The affected pupil in Horner syndrome fails to dilate with 10 % cocaine, but this is a matter to be dealt with by pediatric ophthalmologists. A congenital Horner does not need urgent examination, but an acquired Horner raises suspicion of sympathetic lesions.

5.1.4.1 Examination Techniques for Anisocoria

- Look for the size of pupil and any abnormal configuration.
- Test reactions to light, directly and indirectly with a torch.
- Abnormal swinging flashlight test indicates optic nerve is affected (see below) or relative afferent pupillary defect (RAPD).
- Test papillary reactions to convergence.

- If the pupillary reaction to light and accommodation are abnormal, then check for risks of efferent, parasympathetic, drug-induced, or local structural causes.
- Check the status in dark: if there is a bigger difference in the dark, then a sympathetic lesion causing failure to dilate is present.
- Check the status in bright light: if there is a bigger difference in bright light, then there is a parasympathetic lesion.

The most important maneuver to master and perform is a swinging flashlight test in order to check for an afferent pupil defect which if present is highly suggestive of optic nerve dysfunction. Swinging the flashlight rhythmically back and forth between the eyes should show both pupils stay constricted. A pupil that dilates when exposed to direct light would indicate relative afferent defect in that eye.

5.1.5 Eyelid Examination

Lids can either be droopy (ptosis) or abnormally wide (stare or retraction). Eyelid function should be assessed by symmetry and function of the levator palpebrae superioris, which is innervated by the third cranial nerve. Once again, fixation is important. Eyelid function can be checked by having the child follow a toy superiorly and inferiorly and see if both sides have equal excursion. A lid that doesn't go up can be due to weakened levator muscle. A lid that does not follow the eye downward can indicate a tight levator muscle. Next, have the child forcefully close their eyes and try to open the eyelids with fingers. Children are usually quite expert at shutting their eyelids tight, but if you are able to open the eyelids easily, it indicates a possible cranial nerve seven dysfunction. Droopy eyelid can be seen in ocular myasthenia. Forceful eyelid closure and blinking can be seen in habit blepharospasm but can also be seen more subtly in uncorrected refractive errors.

5.1.6 Optic Nerve Evaluation

An attempt should always be made to examine the optic nerve of a child who presents with vision loss. In older children, this can be quite simple, but younger children require patience and swift technique that allows the practitioner to see the nerve without causing the child physical distress. Once again, fixation is imperative. Using a fixation toy and more frequently a handheld electronic device gets the child's attention at distance. The optic nerve can be viewed with either the traditional direct ophthalmoscope or specially made ophthalmoscopes designed particularly for viewing the optic nerve. It is easier to see the optic nerve of the right eye if the child watches in the direction of your right ear and left optic nerve if the child watches in the direction of your left ear. Fixation can also be obtained by having the child fixate on a video displayed on a monitor or cell phone.

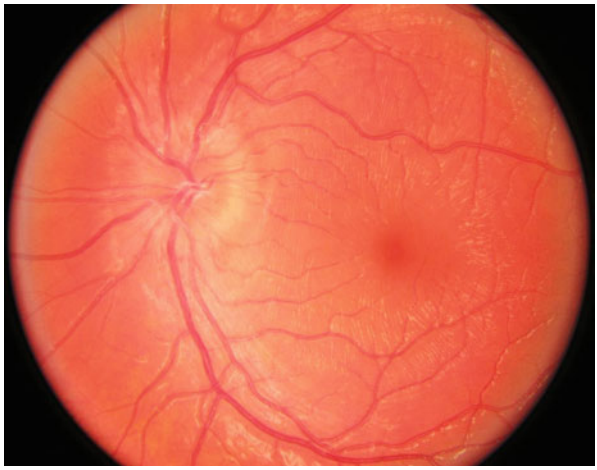

Fig. 5.7 Papilledema characterized by elevation, blurred disc margins, and obscuration of vessels at edge of disc

When viewing the optic nerve, attention should be paid to the optic disc margins to see if the vessels can clearly be seen from their origin in the center of the optic nerve extending radially. Blurriness of the vessels at the margin of the optic nerve can indicate papilledema (Fig. 5.7). The morphology of the nerve should be evaluated to see if the nerve is normal in size and finally the color using the fellow eye as a control to see if there is asymmetry in the appearance of size, shape, or color of the nerve.

5.1.6.1 Acute Vision Loss Due to Acquired Optic Nerve Disorders

Optic neuritis (ON) due to demyelination disease is uncommon in children under 15 years of age but more often reported after recent viral illness (after varicella, mononucleosis, toxoplasma, tuberculosis) or postvaccinal (DT, polio) and more often bilateral. Neuroborreliosis must be excluded. Symptoms can include pain when moving the eye, most often unilateral or sometimes bilateral vision loss within a few days, sometimes severe. Uhtoff's phenomena (vision loss with physical exercise) can be seen more commonly in optic neuritis associated with multiple sclerosis.

5.1.6.2 Examination Technique in Suspected Optic Nerve Disease

- Test visual acuity.
- Test reactions to light, directly and indirectly with a torch.
- Test the swinging flashlight test indicating optic nerve affection (see below) RAPD.
- Test color vision.
- Test visual fields.
- Test ocular motility.

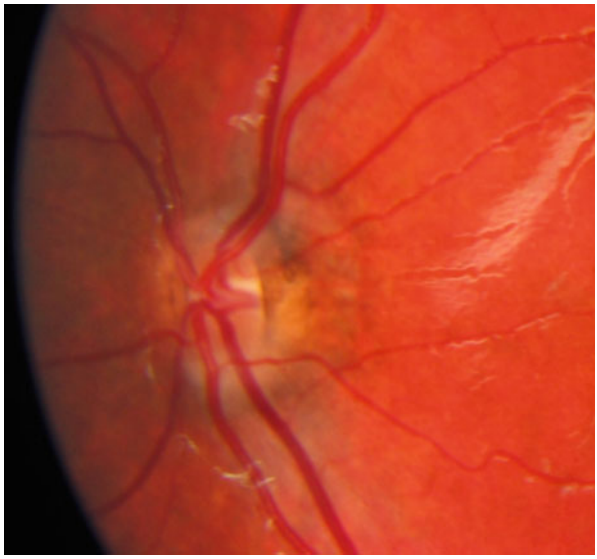

Fig. 5.8 Optic nerve hypoplasia left nerve

After evaluation of ocular fundi by pediatric ophthalmologist, perform MRI and lumbar puncture. Laboratory evaluation should include pressure, testing for Lyme disease, as well as testing for syphilis and markers for neuromyelitis optica.

5.1.7 Vision Loss Due to Congenital Optic Nerve Anomalies

Optic nerve hypoplasia (ONH) is a congenital, nonprogressive malformation characterized by a small and underdeveloped optic nerve with a reduced number of axons in one or both eyes (Fig. 5.8) and should be suspected in any child with poor vision, nystagmus, and a history of neonatal jaundice or hypoglycemia. In the Western countries, it is one of the leading and increasing causes of vision loss and blindness in children [4–6]. ONH may occur in isolation or as a component of a condition that includes various hormonal and/or neurologic symptoms, intellectual disability, and behavioral problems. Some children have midline brain malformations, for example, absent septum pellucidum and/or corpus callosum. The combination of ONH and midline brain defects is referred to as septo-optic dysplasia (SOD) and can, as isolated ONH, be associated to hormonal insufficiencies [7, 8]. The degree of severity varies, and the children can present with acute neurologic symptoms or hormonal deficiencies, for example, hypoglycemia or seizures. Early diagnosis and treatment is vital, especially in cases of hormone deficiencies, as repeated episodes of hypoglycemia increase the risk of brain damage. In bilateral severe ONH, the child usually presents with nystagmus or abnormal visual behavior. In older children or in mildly or unilaterally affected individuals, visual impairment may be suspected when the

child tends to peer closely at objects or pictures, develops strabismus and nystagmus, or has problems with screening tests for preschool or school children. It is important to consider the diagnosis in infant presenting with neonatal icterus or hypoglycemia, growth problems, excessive thirst, enuresis, and recurrent infections.

5.1.7.1 Examination of Congenital Structural Optic Nerve Anomalies

- Test visual acuity or fixation behavior.
- Test reactions to light, directly and indirectly.
- Perform the swinging flashlight test.

After evaluation of pediatric ophthalmologist, one should perform endocrinological assessment and MRI. The cause of ONH remains unknown, but it is likely that several factors are implicated. An underlying genetic predisposition combined with blood vessel damage during the early fetal stage resulting in structural anomalies affecting the brain midline, hypothalamus, pituitary gland, and optic chiasma is probable. ONH has been correlated with prematurity, prenatal exposure to antiepileptic or antidepressive drugs, consumption of alcohol and drugs, infections, or smoking in early pregnancy. Several studies have reported a correlation between optic nerve hypoplasia and young maternal age and primiparity. Hormonal insufficiencies have been reported in over 50 % of all children with ONH. Growth hormone (GH) deficiency is the most common. Hormone deficiencies are sometimes detectable even in newborns. Symptoms include hypoglycemia and seizures. Later in infancy, the child's growth rate may slow down abnormally. Other signs are increased thirst and urination. The child may also be unusually susceptible to infections or have shortage of thyroid-stimulating hormone (TSH). The result may be poor growth and delayed intellectual development. Deficiency in adrenocorticotropic hormone (ACTH) affects adrenal gland function, which in turn decreases the production of cortisone. Lack of antidiuretic hormone (ADH) causes increased urination and dehydration. Shortages of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) may delay or fasten the onset of puberty. The risk of hormonal imbalances increases in cases where both eyes are affected and/or if midline brain defects are present. Hormonal problems, however, may also occur in mild, unilateral cases, with no evidence of brain anomalies. The severity of neurologic symptoms varies considerably between individuals. Some individuals with ONH may have normal intellectual capacity, while others have severe intellectual disabilities. Behavioral disorders and autism have been reported in blind children with ONH [9]. When the diagnosis is suspected in infants, magnetic resonance imaging (MRI) should always be carried out in order to detect structural brain defects and to confirm the underdevelopment of the optic nerve or the optic chiasm. It is also possible to detect the absence of the septum pellucidum (complete or partial absence of the corpus callosum or if the pituitary gland is misplaced or underdeveloped).

All children with ONH should also be assessed by a pediatric endocrinologist, who will evaluate hormonal systems even if MRI scans show no abnormalities or if

only one eye is affected. A pediatric neurologist should evaluate motor coordination and development. If intellectual disability or visual perceptual problems are suspected or autism-like behavior is noted, the child should be referred to a psychologist or neuropsychiatrist for further evaluation.

5.1.7.2 Interventions of Optic Nerve Anomalies

Early diagnosis and treatment is vital, especially in cases of hormone deficiencies. Refractive vision errors are corrected with eyeglasses. Careful patching can be tried over the healthy eye in order to train the affected eye. In some cases, surgery is required. If this is the case, it is very important that hormonal deficiencies are properly analyzed, as there is a risk of severe complications. Habilitation to stimulate the child's development and compensate for functional limitations is important. Children with impaired vision are taught to optimize their capacities by using various types of low vision aids and, if needed, by learning other compensatory skills such as Braille reading and writing.

5.1.8 Examination of Visual Disturbance with Optic Disc Swelling

5.1.8.1 Papilledema

Children presenting with vision loss who are found to have swelling of the optic nerve must undergo emergent neuroimaging to rule out cerebral neoplasm or hydrocephalus, followed by lumbar puncture with opening pressure measurement if imaging is negative. Swelling of the optic nerve due to increased intracranial pressure is called papilledema. In papilledema, there is elevation of the disc, blurring of the vessels as they cross the margin of the disc, and loss of spontaneous venous pulsations. Papilledema can be caused by obstructive hydrocephalus due to tumor, hemorrhage, structural abnormality, infection, trauma, or cerebral venous thrombosis. Papilledema is also present in papillitis (please see above). Papilledema can also be due to hypertension (Fig. 5.9), making it imperative to check the blood pressure of all patients with papilledema. In the early stages of papilledema, there may be normal visual acuity, with only symptoms being photopsias and transient obscurations with change in position from recumbent to upright. If the increased intracranial pressure persists or rises rapidly, peripheral visual fields will become constricted inferonasally then throughout the periphery, followed by loss of central visual acuity. If intracranial pressure is lowered and controlled, vision may return, but chronic papilledema will lead to optic atrophy and permanent vision loss. When papilledema is found with a negative workup—normal neuroimaging, high opening pressure on lumbar puncture, normal CSF parameters, and normal blood pressure—the diagnosis of idiopathic intracranial hypertension should be considered [10, 11].

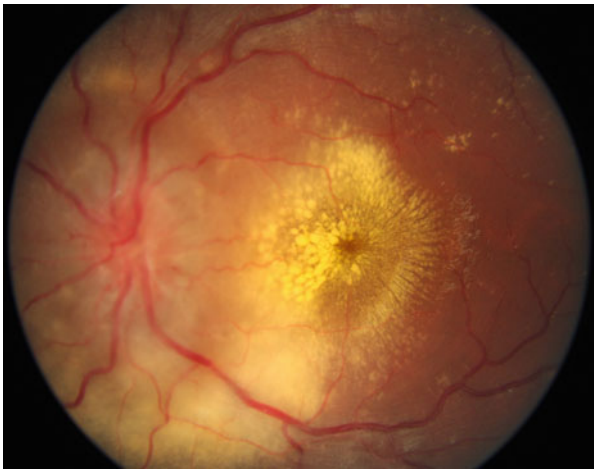

Fig. 5.9 Papilledema in hypertension with blood pressure 240/140

Causes include medications such as tetracyclines, steroids, vitamin A-related compounds, obesity, and cerebral venous thrombosis. Treatment involves cessation of precipitating medications, weight loss, the use of carbonic anhydrase inhibitors, and surgical procedures such as lumboperitoneal or ventriculoperitoneal shunting if medical therapy fails. It is important to remember that a long-standing papilledema will cause optic atrophy.

5.1.8.2 Optic Neuritis

Inflammation of the optic nerve will lead to vision loss and presence of an afferent pupil defect on clinical exam. If the nerve head is involved, the nerve will be elevated on clinical exam, which can simulate the appearance of papilledema, but the findings of decreased visual acuity, deceased color vision, and abnormal pupil response will help differentiate the two conditions.

The causes of optic neuropathy are vast and can involve infectious, inflammatory, demyelinating, toxic and hereditary causes, and radiologic, serologic, and other diagnostic testing will be guided by the history and physical examination findings. Every child presenting with optic neuritis should receive MRI scan to evaluate for demyelinating processes or other inflammatory conditions and should obtain laboratory testing including CBC, sed rate, antinuclear antibody, angiotensin converting enzyme, rheumatoid factor, Lyme and cat scratch titers, FTA-Abs, and metabolic panel. If neuroimaging is unremarkable, lumbar puncture with measurement of opening pressure and CSF analysis including chemistry, cytology, and NMO antibody should be obtained. If infectious processes have been ruled out, consideration of intravenous steroids can be considered as steroids can lead to more rapid improvement of visual acuity. Recognizing that prospective trials evaluating the use of corticosteroids in children with optic neuritis have not been performed, most practitioners follow the guidelines recommended in the Optic Neuritis Treatment Trial [12–15].

5.1.8.3 Optic Nerve Head Drusen

A final condition that can mimic papilledema and optic neuritis is optic nerve head drusen, a condition where amyloid material accumulates in the optic nerve head, causing elevation of the disc margins and enlargement of the blind spot on visual field testing [9, 16]. Unlike papilledema, the vessel on the disc margin will not be obscured by edema, and visual acuity is normal, but visual field defects may be present. Diagnosis is confirmed through the use of ultrasound or ocular coherence tomography.

5.1.9 Fundus/Retinal Evaluation in Non-accidental Injury/ Abusive Head Trauma

Children or infants under 1 year of age, who come to the emergency department with a history of head trauma, seizures, apnea, or unconsciousness, should undergo neuroimaging as well as an ophthalmological evaluation. The fundi must be examined regarding signs for retinal bleedings caused by violent shaking as in child abuse (Fig. 5.10). Retinal bleedings are common in child abuse (non-accidental injury, abusive head trauma, shaken baby syndrome [SBS]) under 1 year of age and are seen in 40–100 % of abused children with shaking or head injury [17–19]. In approximately 15 % of the cases, the bleedings may be unilateral. When retinal hemorrhages are found together with subdural hemorrhages and cerebral edema where there has been minimal external trauma, the diagnosis is highly likely. However, the lack of bleedings does not exclude the possibility that the child has been abused. Assessment of the ocular fundi and the findings of retinal hemorrhages in a child with nonspecific symptoms can be helpful in suspecting SBS. The retinal bleedings are often superficial, but multilayered and deep bleedings strongly

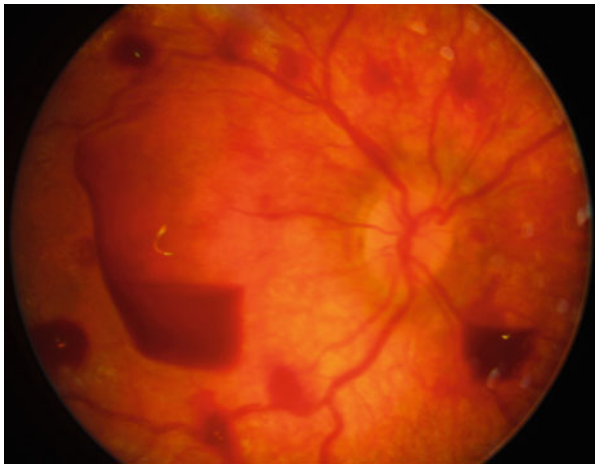

Fig. 5.10 Retinal hemorrhages seen in non-accidental injury

correlate to SBS, and severe hemorrhages were reported to be associated with severe injury such as increased mortality, subdural hemorrhage, and neurologic injury in several studies.

Differential diagnosis of retinal hemorrhage included hemorrhages seen in 30 % of normal newborns born by vaginal delivery infectious retinitis, septic emboli, retinopathy of prematurity, and coagulopathies. With the exception of birth trauma, retinal hemorrhages in the other conditions tend to be few and localized, whereas retinal hemorrhages in SBS are severe and widespread to the periphery. Bleedings after normal birth or birth trauma are resorbed most often within 1–2 weeks. Retinal bleedings are extremely rare in victims of severe head traffic accidents despite skull fractures and/or brain contusions, or bleedings due to direct trauma (0–10 %) are rarely seen and are small and not usually multilayered. Minor falls and blows, for example, to fall off the bed, seizures, vomiting, and prolonged coughing do not cause the type of retinal hemorrhages seen in SBS. The incidence in resuscitation/chest compressions is also reported very low and limited in severity and extent.

The pathogenesis of the ocular findings is the same as that which causes the intracerebral hemorrhage, with acceleration-deceleration forces creating traction on the retina and retinal vessels resulting in rupture and hemorrhage through movement of the vitreous body.

Bechtel and coworkers compared inflicted and accidental head injury and found retinal hemorrhage was more common in the inflicted category, approximately almost 60 % in inflicted cases versus 10 % seen in accidental cases. Retinal hemorrhages in inflicted cases were also more likely to be bilateral and extend to the periphery of the retina. The incidence of brain damage in abused children is reported to be between 25/100 and 45/100 in several population-based studies from North Carolina, Great Britain, and Europe.

Examination of the retina as well as neuroimaging is important for diagnosis of SBS as they often lack other external signs of child abuse although bruises may exist. It is of great importance for the pediatric ophthalmologist to communicate the fact that retinal bleedings are found. If subnormal bleedings and brain edema are seen in combination with retinal bleedings, there are probably few other diagnoses than SBS to be suspected if other major trauma is excluded. Examination should be performed the same day or the next by an experienced pediatric ophthalmologist and after dilation of the pupil. RetCam photographs or other photographs should preferably be taken. Otherwise, the findings should be documented in a detailed way. The pupil reactions should be tested, as trauma to the optic nerve or brainstem trauma will cause sluggish or nonreactive pupils. Posterior visual pathway damage and/or brain damage may lead to decreased visual responsiveness. The majority of bleedings will be resorbed within 4 weeks. Bleedings in the macula can cause visual impairment due to retinal damage, but damage to the visual cortex or posterior visual pathways is the major cause of visual impairment in these children with 65 % of surviving children reported to have visual impairment.

5.2 Management of Acute Pediatric Ophthalmological Problems

5.2.1 Assessment of a Child with Acute Visual Disturbance

A systematic approach to the assessment to a child who presents with disturbance of vision is imperative to determine if this is a sudden discovery of a benign refractive condition or incidental finding of a potentially lethal neurologic disorder. Directed questioning of the parent and child can help narrow the diagnostic possibilities, and specific findings on the ocular examination will help guide whether the child needs further neurologic diagnostic evaluation such as neuroimaging or whether the child simply needs to be seen by an ophthalmologist (see Table 5.1).

5.2.1.1 Four Most Essential Questions

There are four primary questions that will help differentiate further diagnostic and therapeutic pathways (Table 5.1). The first branch point is as follows: how was the vision loss discovered? Was this found during a routine examination in the pediatrician's office or at a school screening examination, or was it discovered because the child complained of blurred vision? Usually when a child complains of blurred vision, it is most often bilateral or determined by behavioral signs of poor vision. The second branch point is as follows: is the vision loss unilateral or bilateral? Unilateral vision loss usually is undetected by the child who uses their better seeing eye and ignores the poor vision in the bad eye. Sudden onset of poor vision in both eyes is always noted by older children. The third branch point in the evaluation of

Table 5.1 Child with vision loss: what to ask

Question	Answer	What it means
1. Unilateral or bilateral?	Unilateral	Refractive error, pathology in eye or optic nerve, amblyopia due to strabismus or anisometropia
	Bilateral	Refractive error, symmetric disease (inflammatory, degenerative), or chiasmal/cerebral
2. Acute or chronic?	Acute	Inflammatory/postviral/traumatic/demyelinating
	Chronic	Refractive error/degenerative/compressive/congenital
3. How discovered	Sudden discovery	Can indicate long-standing process
	Sudden onset	Usually accompanied by change in behavior or function, functional visual loss
4. Associated signs or symptoms	Neurologic	Demyelinating/degenerative/compressive/infectious
	Systemic	Metabolic/inflammatory/neoplastic
5. Family history of vision loss	Yes	Hereditary/neurometabolic/neurocutaneous/hereditary optic atrophy or neuropathy/retinitis pigmentosa
	No	Inflammatory/compressive/degenerative/demyelinating

Table 5.2 Vision loss: what to check?

What to check	Result	What does it mean/what to do next
Visual acuity at distance	Poor	Check with pinhole
Visual acuity with pinhole	Still poor	Check at near
	Better/normal	Probable refractive error—check pupil response
Visual acuity at near	Still poor	Check pupils
	Normal	Probably not pathologic—send to ophthalmology
Check pupil	Brisk/symmetric/no afferent pupil defect	Not demyelinating or acutely compressive
	Sluggish/asymmetric afferent defect present	Demyelinating/compressive/ congenitally anomalous
Check visual field	Full with no constriction or hemianopia	Unlikely chiasmal or cortical process
	Hemianopia	Chiasmal/cerebral—get MRI
	Severely constricted or tubular	Consider retinal disease or factitious
Direct ophthalmoscopy	No view	Cataract or vitreous opacification—ophthalmological consult
	Papilledema	Consider increase ICP—MRI/LP with opening pressure
	Optic atrophy	Consider compressive lesion—MRI and ophthalmology consult

vision losses is as follows: are there associated ocular visual signs or symptoms? The presence of cranial nerve findings, abnormal behaving pupil, or eye movement abnormality greatly increases the risk that vision loss is due to a neurologic abnormality and not simply refractive error. Finally, associated physical neurologic signs and symptoms will indicate further diagnostic evaluation by the practitioner to rule out potentially lethal conditions (Tables 5.2 and 5.3).

The causes of vision loss can be divided into four main categories, refractive errors, disorders of the optic pathways, disorders of the eye, and amblyopia. Hysterical or functional visual loss must also be kept in mind as a not uncommon differential diagnosis.

5.2.1.2 Refractive Error

Refractive errors are the most common causes of vision loss in children. They may be bilateral or unilateral. The most common cause for a child who can't see at distance is due to myopia or astigmatism. These children will not see well at distance but will normally on a near card. The distance visual acuity will be improved by viewing an object through a pinhole. Hyperopia or "farsightedness" usually is not accompanied by vision loss unless there is asymmetry between the two eyes, which can lead to amblyopia (see below). When the ophthalmologist can refract a child to perfect vision, this indicates that there is no organic reason for the vision loss if the visual fields are normal.

Table 5.3 Dangerous causes of vision loss: when to scan and who to consult

Condition	Features	What to do
Retinoblastoma	Leukocoria, strabismus, red eye	Urgent ophtho consult, MRI brain
Papilledema	Headache, vomiting, sunsetting	MRI/MRV/LP with opening pressure
Chiasmal compression due to pituitary apoplexy	Panhypopituitarism	MRI/endo consult/ophtho consult/visual field
Optic neuropathy with transverse myelitis (Devic's)	Vision loss, weakness, respiratory depression	MRI/LP/NMO serology/ophtho consult/observation in ICU
Neoplastic compressive optic neuropathy	Slow vision loss, neurofibromatosis, optic atrophy	MRI/ophtho consult/visual field/endo evaluation
Occipital/cortical infarction/ischemia	Severe focal neurologic symptoms	MRI/ophtho consult/rheum eval/heme eval for hypercoag state
Optic nerve hypoplasia	Poor vision, nystagmus, hypoglycemia	MRI to r/o septo-optic dysplasia, endo consult, ophtho consult

5.2.1.3 Ocular Anomalies

Any organic process that interferes with the clear focus of an image onto the retina can lead to loss of vision. This can be secondary to opacification or irregularity of the surface of the cornea secondary to inflammatory infectious or congenital cornea disorders. These changes can be seen through the slit lamp or with magnification using the direct ophthalmoscope and the green +20 diopter lens included which is present in every direct ophthalmoscope and can be used for high magnification. Cataracts or opacification of the crystalline lens can be detected by abnormal red reflex when the eye is examined with the direct ophthalmoscope and can be confirmed through examination with the slit lamp. Opacification of the vitreous through hemorrhage or inflammation is also detected through an ophthalmoscopic examination in which the retina view will be obscured by the vitreous opacification. The disorders of the retina can be congenital such as congenital structural malformations, inherited retinal dystrophy, abnormal development of the retina secondary to albinism or aniridia, or acquired secondary to inflammation, infection, or trauma. Disorders of the optic nerve will be either congenital or acquired. Congenital anomalies such as optic nerve hypoplasia, if bilateral, will lead to nystagmus at two months of age. If unilateral, they will lead to strabismus and profound loss of vision, usually accompanied by strabismus within the first year of life. Acquired optic nerve dysfunction such as optic neuritis or papilledema can present with vision loss, either unilateral or bilateral, as described above.

5.2.1.4 Visual Pathway Disturbance

Since visual information from each eye has bilateral cortical representation, disorders of the optic pathways posterior to the chiasm will present with bilateral visual disturbance. Optic pathway gliomas can originate at the optic nerve anterior to the

chiasm but most often involve the chiasm and frequently have hypothalamic involvement with bilateral albeit asymmetric vision loss. Tumors of the cortex involving the temporal and parietal optic radiations can present with visual field dysfunction. Congenital structural anomalies of the cortex can lead to congenital hemianopia, which frequently presents with exotropia with the eye deviating outward into the hemianopic visual field. Premature infants or infants who suffer from hypoxic ischemic encephalopathy frequently present with vision impairment, which is often accompanied by poor vision, visual perceptual problems, for example, identifying faces or recognizing information in a crowded environment, as well as poor ocular motor function leading to apraxic eye movements, strabismus, and nystagmus.

5.2.1.5 Amblyopia

Amblyopia is a loss of vision due abnormal visual experience early in life resulting in the abnormal development of the cerebral cortex in the areas of the brain responsible for visual function [20]. Abnormal early visual experience may be secondary to visual deprivation such as congenital cataract, may be secondary to strabismus or misalignment to the eyes with secondary amblyopia, or may be due to anisometropia or asymmetrical refractive errors. Amblyopia can be reversed with early diagnosis in the first 5–6 years of life by correction of the underlying anisometropia, strabismus, or visual deprivation and patching therapy of the sound eye to stimulate vision development in the amblyopic eye. Visual deprivation such as cataract must be reversed within the first two few months of life, or amblyopia will be profound and irreversible.

5.2.2 Assessment of a Child with Strabismus

Strabismus, or misalignment of the eyes, is usually rapidly detected by the parent or caretaker who notices a change in appearance of the child, or it may be noticed by the child who may complain of diplopia or double vision. The neurologist must determine which children should be sent to ophthalmology for evaluation and which child needs prompt neuroimaging or diagnostic evaluation. Like the evaluation of acute visual loss, a systematic approach will help the clinician make the most appropriate and cost-effective decisions so that unnecessary expense and delay can be avoided (Table 5.4). Children with strabismus due to new onset cranial nerve paresis or those with associated neurologic symptoms or findings will most likely require neuroimaging, while those without can usually be evaluated by ophthalmology prior to imaging.

Table 5.4 Sudden-onset strabismus: what to consider and what to do

Condition	Etiology	Features	DDX	Workup
Esotropia	6th Nerve palsy	Abduction deficit/large angle esotropia/ diplopia	Traumatic/postviral/pontine glioma/ Gradenigo's/meningioma/increased ICP/infiltrative/leukemia/Lyme	Acute MRI/consider LP/CBC/ Lyme/ophthalmology consult
	Duane's syndrome	Straight eyes but large abduction deficit, no diplopia, enophthalmos on attempted adduction	CN 6 palsy, accommodative esotropia	Ophthalmology consult, hearing test, no MRI
	Accommodative esotropia	No abduction deficit, variable esotropia, no diplopia, amblyopia common	6th nerve paresis	Ophthalmology consult
Exotropia	3rd nerve palsy	Ptosis/pupil enlarged and not reactive/ horizontal and vertical limitation of movement	Aneurysm/neoplasm, NF2/meningitis	Acute MRI/MRA/ophtho consult
	Intermittent exotropia	Intermittent deviation worse when tired, ill, no diplopia, squint in sunlight, fuse at near fixation		Ophthalmology consult
Hypertropia	4th nerve paresis	Congenital—long-standing head tilt Acquired—diplopia	Trauma? Skew deviation	Ophthalmology consult
	Skew deviation	Cerebellar/brainstem disease/head tilt and nystagmus		MRI/ophtho consult
	Myasthenia gravis	Variable horizontal and vertical strabismus/may or may not have ptosis		Ophthalmology consult/Tensilon test/ACR antibody testing/ Mestinon trial
Nystagmus	Congenital	Present since two months	Congenital motor nystagmus (benign)/ ocular diseases like Leber's amaurosis/aniridia/albinism/cone dystrophy/optic nerve hypoplasia, chorioretinal coloboma	Ophthalmology consult
			If opsoclonus rule out—neuroblastoma	Consider neuroblastoma
	Acquired	Onset after 2 months	Cerebellar/brainstem neoplasm or degeneration, spasmus nutans	MRI and ophthalmology consult

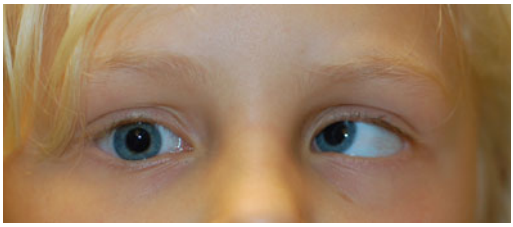

Fig 5.11 Esotropia in the left eye

5.2.2.1 Esotropia

Esotropia (Fig. 5.11) in children is most often due to refractive error associated with hyperopia, a condition called accommodative esotropia. This condition usually has an onset as an intermittent deviation at age 2–4 years, which is at first intermittent then becomes constant. Reports of diplopia are not common as children rapidly suppress the image from the turned eye which then leads to amblyopia. Diagnosis is made by ophthalmology, and treatment is with spectacles. Acute comitant/incomitant esotropia with an onset after 5 years of age, diplopia, and neurologic signs especially with unilateral or bilateral abducens palsy and nystagmus should have prompt neuroimaging.

Esotropia due to cranial nerve VI paresis can be due to hydrocephalus, meningitis, trauma, pontine neoplasm, demyelinating or postviral, and conditions that almost always manifest additional neurologic symptoms which will require neuroimaging and possible lumbar puncture. It is important not to confuse Duane's syndrome with abducens paresis, as Duane's syndrome is a congenital mis-wiring of the cranial nerve that does not need imaging or additional neurologic evaluation. In Duane's syndrome, there is an inability to abduct the eye, but there will be minimal esotropia when the child is looking forward, while in an abducens paresis, there will always be esotropia associated with the abduction deficit, and there may be narrowing of the eye fissure.

5.2.2.2 Exotropia

The most common cause of exodeviation in children is intermittent exotropia, a condition where the eye will deviate outward for variable periods of time when the child is tired and fatigued during distance fixations. Eye movements are full and complaints of double vision are rare. In contrast, exotropia due to CN III paresis will always be accompanied by ptosis and often involve the pupil as well, and neuroimaging is mandatory.

5.2.2.3 Hyperdeviation

The most common cause of hyperdeviation in children is congenital CN IV paresis, which will present with anomalous head position, and diplopia is uncommon, being reported usually only in acquired cases. Acquired trochlear paresis is rare unless

caused by trauma. Other causes of vertical deviation include posterior fossa and cerebellar disease which will always be accompanied by other neurologic findings. Myasthenia gravis should always be considered in children with acquired strabismus that is both vertical and horizontal and variable in nature, especially when accompanied by ptosis.

5.2.2.4 Nystagmus

Nystagmus is rarely seen prior to 2 months of age, and parents often have difficulty remembering when the onset began. It results from either poor sensory input or abnormal motor output. Congenital abnormalities of the eye such as retinal coloboma, optic nerve hypoplasia, retinopathy of prematurity, albinism and aniridia, and congenital photoreceptor abnormalities will all lead to nystagmus during infancy [21]. Bilateral visual deprivation from congenital cataracts will also result in nystagmus. Central cerebral causes of nystagmus are much less frequent, so all infants with nystagmus should be seen by ophthalmology prior to any neuroimaging.

5.3 Conclusion

All children with decreased vision or abnormal eye movements should be seen by an ophthalmologist promptly, as the ophthalmologist can often localize underlying disease processes, guiding further diagnostic testing and avoiding unnecessary expense. By careful directed questioning, the primary care provider can help determine if the child with new visual or ocular signs or symptoms is manifesting sudden discovery of long-standing problems or truly sudden onset of new neurologic processes which require prompt evaluation and treatment.

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Chapter 6
Dizziness and Vertigo

Daune L. MacGregor and Maja Steinlin

Abstract Dizziness is not an uncommon presentation for acute pediatric care and accounts for 4–5 % of assessments in emergency departments and walk-in clinics. The cause may be part of an acute medical condition but is formally approached as vertigo, presyncope, or light-headedness.

As presenting symptoms, dizziness and vertigo can represent the nonserious to serious conditions—a focused medical history with attention to associated aural, ocular, and neurological symptoms is important. Bedside testing for vestibular function with appropriate laboratory investigations and diagnostic imaging will lead to accurate diagnosis and management.

Keywords Dizziness • Vertigo • Presyncope • Light-headedness

6.1 Introduction

Although dizziness and vertigo are felt to be relatively uncommon in presentation for acute pediatric management, either in an office setting or an emergency room, epidemiology studies suggest that dizziness is not uncommon. These symptoms are alarming for parents however, and they then seek urgent medical attention for their children [1].

A recently published study from the United Kingdom [2] reported that 400 children seen for a balance assessment (as part of a larger epidemiology study of almost 7,000 children) had rotary vertigo with a prevalence of 5.7 %. Over half had to limit activities because of feeling unwell at the time of these episodes. An earlier study

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from Finland found 8 % of children screened by questionnaire had vertigo with 23 % reporting activity limitation [3].

There are no studies that review pediatric experience for acute care of dizziness or vertigo; however, children are included in some studies [4, 5] which suggest that dizziness as a symptom accounts for 4 % of emergency visits and 5 % of assessments in a walk-in clinic setting often without resolution of the cause or diagnosis and with considerable expenditure of resources.

Over a 10-year period, a combination of vertigo and/or dizziness represented 2.5 % of all emergency visits with a significant increasing trend [6] and increasing utilization of diagnostic tests including CT and MRI scanning.

6.2 Definitions

Dizziness as a presenting complaint is considered to imply a sense of disorientation [7] or varying sensations including light-headedness, unsteadiness, dizziness [8], or presyncopal symptoms including faintness. Dizziness can also occur as part of the presentation of an acute medical condition in children (fever, vomiting, and dehydration) or have a psychosomatic origin including depression, anxiety, and exhaustion. The formal classification of dizziness includes vertigo, presyncopal disequilibrium, and light-headedness.

Children, particularly small toddlers who develop vertiginous or dizziness symptoms, may lack the language sophistication—either capacity or vocabulary—to describe their symptoms clearly. The young child may use "playground synonyms" such as spinning, swinging, sliding, or like a "merry-go-round" or "roundabout." [7] It is understood that although many of the vestibular diseases well recognized in adults can occur in children, there is a much different frequency [9]. Ocular or vision system problems (especially vergence and refractory problems) may also become symptomatic by dizziness in toddlers and children as there are developmental changes in the vision system and may present with dizziness or vertigo.

Children can present with a variety of problems that represent pathophysiology of the labyrinth, brain stem, or cerebellum which can be either acute or chronic. These may include balance difficulties, frequent falls, episodic problems with walking, clumsiness, strange behavior, fear or panic, or abnormal "strange" eye movements [3].

It has been stated that "although all vertigo is dizziness, not all dizziness is vertigo" [10]. Vertigo is defined as an illusion of movement [7]—most frequently sensation of rotation or less often linear displacement or tilt. Vertigo can represent peripheral vestibular (labyrinth) pathology but is also symptomatic of other central neurological disorders including seizures or migraines. There may be accompanying nausea, vomiting, pallor, and sweating—but no loss of consciousness. Vertigo may be due to either peripheral (more commonly) or central lesions of the vestibular

system [11]. Peripheral disorders are accompanied by nystagmus and often with symptoms involving the cochlear system (hearing loss and tinnitus) and are typically detected by head impulse tests. Central vestibular problems are searched by ocular motor testing and a careful neurological examination.

As presenting symptoms in the emergency department, dizziness and vertigo represent a number of benign to serious disorders and are difficult to differentiate. In children, knowledge of the most common conditions presenting in this fashion with thoughtful conservative use of diagnostic testing and screening should allow for accurate emergency department diagnosis and initial management planning. It has been suggested [4] that the type of dizziness can be of assistance in analysis of the diagnosis ("vertigo is vestibular, presyncope is cardiovascular, disequilibrium is neurological"). However, the variability and overlap [12] of the symptoms can create diagnostic difficulties. An alternative approach in adults is based on timing (duration) and triggers [4]. Brief recurrent episodes of dizziness are suggested as representing a set of differential diagnoses which can include benign paroxysmal positional vertigo. A single acute prolonged period of vertigo is considered more in keeping with vestibular neuritis or cerebellar stroke. These elements (duration and triggers) have been found to be clearly reliable and consistently reported [4] in patients with dizziness.

6.3 Approach

A focused medical history [13] seeking the key symptom of a sensation of motion that is either rotatory or linear will act in the determination of the vestibular causes of dizziness and vertigo. An abnormal sensation of motion points to vertigo, and a difficulty or impossibility to maintain upright position is more likely to be a problem of disequilibrium. Exact time course of the sensation is important for first differential approach: An acute single episode is most likely an infectious or parainfectious etiology (labyrinthitis, vestibular neuritis), a recurrent problem is most likely of migrainous etiology, and a chronic vertigo is most commonly of somatoform etiology.

Associated aural, ocular, and neurological symptoms [7] include:

- Sensation of fullness or pressure
- Objective evidence of hearing loss (maybe fluctuant) as a cochlear problem pointing to peripheral etiology
- Tinnitus (or ringing)—continuous, intermittent, or pulsatile as a cochlear problem pointing to peripheral etiology
- Headache pointing to a migrainous etiology (about 40 % of vertigo in children)
- Visual changes pointing to oculomotor problems and thus more likely to be of central etiology
- Seizures or loss of consciousness pointing to a central etiology

6.4 Bedside Clinical Evaluation for Acute Vertigo and Dizziness

The following elements are helpful in diagnosis:

- General findings including abnormal head posture—tilt or turn [14]—or abnormalities of the eyelids (ptosis) or pupils. These signs point most likely to an oculomotor (central) problem.
- Neurological evaluation of the cranial nerves and cerebellar function including ocular examination with evaluation of range of eye movement, vergence, and smooth pursuit (if saccadic or jerk-like movement indicates a dysfunction of the optokinetic system and thus central vestibular cerebellar involvement).
- Examination of the auditory canal and tympanic membranes to search for middle ear problems as otitis media or tympanic membrane perforation.
- Screening testing for hearing for middle ear problems but even more important for the differential diagnosis of Meniere's disease.

6.4.1 Fistula Test

Using a pneumatic otoscope or tragus (in a cooperative child), the child is instructed to look straight ahead while continuous positive and then negative pressure is applied; with a perilymphatic fistula, the eyes may drift slowly away from the ear with positive pressure and back toward the ear with negative pressure [7].

6.4.2 Assessment for Spontaneous or Induced Nystagmus

End point or physiological nystagmus is seen in normal children at a 40° deviation of the eyes [7]. As peripheral and vestibular nystagmus might be suppressed by fixation, an examination with Frenzel goggles is important. Horizontal and torsional nystagmus is typical for peripheral problems, but vertical nystagmus is almost always a sign of a central problem.

6.4.3 Balance Testing

The Romberg test (standing in a still position with feet together in parallel, arms stretched to the side, eyes closed) evaluates proprioceptive function.

The Unterberger–Fukuda test is performed with arms out straight at shoulder height with vision excluded; the child is instructed to maintain original position and

march in place for a total of 50 marching steps. A patient with a chronic peripheral vestibular lesion will march slowly toward the side of the lesion.

6.4.4 *Vestibular–Ocular Reflex Tests*

These tests may be difficult to interpret except for the experienced neurologist or otolaryngologist, but their routine use is encouraged, in particular the head thrust and rotational test. The simplest bedside test is considered to be the head thrust or turn. The head thrust or Halmagyi [15] maneuver is done as the head is turned by the examiner to the right and left with the instruction to the patient to fixate on the examiner's nose. If the vestibulo-ocular reflex function is normal, the eyes stay on the target, and the image on the retina remains stable. The test is positive if the eyes move together with the head and a reset saccade is activated to keep the eyes on target (the corrective saccade toward the affected side). This test is difficult to interpret if there is an extraocular movement problem or dysconjugate gaze (central problem).

Another easy-to-perform test is the rotational test to determine the presence or absence of vestibular function [16]: The child sits on the lap of the mother during the rotation of a chair (about 180 degrees/second for 5–10 rotations). After a quick stop, the investigator looks for provoked optokinetic nystagmus: The quick phase beats opposite to the direction of rotation. Duration of nystagmus should be symmetrical for left and right rotations.

Other tests include head heave and head shaking. Head shaking produces nystagmus away from the side of unilateral vestibular loss [16]. Other clinical tests including vibration-induced nystagmus test can be useful but are usually performed by otolaryngologist. These tests are felt to be as effective as caloric testing for examination of vestibular function loss (vestibular neuritis) [17, 18].

Valsalva-induced nystagmus can be assessed clinically at the bedside either with closed nostrils (pinch nose and blow) or closed glottis (and strain). The increase of pressure in thorax and middle ear is transmitted to the inner ear, thus pointing to problems of middle ear (cholesteatoma, perilymph fistula) or vestibular dysfunction. This test is positive if symptoms of dizziness or vertigo develop and nystagmus beating toward the affected ear is seen.

6.4.5 *Testing for Benign Paroxysmal Positional Vertigo [19]*

The Dix–Hallpike maneuver can be used during neurological examination to produce paroxysmal positional nystagmus. The child is placed in a sitting position midway on a flat examining table and instructed to look ahead at all times [7]. The examiner first turns the head to the side, and then the patient is quickly placed backward such that the head is over the end of the table. If a patient has positional

vertigo, there is horizontal rotary nystagmus with the fast phase toward the downward ear. There may be a latency of 1 or 2 s to onset of nystagmus which that lasts for 10–12 s. The patient will have a sensation of rotational vertigo. The Dix–Hallpike maneuver determines the side of the effected ear depending on intensity of subjective symptoms and nystagmus.

This maneuver should not be performed if there is high clinical suspicion for paroxysmal positional vertigo. In those circumstances, ENT assistance, if available, should be used to perform particle repositioning maneuvers (as should the Epley or Semont maneuver). The Epley maneuver is used for the management of horizontal canal partial repositioning, and Semont maneuver will reposition in the anterior or posterior canal. If the Dix–Hallpike maneuver fails, then head roll tests should be performed [20].

In the bow-and-lean test, bowing (bending the neck to greater than 90°) or leaning (the head is moved backward to 45°) is used to determine the direction of nystagmus. The patient remains in a seated posture [20] (see key point 1).

6.4.6 Laboratory Investigations

For patients seen in the emergency department with an acute presentation and depending on the findings of the clinical bedside evaluation, laboratory testing can help for differential diagnosis. Search for acute infection (as otitis media) by complete blood count and CRP or viral testing for triggering recent viral infections (herpes, Epstein–Barr, influenza and parainfluenza, cytomegalovirus, and adenovirus). In cases of suspicion of a central problem or neurocardiac syncope, checking on hemoglobin, electrolytes, and glucose might be helpful.

Audiology (pure tone and impedance) and neurological evaluation (auditory brain stem responses) are usually not available on an emergency basis but may be required after the initial visit with ENT referral for vestibular assessment [9, 21].

If epilepsy seizures are considered as part of the differential diagnosis, then arrangements for follow-up electroencephalographic studies and neurological consultation will be required.

If neurocardiogenic syncope is considered, Schellong test and maybe ECG might be indicated.

6.4.7 Diagnostic Imaging

The value of imaging studies for assessment of vertigo or dizziness was reviewed retrospectively [22] in 87 children presenting over a 1-year period. The studies done (CT and MRI) were not categorized by origin of request. It was concluded that if vertigo is the only symptom, then imaging studies are unlikely to be helpful.

Imaging is indicated for children who show in clinical investigations symptoms or signs of a central pathology as vertical nystagmus, dysconjugate gaze, disturbed smooth pursuit, neurological deficits, persisting headache, or head trauma.

First choice of imaging is considered to be MRI (which should include MRA studies if there is a possibility of an arterial dissection) unless a skull fracture is suspected (see key point 2).

6.5 Diagnosis and Differential Diagnoses of Vertigo and Dizziness

6.5.1 Common Disorders Presenting to the Emergency Department

Acute-onset paroxysmal vertigo can be approached based on the presence or absence of hearing loss, assessment of the symptom as being continuous or remitting, and whether or not there are neurological abnormalities. There are many causes of vertigo and dizziness which may result in children being brought for emergency assessment. The differential diagnosis of acute-onset vertigo and dizziness include:

- Otitis media and middle ear effusion
- Migraine or migraine equivalents
  - Benign paroxysmal vertigo of infancy
  - Basilar migraine—older children
- Posttraumatic vertigo
  - Labyrinthine concussion
  - Temporal bone fracture, temporal lobe diffuse axonal injury, or perilymphatic fistula
- Labyrinthitis
  - Serous
  - Suppurative
- Vestibular neuritis
- Cerebellar and brain stem tumors
- Brain stem stroke or posterior circulation arterial dissection
- Behavioral or psychogenetic
- Benign positional vertigo (BPV)
- Meniere's disease
- Demyelinating disorders
  - Acute disseminated encephalomyelitis (ADEM)
  - Multiple sclerosis (MS)

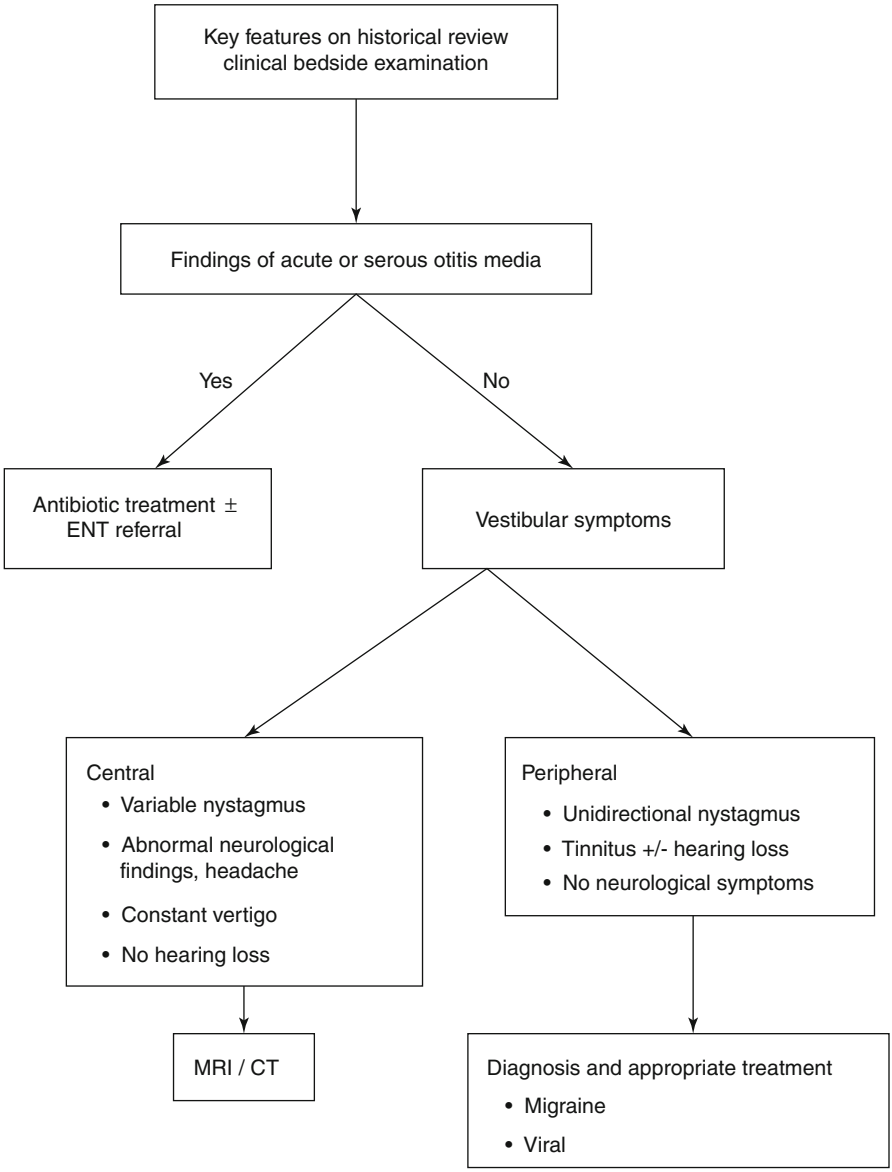

Fig. 6.1 Approach to vertigo and dizziness in the emergency department. *ENT* ears, nose, and throat specialist, *MRI* magnetic resonance imaging, *CT* computed tomography

A simple algorithm for management based on the clinical history and bedside assessment allows for diagnosis and immediately treatable disorders (Fig. 6.1) and evaluation of central or peripheral origin of vestibular symptoms.

6.5.2 Peripheral Vestibular Disorders

6.5.2.1 Otitis Media

There are commonly other diagnostic symptoms with acute otitis media (pain, discharge, or hearing loss) [11]. Otitis media is considered by some authors [23] as the most frequent cause of vestibular disorder in children. Secretory or serous otitis media results from a middle ear infusion and produces disequilibrium rather than true vertigo.

6.5.2.2 Labyrinthitis

There are several subtypes of labyrinthitis (serous and suppurative) which may present with vertigo which maybe severe and associated with sudden sensorineural hearing loss. There is often a history of preceding infection. The child is most comfortable lying on the unaffected side [7]. Treatment is directed at the source of the infection.

6.5.2.3 Vestibular Neuritis

This disorder usually occurring primarily in adolescents follows a respiratory infection and has sudden onset with vomiting, nystagmus, and vertigo without tinnitus or hearing loss. The vertigo is made worse by head movement. There are no signs of central pathology in the clinical examination, especially no signs of ataxia (tested in lying in bed, as standing might be impossible due to severe vertigo). It is usually self-limited (over a 2- to 3-week period).

The etiology is felt to be multifactorial but can include herpes simplex (type 1), cytomegalovirus, Epstein–Barr virus, and enterovirus. Management is with short-term high-dose steroid therapy (methylprednisolone) followed by slow discontinuation over 2–3 weeks [24, 25]. Long-term recovery of vestibular function is thought to improve by this treatment.

Meniere's disease, in children more often a secondary problem to a viral infection, has to be differentiated from vestibular neuritis [16]. The attacks last shorter (minutes to hours) and are accompanied by cochlear symptoms like hearing loss, tinnitus, and pressure in the ear.

6.5.2.4 Vestibular Paroxysmia

Children present with attacks of vertigo lasting for seconds, provoked by head movements and sometimes hyperventilation. Pathophysiology is thought to be a

nerve vessel compression of the vestibulocochlear nerve at the entry zone to the brain stem. Low-dose treatment with carbamazepine is also diagnostic [16].

6.5.2.5 Benign Paroxysmal Positional Vertigo

BPPV is rare in children but is considered to have causal relationship to head trauma [23] or vestibular neuronitis in some cases. It is provoked by positional changes and lasts for seconds only. A specific treatment is by the use of particle repositioning maneuver (see above).

6.5.3 Central Vestibular Disorders

6.5.3.1 Migraine and Migraine Variants

Benign paroxysmal vertigo (BPV) as a migraine variant or equivalent (see also Chap. 12) can present as early as 1–2 years of age with extreme unsteadiness, anxiety, and fearfulness [26]. Nystagmus may or may not be present. The child is fully conscious. There is spontaneous resolution after minutes to hours. Migraine may subsequently develop later in life. Drug treatment is rarely necessary; in case of frequent recurrent episodes, prophylactic treatment with flunarizine might be considered [16].

Basilar artery migraine has a stereotypic presentation with brain stem and cerebellar dysfunction which can include vertigo and is associated with other clinical features of ataxia, tinnitus, and dysarthria followed by a typical pounding or pulsatile headache. Some authors will consider any headache with dizziness in the spectrum of basilar migraine [27], but formal criteria require bulbar and bilateral sensory motor symptoms. Some authors separate vestibular migraine (dizziness and vertigo without neurological brain stem symptoms) from basilar migraine [28]. In one study [24], migraine with vertigo was the most frequent diagnosis with peripheral disorders less common in children seen in ambulatory clinics.

6.5.3.2 Epileptic Seizures

Vertigo may be an aura symptom proceeding a generalized seizure [7] or present as an ictal feature of complex partial epilepsy. There is a very rare form of vestibulogenic seizures—reflex sensory epilepsy induced by spinning.

Epileptic nystagmus and vertigo have been described in children in response to topiramate therapy [29].

6.5.3.3 Neurocardiogenic Syncope

Syncope (a transit self-limited loss of consciousness with falling) and presyncope (dizziness, sweating, weakness, and headache) are common clinical problems requiring emergency room assessment. Approximately 15–25 % of all children will experience a syncopal episode [30, 31].The cause is often speculative, but triggers include a warm environment, prolonged standing, or pain. Children and adolescents with neurocardiogenic syncope may have chronic autonomic differences [30].

Adolescents with orthostatic hypotension syncope (occurring with upright positioning and relief by recumbence) have bradycardia and peripheral vasodilatation with thoracic hypovolemia [31].

Postural orthostatic tachycardia syndrome (POTS) is seen in previously healthy adolescents with extreme debilitating fatigue, dizziness, blurred vision, and cognitive problems [32]. The primary form is often idiopathic and appears to be the result of the lack of peripheral vasoconstriction in response to orthostatic stress and may have rapid onset after an acute febrile illness or trauma. Improvement is provided by the prescription of midodrine (see key point 3).

6.6 Acute Management

Treatment of dizziness or vertigo in the emergency department depends on the degree of discomfort experienced by the child and whether or not there has been the determination of the underlying pathology. Acute vertigo can be treated symptomatically; then pending diagnostic workup, appropriate referrals can be made. Most children with acute vertigo recover spontaneously [7] over a period of several weeks to months.

It may be necessary to arrange follow-up ENT evaluation for detailed vestibular assessment [33]. Symptomatic treatment includes rectal or intramuscular antiemetics or vestibular sedation (meclizine, dimenhydrinate, promethazine, diazepam).

Key Points

1. In children with normal otoscopic findings, vertigo is most commonly caused by migraine and migraine equivalents: benign paroxysmal vertigo of children (BPV) [1].
2. If vertigo is the only symptom and there is no history of head trauma, imaging studies (CT or MRI) will not aid diagnostic assessment in the emergency department [3].
3. All patients with vertigo or dizziness have a Dix–Hallpike maneuver performed to assess for benign paroxysmal positional vertigo (BPPV) before referral for vestibular assessment [33].

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Chapter 7
Acute Changes of Behavior and Memory

Per-Anders Rydelius

Abstract Acute changes of brain physiology present with both mental and neurological symptoms. It is fruitful to assess them separately in the categories symptoms of the mind and symptoms of the brain to have a baseline for treatment. The clinician must remember that a child's mind responsible for his/her memory and cognitive executive functions matures gradually, at an individual speed, and reaches full maturity in young adulthood. Girls are ahead of boys until adolescence. Chronological age is not always a useful measure when assessing growing children. Cognitive deficits and problematic behavior are easily mistaken as expressions of psychopathology, although they may be normal according to the child's mental age. A 10-year-old boy with an IQ of 75 has the mental age of 7.5 years and should be assessed as such to avoid mistakes in the evaluation. The pediatric disciplines and child and adolescent psychiatry are closely related. Disorders such as anxiety, dissociative disorders, apathy, somatic symptoms without an obvious somatic disorder, and conversion syndromes have somatic/neurological components of an intrinsic kind which often make the patients seek help at pediatric departments. As children and parents have identified somatic symptoms as a problem and in order to avoid iatrogenic problems, the pediatrician needs to consider the best way to refer to a child and adolescent psychiatric unit when a psychogenic explanation seems to be the cause.

Keywords Mind • Brain • Mental symptoms • Emotional stress • Dysfunctional families • Chronological vs. mental age

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7.1 Introduction

Acute changes of brain physiology may give both mental and neurological symptoms of different kinds. Such symptoms are seen in the emergency room, during initial treatment of acute brain disorders, and later on at follow-ups of patients. When examining children and adolescents, it is helpful to use a dichotomized thinking. Although mental symptoms, or symptoms of the mind and neurological symptoms, or symptoms of the brain, are truly integrated, it is fruitful to assess them separately to have a baseline for future follow-ups.

In clinical practice, it is important to keep in mind that there is a great variance of normal growth and maturation including sex differences. There is a tendency by parents and professionals (doctors, teachers, psychologists, etc.) to use chronological age as a measure when assessing children's abilities, forgetting that irrespective of chronological age the mental age must be evaluated on an individual basis.

Over time, during growth and maturation, the body, the brain, the behavior, and academic achievement may change considerably both within the same person and when comparing groups of same chronological age.

Results from modern [1–3] as well as old studies [4, 5] have shown that the brain is growing from fetal life until the age of 25 years when prefrontal cortex reaches maturity. Results also show sex differences when comparing growth of girls' vs. boys' brains. Keep in mind that girls until the age of around 16–17 years are more mentally mature compared to boys. In average, girls are approximately 1 to 2 years ahead of boys of the same chronological age up till around 17 years.

Similarly, results from modern [6–8] and old studies [9–13] have shown that behavior, IQ, and academic achievements can change. IQ may increase by some 15 IQ points until late adolescence and in individual cases even more.

Both the pediatrician and the child and adolescent psychiatrist need to use a developmental perspective when assessing children and youth. The border area between normal behavior and psychopathologic behavior is rather broad. Symptoms of hyperactivity are traditionally looked upon as symptoms of brain damage/brain dysfunction but are also found among average normal children, in children living in dysfunctional families, and in children suffering from PTSD.

Chronological age per se is not a good measure to rely upon when assessing and talking to children and adolescents. Much better is to use the concept of mental age/developmental age in order to adjust to the individual's mental competence. IQ tests measure the relationship between mental age and chronological age. For example, a 10-year-old boy with an IQ of 75 has the mental age of 7.5 years, which means that he should be met and assessed according to his *mental age*. Mistakes and expectations based on an individual's chronological age are avoided if this is taken into consideration in the assessment.

7.1.1 The Mind

To understand mental symptoms it is essential to be familiar with some concepts related to the mind. A pragmatic definition of a person's mind is awareness, i.e., his/her unique capacity to receive information by the sensory system and to process incoming information through thinking and reasoning to make decisions, to communicate, and to take actions. Awareness per se is also defined as "the ability to be conscious of events, objects, or sensory patterns." The mind attributes mainly to the higher cognitive intellectual functions of humans rather than to emotions and feelings. As a metaphor you may say that the brain is the computer of the mind receiving, organizing, processing, and storing incoming data as well as managing the output.

Awareness is a concept closely linked to consciousness. When assessing patients, consciousness can from a practical point of view be seen as a "continuum of states ranging from full alertness and comprehension to disorientation, delirium, loss of meaningful communication, and finally loss of movement in response to painful stimuli."

The mind of a child as well as his/her brain develops from birth to adult life. Therefore, it is essential to realize that a more mature mind capable to deal with existentially reasoning usually does not exist before prepuberty/puberty.

The concepts related to the mind—perception, attention, concentration, impulsivity, and memory—are used when assessing consciousness and other aspects of the mind to understand psychopathology.

Perception refers to the mind's ability to receive and take care of the sensory input.

Attention has often been called the perception's helmsman, i.e., the mechanism steering the focus of perception to the element/subject/object/event, etc., which for the moment is interesting, important, and/or essential. Attention span refers to the number of different elements that can be handled simultaneously. The visual attention span in adulthood is approximately six or seven elements.

Concentration is the ability to focus attention on the same element over time. This ability differs between children. Some children are vigilant. They have the ability to maintain focus over a long time while other children have a weak ability to do so and are easily distracted by new stimuli. The ability to concentrate is also dependant on whether the child is tired. Average children who are tired from disturbed sleep often have problems with concentration.

Impulsivity is a personality trait similar to, but quite different from, being easily distracted. While being easily distracted refers to attention, impulsivity implies acting before thinking, i.e., refers to an individual's judgment and ability to foresee/evaluate the consequences of his actions.

Memory is an essential tool for the mind's processing of information, the thinking, and the problem-solving capacity. The memory consists of at least three components: short-term memory, long-term memory, and working memory. There are a

number of theories to understand the similarities and differences of the three aspects of memory. A pragmatic definition for clinical work is as follows.

Short-term memory means how much you can recall of what you just heard, saw, etc. In tests used to measure the short-memory span using words or digits, average adults usually remember 5–7 elements. Because of this the capacity of the short-term memory sets limits for new information to be stored.

Long-term memory means that information is stored for a longer time. If the information is not used, it will gradually fade away. The mechanisms explaining how information and memories are stored over time is not well known.

Working memory is a concept linked to perception, attention, and the executive processes behind thinking and problem solving. In a simple way the working memory can be looked upon as the mind's tool to compute actual information for reasoning, comprehension, etc.

The capacity to remember events is an important quality of the mind and the brain. There are theories to explain how this part of the memory works, but the mechanisms are still not fully understood. During infancy children may experience, and probably remember, both nontraumatic events and traumatic events but cannot tell about them. From around the age of 3 years, average children (the quality is depending on the development of their language) may recall and tell about past experiences [14]. In a Canadian study [15] of children who at ages 13–18 months, 20–25 months, and 26–34 months had experienced traumatic injuries, initial interviews were conducted followed by new interviews 6, 12, and 18 or 24 months later. The results showed that the youngest children demonstrated little long-term verbal recall, whereas a few children in the intermediate group, who could not narrate about past events at time of injury, could verbally recall the target events 18 months later. Most of the oldest children, who had narrative skills at time of injury, demonstrated good verbal recall 2 years later. Accuracy of recall was low for the youngest children, and although the majority of older children's recalled information was accurate, there were still many errors. A recent study [16] of injured children, between 2 and 13 years of age, followed over 2 years supports previous findings.

Children with intellectual disabilities seem to have a similar capacity to memorize events as average children, but as their stories usually do not have enough details, they are looked upon as unreliable [17]. However, as children with intellectual disabilities and verbal children with autism spectrum disorders usually have concrete thinking and behavior, the clinician should keep in mind that their narrative description of their memories can be adequate in relation to what happened.

There is a growing interest in how negative emotional events are memorized and what effects such memories may have on later perception and behavior. It appears that stress and negative emotional events, managed by the amygdala and hippocampus, may create fear and avoidant behavior when the person faces a similar event in the future [18, 19] and that sex differences may play a role in this effect of memory on behavior [20].

In summary it is essential for the pediatrician and the child and adolescent psychiatrists to remember that children and adolescents seen in the emergency room may present with symptoms of a disturbed brain and mind in the form of somatic symptoms, hallucinations, delusions, a change of consciousness, acute anxiety, aggressive acting out behavior, or symptoms due to intoxications, brain infections, brain trauma, brain tumors, etc.

7.2 Presenting Acute Symptoms, Diagnosis, and Differential Diagnosis

7.2.1 The Disturbed Brain

A disturbed physiology of the brain may result from different causes. It may follow from brain damage during pregnancy and delivery, from intoxication of legal and/or illegal drugs, brain infections, brain trauma, and brain tumors but may also be consequent to therapeutic efforts (i.e., chemotherapy, radiation to the CNS). When brain physiology is disturbed, the mind is impaired.

The consequences of a disturbed brain physiology include both neurological and mental/psychiatric symptoms. Delirium acutum illustrates the consequences of a severely disturbed brain for mind and awareness.

7.2.2 Delirium Acutum

A delirium is an acute brain disorder and a serious condition with mental and somatic symptoms. The mental symptoms derive from the patient's changed attention, perception, and state of consciousness. The changed attention means that he cannot focus on what is important for the moment; he cannot concentrate, is easily distracted, impulsive, and cannot control himself in a proper way. The changed perception means that he misinterprets what he sees around him. Illusions and hallucinations are common. True delusions may occur. Early on, the change of consciousness often presents as agitation with motor restlessness and as sleep disturbance. The disturbed perception and attention, together with the change of consciousness, result in disturbed memory and disturbed awareness. He does not recognize family members and cannot orientate himself and describe where he is, what day it is, etc. The mental symptoms of a delirium can only be properly described by a child mature enough to have a language and a mental capacity to describe himself, his family, and overall life situation. This means that among infants and preschool children, a delirium is best identified by associated neurological and somatic symptoms.

7.2.3 Neuroleptic Malignant Syndrome and Serotonin Syndrome

Patients prescribed neuroleptics and antidepressive medication may in rare situations develop a neuroleptic malignant syndrome (NMS) or a serotonin syndrome (SS) [21]. These are adverse life-threatening reactions to the prescribed drugs and may be seen in teenagers. The pathophysiologies behind these conditions are not known, and they present with a mix of mental and neurological/somatic symptoms. NMS usually presents as muscle rigidity, hyperthermia, mental status changes, and autonomic instability, while SS presents as mental status changes, autonomic nervous system disturbances, neurologic manifestations, and hyperthermia. As the conditions are serious and life threatening, they are true emergency cases and should be handled in cooperation between intensive care and psychiatry. See also Chap. 17 for motor system symptoms.

7.2.4 Intoxications

Schoolchildren and teenagers may abuse solutions (e.g., glue sniffing), alcohol, and illegal drugs of different kinds. Besides the simple effects of drunkenness, some of these drugs may give acute mental symptoms including hallucinations and aggressive behavior. These symptoms disappear gradually and usually need no specific treatment. In some cases the patient has terrifying hallucinations that may lead to impulsive suicidal acts, for which reason the patient needs protection.

A delirium may occur but is rare. However, methanol intoxication is a condition important for the clinician to be aware of because of its bad prognosis if untreated. It starts with an initial drunken state but after a symptom-free interval of 6–24 h; as the speed of metabolism slows, a serious condition develops. Methanol is oxidized to formaldehyde and formic acid. These metabolites induce metabolic acidosis and have severe toxic effects on the brain. Initial neurological visual disturbances develop (important to differentiate from illusions and hallucinations) followed by change of consciousness. Apathy and somnolence occur followed by motor restlessness, hyperventilation, coma, and eventually death.

7.2.5 Acquired Brain Injury

When the brain suffers acute damage, irrespective of cause, the acute symptoms are best explained by the increased intracranial pressure and possible local damage. The core symptoms are the somatic and neurological signs of the disorder causing the damage. In the emergency room the most important mental sign for the clinician to consider is the level of consciousness. When the child is suffering from a

life-threatening disorder the psychiatrist may play an important caring role supporting the family to avoid post-traumatic stress symptoms. See also Chap. 19.

7.2.6 Acute Anxiety and Agitation

Acute anxiety presenting with intensive fear, pressure over the chest, restlessness, tachycardia, and tachypnea can be seen in teenagers. In the emergency ward this is best managed by applying psychological supportive measures. If drugs are needed, then benzodiazepines are recommended. These patients should be referred to psychiatrists.

Nightmares, *night terrors, or pavor nocturnus* in smaller children may be a reason for a visit to an emergency ward. In a state between being awake and asleep, the child may scream and tell about seeing things, provoked by a dream or illusions. Sleep problems including nightmares are rather common among small children and should not be interpreted as anxiety [22]. Sometimes the history will indicate the need for an EEG analysis.

Agitation is a more severe form of anxiety, when the restlessness presents as unintentional and purposeless motor activities ranging from walking around the room to aggressive actions towards oneself or the surroundings. It can be seen in depressive and bipolar disorders as well as being one of the symptoms in delirium. In these cases there is usually a change to the level of consciousness. Among teenagers agitation is a rare condition but can be seen as consequence of illegal drug abuse. Agitation is a serious condition and needs psychiatric assessment and care.

7.2.7 Aggressive Acting Out Behavior

The results from prospective studies monitoring child development (i.e., the Gesell studies [10] and the California Child studies/the Berkeley Growth Study [11, 13] published in the 1940s and 1950s) showed that child behavior will change considerably over time. Overactivity, a behavior with criteria very similar to today's ADHD, was very common among children aged 5–7 years (especially in boys, where almost every second boy showed such a behavior) but gradually disappeared over time except in a small group of children. At different ages, different single children were looked upon as a nuisance by parents and teachers because of their hyperactive behavior. The same was found for destructive behavior (symptoms like (a) biting, kicking, striking, throwing things, destruction of property, banging head; (b) swearing, screaming, shouting accompanied by marked emotional reactions). Almost 1/3 of average boys showed such a behavior at 5–7 years of age, following which this behavior usually faded away. In an ongoing Swedish prospective study of children [8] from the average population, using both Macfarlane's criteria and DSM criteria for ADHD, the results show, similar to Macfarlane's findings a long time ago, that

an ADHD-like and destructive behavior is very common among average preschool children. This is a tricky situation as such symptoms can be symptoms of a normal childhood as well as indicating psychopathology including PTSD [23].

Some children (girls more often than boys) react to emotional stress with anxiety and somatization (internalizing symptoms), while other children (boys more often than girls) instead react with acting out aggressive behavior (externalizing symptoms). This means that a child showing a disturbing acting out behavior or being a nuisance may be a sad child showing emotional stress.

From a clinical point of view, children brought to the emergency ward because of bad behavior are often children in psychosocially stressful life circumstances and should be met in the same way as sad anxious children are.

Among teenagers aggressive acting behavior may also be part of intoxications, alcohol and drug abuse, or be symptoms of a psychiatric disorder. They should be handled by psychiatrists.

7.2.8 Hallucinations and Delusions

True hallucinations and delusions resulting from psychiatric disorders such as bipolar disorders and schizophrenia are rare in childhood. Most probably this reflects the overall maturation of the brain, as these disorders usually present with typical symptoms from adolescence and young adulthood when the brain is reaching full maturation [24]. However, hallucinations may result from drug abuse; children sniffing glue and solutions may describe hallucinatory effects before age 10. Delusions described by a child before puberty may be clinical information that one of the parents is suffering from a psychotic disorder, a condition called *folie à deux*.

7.2.9 Symptoms of Dissociation and Apathy, Somatic Symptoms Without an Obvious Somatic Disorder, and Conversion Syndromes

Children and adolescents who live in traumatic situations impaired by long-standing emotional stress or in dysfunctional family settings with alcoholic and/or abusive parents may react by showing mental and somatic symptoms [25].

A mental symptom such as *dissociation* may be seen and is best understood as the mind's defense mechanism to cope with stress and avoid anxiety. Dissociation means that the child/adolescent in a way isolates him-/herself from the surrounding stressing reality, showing an avoidance behavior. This means a change of personality and a change of the social interaction with others often including amnesia for the most severe traumatic experiences.

Apathy. In the most extreme forms, dissociation can develop into an apathetic state. During the past 20 years, such condition has been described as depressive devitalization or pervasive refusal syndrome, which is a "potentially life-threatening condition manifested by profound and pervasive refusal to eat, drink, walk, talk, or care for themselves in any way over a period of several months" [26]. The children are bedridden, need feeding by gastric tube, and are in an apathetic unconscious state. They have histories of long-standing psychic traumas. In Sweden there has been an epidemic with apathetic children. They were asylum-seeking refugee children from regions with civil wars and had histories of severe and long-standing psychological stress [27, 28].

Somatic symptoms without an obvious somatic disorder can be also seen in children living in emotional stress of different kinds. Typical symptoms are tiredness, chest pain, aching stomach, headache, pain in the joints etc. In the assessment of these children you will often find family conflicts of different kinds and/or parents with alcohol abuse. Another common situation is a child with very competent and achieving parents, where the child has a borderline IQ and cannot cope with the parent's expectations on school achievements [29].

Conversion syndromes. These conditions are showing themselves as neurological motor symptoms where no neurological disorders can be found. The prevalence among children and teenagers is difficult to estimate, but conversion syndrome has in many cohorts been estimated to represent up to 10 % of children in pediatric neurology clinics. Diagnosis may be difficult, especially as presence of a (neurological) disorder in no way excludes presence of conversion syndrome adding to the burden. Typical symptoms are paralyses of different kinds, impaired coordination or balance, nonepileptic seizures, gait problems, other movement dysfunctions, blindness, deafness, or syncope. Inconsistencies between symptoms and neurological findings are important diagnostic clues. These conditions are also related to psychological stress, the presence and nature of which is not always easy to identify.

7.3 Assessment

Children and adolescents may come to the emergency ward alone, with parents, with police, with social service authorities, or with peers. From the age of 6–7 years, and if he/she is conscious, you should start to have an individual talk with, and assessment of, the child him-/herself before talking to parents and/or police, authorities, and peers. By doing so you show respect to the individual's integrity and you get his/her own version of the events bringing him/her to the hospital. This will make the child/adolescent have confidence for you. Further, it gives you the opportunity to consider the developmental age, the individual's mental status, and the somatic and neurological symptoms in relation to the individual's own history to compare with what relatives, authorities, and peers will later tell.

If you start the other way, talking to the adults first in the presence of the child/adolescent, it will make it difficult for him/her to tell his/her version. An opportunity to have important information for a correct assessment may be lost. This is especially important when symptoms of neglect and abuse are suspected as well as when oppositional defiant symptoms and conduct problems are present.

A clinically useful way to assess child and adolescent psychiatric issues consists of the following nine steps:

1. Careful history
2. Validation of the history
3. Somatic investigation incl. neurology, laboratory tests, chromosomes, X-ray, vision, and hearing
4. Psychological investigations
   - Psychometric assessments
   - Projective test
5. Social evaluations
6. Pedagogic/educational assessments
7. Psychiatric assessments of both the child and the parents
8. Observation in different social settings
9. A multidisciplinary diagnosis

Of course, the nine steps cannot be used in the emergency ward. However, the disposition can be used for the clinical thinking when you meet a patient with acute symptoms. Besides examining the patient incl. the level of consciousness (perception, attention, concentration, impulsivity, memory) if indicated, information on the social situation (home environment, peers), school achievements, and the psychosocial functioning of the parents gives enough and sufficient information to decide upon the actions needed.

If you have information on parental psychosocial problems, bad peers, and school problems, you are most probably facing a patient at risk who should be referred to a child and adolescent department.

7.4 Conclusions

The pediatric disciplines and child and adolescent psychiatry are closely related. In a Swedish study of consecutive new patients over 1 year at a pediatric university outpatient department, it was found that approximately every seventh new patient had a child and adolescent psychiatric problem as a minor or a major reason for the need of help [30]. This refers especially to symptoms with somatic components as exist in anxiety, dissociation and apathy, somatic symptoms without an obvious somatic disorder, and conversion syndromes. As children and parents have identified somatic symptoms as a problem, the pediatrician needs to consider the

following to avoid iatrogenic problems when a psychogenic explanation seems to be the cause:

1. When the history and the clinical status do not indicate a somatic disorder and there is a need for X-ray and laboratory examinations for the doctor to be sure, it is essential to explain for the child/adolescent him-/herself and the parents that an emotional stressful life situation may give similar symptoms. The X-ray examination is done, not to find but to rule out a somatic disorder. If this is done it is much easier to explain the X-ray results when nothing pathological is found.
2. If a drug is prescribed, it should be explained that this is done not to cure but to make it easier until the family will meet the psychiatrist.
3. It is advisable that the pediatrician and the child and adolescent psychiatrists have the first meeting together with the family.

If these steps are followed, the families usually accept a psychogenic explanation for their child's problems.

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Part II
Management of Acute Neurological Conditions

Chapter 8
Ischemic and Hypoxic Insults: Near Drowning, Asphyxia, Carbon Monoxide Poisoning

Fenella J. Kirkham and Rebecca N. Ichord

Abstract Cardiac arrest in childhood is a different clinical problem from that in adulthood as myocardial infarction is rare. Out-of-hospital cardiorespiratory arrest does occur in childhood for a variety of reasons, and with the increasing number of therapeutic options for serious but not necessarily fatal disease, inpatient cardiac arrest and hypoxic-ischemic encephalopathy are not uncommon. The prognosis for patients who are unconscious on admission after out-of-hospital arrest (including sudden infant death and near drowning) is poor and can usually be predicted by clinical signs and general information about the arrest. The outcome for children who suffer an inpatient cardiac or respiratory arrest or profound hypotension is often determined by the underlying illness. Since clinical signs are often obscured, additional prognostic information from investigations such as EEG, evoked potentials, and neuroimaging may be very useful. In both groups, there are patients who would be predicted to survive intact but who deteriorate secondarily and either die or survive in a vegetative state. Neurophysiology may also useful in predicting deterioration in these intermediate prognosis patients, who may benefit from hypothermia and control of intracranial hypertension and status epilepticus. Results

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from randomized controlled trials of therapeutic hypothermia for pediatric cardiac arrest, and further study of the predictive significance of early markers of brain injury in children treated with new neuroprotective strategies like therapeutic hypothermia (TH), are urgently needed. Other treatments proposed on the basis of basic science research into pathogenesis of ischemic damage cannot be recommended at the present time.

Keywords Ischemia • Hypoxia • Hypoxic-ischemic encephalopathy • Anemia • Hypotension • Hypertension • Near drowning • Electrocution • Hanging • Strangulation • Asphyxia • Carbon monoxide poisoning • Smoke inhalation

8.1 Introduction

Unexpected hypoxic-ischemic encephalopathy in a previously well child is uncommon [1, 2], but acute neurological complications associated with cerebral hypoxia and/or ischemia occur frequently in sick children [3]. The pathophysiology of an acute reduction in oxygenation alone, e.g., during acute anemia, severe asthma, acute chest syndrome in sickle cell disease, exposure to altitude, or after smoke inhalation or carbon monoxide poisoning, may initially be different from acute ischemia secondary to cardiac arrest, although severe hypoxia typically leads to systemic, cardiac, and cerebral dysfunction eventually. Respiratory arrest may also occur after brain stem damage, e.g., secondary to trauma or during cerebral herniation related to acute intracranial hypertension. The highest incidence of cardiac arrest occurs in infants (sudden infant death syndrome) [1], but older children with predisposing cardiac conditions such as hypertrophic cardiomyopathy or prolonged QT syndrome are at risk during exercise, and hypoxic-ischemic encephalopathy is a common complication in children with surgically and medically treated cardiac disease [3], as well as after accidents such as trauma, near drowning, electrocution, and hanging or strangulation. Initially, the probability of survival is higher for those with respiratory, rather than cardiac, arrests, but the probability of survival for a cardiac arrest remains stable over the first hour, whereas the probability of surviving a prolonged respiratory arrest is very low [4]. The outcome for cardiac arrest varies greatly from series to series, depending on the selection of patients. Historically, the prognosis for neurological recovery after hypoxic-ischemic encephalopathy in childhood was poor [5, 6], but recent prospective series have found that the majority of children surviving inpatient cardiac arrest have good neurological outcome.

8.1.1 Epidemiology and Outcome

8.1.1.1 Inpatient Cardiac Arrest

The improvement in the management of complex conditions in children means that in-hospital pediatric cardiopulmonary resuscitation (CPR) is now commonplace in casualty, on the ward, in theatre, and in intensive care [7]. Cardiac arrest

occurred in a total of 111 of 104,780 admissions to a pediatric hospital in Melbourne (10.06/10,000), while respiratory arrest alone occurred in 36 (3.4/10,000) [8]. In a Finnish study from a tertiary pediatric center, the incidence of cardiac arrest was 0.7 % of all hospital admissions and 5.5 % of PICU admissions, with just under half declared dead at the scene so that the incidence of CPR attempts was 0.4 and 2.5 %, respectively [9]. There were 94 cardiac arrests per 10,000 admissions in a PICU setting in Canada [10]. A study in Pakistan found that the incidence of perioperative cardiac arrest was 4.95/10,000 [11], while Brazilian [12] and Indian [13] studies found incidences of 22.9/10,000 and 22.2/10,000, respectively.

In a London study of 169 cardiac arrests (154 inpatient) in 164 children, underlying disease was present in 89 %, the majority cardiac ($n=91$), respiratory ($n=26$), or neurological ($n=13$); 34 % survived, with 24 % of patients achieving favorable neurological outcome at 1 month irrespective of etiology [14]. Some of these children had died of their underlying disease by the time of the more detailed 2-year follow-up, but in the survivors, good outcome or moderate handicap was much commoner than severe handicap or vegetative state. In other studies with ventilation available, one fifth of inpatients [15] and one third of those arresting on pediatric intensive care (PICU) [16] survived to leave hospital, with the majority having favorable neurological outcomes [15, 16]. However, survival is unusual in settings without access to ventilation [17].

8.1.1.2 Out-of-Hospital Cardiac Arrest

In a North American study, the incidence of pediatric out-of-hospital cardiac arrest was 8.04 per 100,000 person-years (72.71 in infants, 3.73 in children, and 6.37 in adolescents) versus 126.52 per 100,000 person-years for adults. Survival for all pediatric out-of-hospital cardiac arrest was 6.4 % (3.3 % for infants, 9.1 % for children, and 8.9 % for adolescents) versus 4.5 % for adults ($P=0.03$) [1]. In one province of the Netherlands, the incidence of out-of-hospital cardiac arrest in those aged <21 years was 9.0 per 100,000 pediatric person-years (95 % confidence interval: 7.8–10.3), whereas the incidence of pediatric out-of-hospital cardiac arrest from cardiac causes was 3.2 (95 % confidence interval: 2.5–3.9) [18]. Fifty-one patients were resuscitated, 12 (24 %) of whom survived and 10 neurologically intact. In a Korean study, the incidence of pediatric out-of-hospital cardiac arrest was 4.2 per 100,000 person-years (67.1 in infants, 2.5 in children, and 3.5 in adolescents) [2]. The overall incidence of nontraumatic pediatric out-of-hospital cardiac arrest in the population-based study in Osaka was 7.3 cases per 100,000 person-years, compared with 64.7 cases per 100,000 person-years for adults (aged >18 years) and 65.5 cases per 100,000 person-years for infants [19]. Children were more likely to survive (8 % vs. 5 %) and were more likely to have favorable neurological outcome (3 % vs. 2 %) than adults. One-month survival with favorable neurological outcome was seen in 1 % of infants, most of whom had unwitnessed cardiac arrests in the home, 2 % of children aged 1–4 years, 2 % of children age 5–12 years, and 11 % of adolescents aged 13–17 years. Nearly half of the adolescent arrests occurred outside the home, while over a third were witnessed by

bystanders [19]. In a nationwide study of people over the age of 10 years in France, the overall burden of sports-related sudden death was 4.6 cases per million population per year, with an incidence ranging from 5 to 17 new cases per million population per year allowing for suspected underreporting; 6 % of cases occurred in young competitive athletes [20]. A study in Melbourne, Australia, found that overall 7.7 % of children under the age of 16 years survived out-of-hospital cardiac arrest [21]. In an earlier meta-analysis, 12.1 % survived to discharge, while only 4 % had good neurological outcome [22].

8.1.2 Preexisting Clinical Factors

Recovery of consciousness is possible after cardiac arrest at any age. In the London study of mainly inpatient cardiac arrests, those who recovered consciousness by 1 month were significantly younger (median 5 months) than those who did not (median 2 years) [14]. Although etiology does not generally appear to be predictive of outcome for pediatric inpatient arrests [14], hematological, oncological, or immunological conditions and coma or endotracheal intubation before cardiopulmonary resuscitation are associated with death [23]. Mortality is higher for obese children [24].

8.1.3 Nature and Duration of Arrest

The prognosis for survival and/or good neurological outcome appears to be better if cardiac arrest is related to hypotension-bradycardia, pulseless electrical activity, ventricular fibrillation, or ventricular tachycardia than if it is asystolic [8]. Although those who arrest in theatre or postoperatively on PICU and who receive prompt and effective resuscitation may do unexpectedly well, duration of arrest is an important predictor. An initial cardiopulmonary resuscitation duration longer than 10 min was associated with an unfavorable outcome (positive predictive value 91 %, sensitivity 50 %) in the French study from Lille [25]. In the London study, death was predicted by the duration of cardiac arrest and accompanying hypotension and by pyrexia and minimum (but not mean) mean arterial pressure over the first 6 h, but clinical signs (see below and Chap. 1) were better predictors of neurological outcome [14].

8.2 Recommended Assessments

Etiologies and suggested initial assessments of unexpected cardiac arrest are shown in Table 8.1.

Table 8.1 Etiology of unexpected cardiac arrest

Setting	Imaging investigation	Laboratory investigation	Management
Severe acute anemia	Neuroimaging may show new focal infarction	Full blood count, Parvovirus	Slow blood transfusion avoiding hypertension
Severe acute hypoxia	Chest X-ray		Oxygen, treat pneumothorax, pneumonia
Severe acute hypotension	Neuroimaging may show potentially reversible abnormality in border zones between middle, anterior, and posterior cerebral artery territories		Volume expansion, inotropes
Severe acute hypertension	Neuroimaging may show posterior reversible encephalopathy syndrome		Avoid hypotension, slow reduction of blood pressure
In-hospital cardiac arrest (cardiac)		pH, glucose	Conventional/compression-only/ open-chest CPR/CPB/ECMO
Hypothermia			
In-hospital cardiac arrest (neurological)	Exclude treatable cause of raised ICP, e.g., hydrocephalus		
	Exclude status epilepticus	pH, glucose	Reduce ICP with ventilation, hypertonic saline, decompression; treat seizures
Out-of-hospital sports		pH, glucose	Conventional bystander CPR
Out-of-hospital near-miss sudden infant death	Exclude non-accidental injury	pH, glucose	Conventional bystander CPR, hypothermia, treat seizures
Out-of-hospital near drowning		pH, glucose	Conventional bystander CPR, rewarming with CPB
Out-of-hospital carbon monoxide poisoning	Neuroimaging	Carboxyhemoglobin, white cells, CRP	Normobaric oxygenation
Out-of-hospital smoke inhalation with carbon monoxide poisoning		Carboxyhemoglobin, white cells, CRP	Normobaric oxygenation
Out-of-hospital electrocution			
Out-of-hospital lightning injury			

8.2.1 Clinical Examination

8.2.1.1 Nature and Timing of Assessment

A full general and neurological assessment should be undertaken (Chap. 1) as clinical signs have prognostic value and detection of signs of raised intracranial pressure and incipient herniation or seizures [26] may alter management. There is no doubt that survival and good neurological outcome are less common for those in coma after cardiac arrest and that duration of coma is predictive of outcome. The timing of the clinical examination is very important, and there is a lot of evidence that serial testing is preferable to a single examination. Although some isolated clinical signs and combinations of signs appear to be highly predictive of good or poor outcome [14, 25], it may be impossible to predict outcome accurately at an early enough stage to influence management. Clinical deterioration after initial improvement is well recognized after pediatric cardiac arrest [5] and is associated with poorer outcome.

8.2.1.2 Pupillary Response to Light

Absent pupillary response to light is common immediately after cardiac arrest and may be compatible with recovery. However, in the London pediatric series, only one patient with an absent pupillary response to light at 6 h regained consciousness within the first month [14]. In a multicenter series, reactive pupils were associated with lower mortality [23]. In a recent series of comatose survivors of pediatric cardiac arrest treated with therapeutic hypothermia (TH), absent pupillary response to light had a positive predictive value for poor outcome or death at hospital discharge of 94 % when present early after the start of TH, increasing to 100 % when present at 24 h after rewarming [27].

8.2.1.3 Depth of Coma

In a study of hypoxic-ischemic encephalopathy in 54 children, Glasgow Coma Scale (GCS) <5 at 24 h after admission predicted poor outcome with positive predictive value [PPV] 100 and 54 % sensitivity [25]. Neurological signs and other clinical variables were recorded prospectively following 169 arrests in 164 (92 boys, 56 %) children aged from 1 day to 15 years (median 9.5 months) in the London area [14]. Important clinical signs predicting favorable outcome included eye signs, with the eye component of the Glasgow/Adelaide Coma Scale and the presence of eye movements remaining significant predictors from the immediate post-arrest period through to 48 h later. Better motor response predicted

favorable outcome by 6 h and the return of doll's eye and caloric reflexes by 12 h post-arrest [14]. Absent motor response early after starting TH had a PPV for poor outcome or death of 67 %, increasing to 100 % at 24 h after rewarming [27]. The use of paralytic agents contributed to diminished PPV of motor signs during TH in this study.

There is ongoing uncertainty regarding the predictive significance of pupillary and motor signs [28] for long-term outcome, especially among children receiving TH. Larger studies with longer periods of follow-up and more detailed functional outcome assessments are urgently needed [28].

8.2.2 Laboratory

The pH of the first gas predicted mortality in a multicenter study [23] and was significantly lower in those who did not recover consciousness compared with those who did (mean 7.058 vs. 7.238) in the London study [14].

8.2.3 Neurophysiology

Most children have an inpatient cardiac arrest in the context of another illness. As part of their management, they are often already paralyzed for ventilation on the intensive care unit and may be undergoing therapeutic hypothermia; they are thus not accessible for clinical examination. Prediction of outcome and monitoring for seizures using neurophysiological techniques may be essential in these patients [26].

8.2.3.1 Background EEG

Several authors have described grading systems for looking at EEGs after cardiac arrest (Fig. 8.1) [28, 30]. Serial EEG appears to be useful prognostically in nontraumatic coma including hypoxic-ischemic encephalopathy [26, 31]. In the absence of sedating drugs, EEGs which are isoelectric or show only burst suppression (Fig. 8.1, I and II) are associated with poor outcome [25, 26], particularly if these patterns persist for more than 24 h after cardiac arrest. A normal EEG (Fig. 8.1, VI) within the first few hours after cardiac arrest is usually predictive of good outcome provided that no other insult supervenes. Intermediate gradings, such as diffuse slowing with (Fig. 8.1, V) or without (Fig. 8.1, IV) some faster frequencies present or low amplitude (Fig. 8.1, III), have less predictive power.

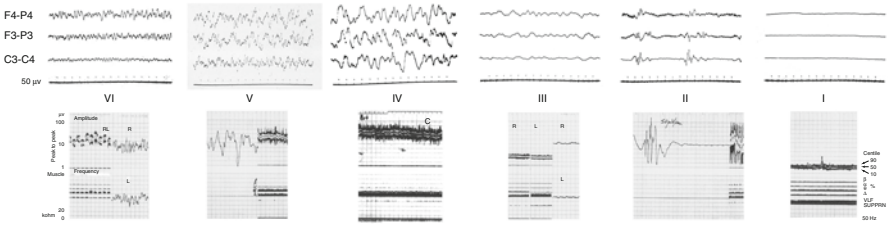

Fig. 8.1 Continuous electroencephalography (cEEG) grading for Oxford Medilog (*upper*) and cerebral function monitor (CFAM) (*lower*) traces in children after cardiac arrest. Biparietal montage (P3-P4 on international 10–20 system) was used with paper speed 30 cm/h unless otherwise stated. VI = Normal as for an awake child (10th centile for amplitude >9 µV and % fast >15 %). V = Excess slow activity as seen in a child asleep (fast 3–15 % and 10th centile for amplitude >9 µV). IV = Excess slow activity with less fast activity than seen in normal sleep (fast <3 %) and 10th centile for amplitude >9 µV. III = Low amplitude trace (10th centile <9 µV). II = Burst suppression. I = Isoelectric for grades VI and III; the CFAM compressed trace was alternating between right (F4-P4) and left (F3-P3) hemispheres every 1 (VI) or 5 (III) minutes (Reproduced with permission from Kirkham and Ashwal [29])

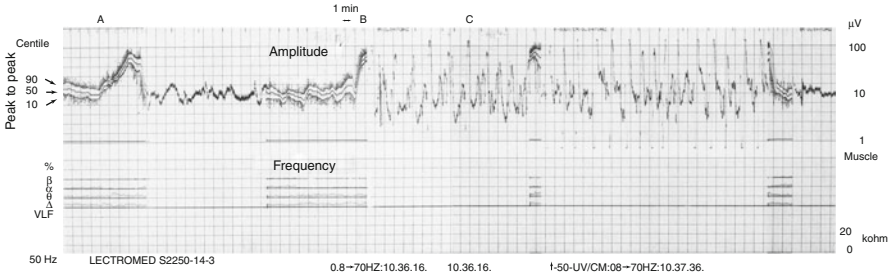

Fig. 8.2 Cerebral function monitor (CFAM) tracing showing subclinical seizure discharge with increase in amplitude (amplitude trace, **a**, **b**) and spike-and-wave (raw EEG, **c**) after cardiac arrest (Reproduced with permission from Kirkham and Ashwal [29])

A simple and reliable three-category classification system for EEG background abnormalities based on continuity and reactivity in comatose critically ill infants and children was evaluated for predicting outcome after cardiac arrest [28, 30]. Unreactive or discontinuous EEG recordings were associated with poor neurological outcome [28]. This relationship was robust for recordings obtained during TH and after rewarming.

8.2.3.2 Monitoring EEG

Several centers have used either the original cerebral function monitor, which records an amplitude trace only, or the cerebral function analyzing monitor (CFAM) [26] or the compressed spectral array (CSA), both of which display amplitude and frequency. Using the CFAM, the traces may be graded [26] (Fig. 8.2), although

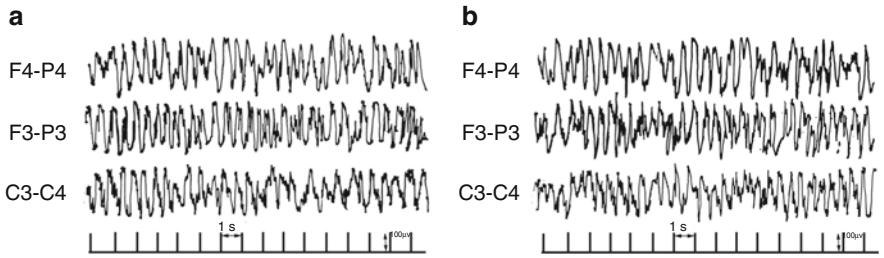

Fig. 8.3 Oxford Medilog trace from a girl of 4 years with cavernous sinus thrombosis and a cardiac arrest showing a very prolonged electroencephalographic seizure, which commenced at 01:30 (**a**). The discharges continued unrecognized by the nursing staff until 05:00 (**b**). Subsequently the EEG became isoelectric and the child died of brain death (Reproduced with permission from Kirkham and Ashwal [29])

subtle features may not be recognized. For the CSA, an unchanging trace is usually associated with poor outcome. Deterioration of the pattern is also a poor prognostic sign, but this may be more distressing for relatives and nursing staff than serial EEGs.

EEG monitoring may be useful in the management of status epilepticus [26]. It is becoming widespread practice that unconscious children have an EEG to determine whether clinically recognized seizures have terminated or to distinguish subtle seizures from movement disorders secondary to drug withdrawal. Routine or continuous EEG (cEEG) with or without video recording may be used to diagnose nonconvulsive seizures (NCS) or nonconvulsive status epilepticus (NCSE) (Fig. 8.3). There are few follow-up studies, but the available evidence suggests that nonconvulsive seizures predict poor outcome, particularly severe disability or vegetative state [26].

8.2.3.3 Evoked Potentials

Visual, auditory brain stem and somatosensory evoked potentials have been elicited in studies of children with HIE [25]. Brain stem and somatosensory evoked potential have a role in the prediction of outcome, particularly if the EEG is in an intermediate group. Somatosensory evoked potentials appear to be the most useful, while visual evoked potentials may be misleading but predictive value is greater if the data from all three modalities are combined.

8.2.4 Neuroradiology

Neuroimaging performed soon after cardiac arrest may show cerebral swelling with effacement of the sulci or widespread loss of grey-white differentiation or low

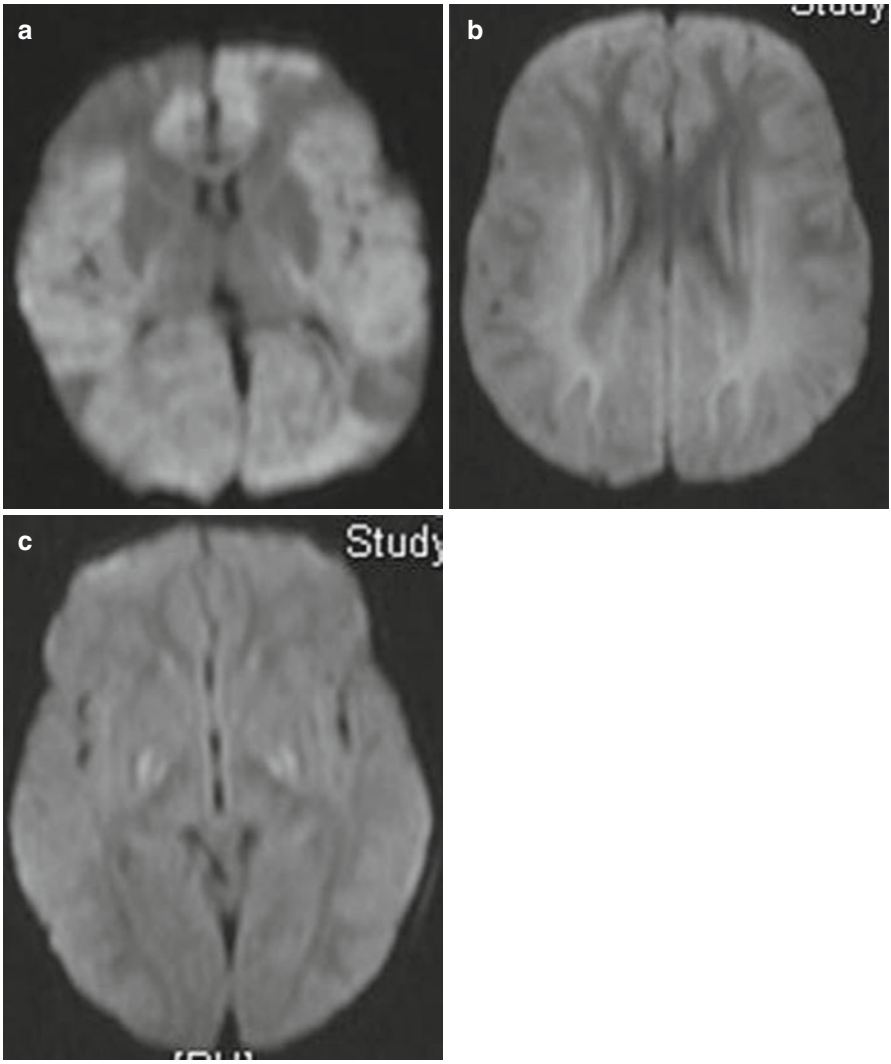

Fig. 8.4 Diffusion-weighted imaging in pediatric hypoxic-ischemic encephalopathy. (**a**) Bilateral abnormality after several cardiac arrests in an infant with supraventricular tachycardia. (**b**) White matter abnormality after near drowning. (**c**) Bilateral globus pallidus abnormality after near drowning in a child who remained cognitively intact

density in the basal ganglia or in the watershed regions (Figs. 8.4, 8.5, and 8.6). The "reversal sign" with low density in the cerebral hemispheres and relatively higher densities in the basal ganglia on computed tomography is not uncommon in infants (Fig. 8.6). All these patterns are associated with poor prognosis, and several series suggest that neuroimaging is useful prognostically, but a normal CT scan does not guarantee a good outcome [32].

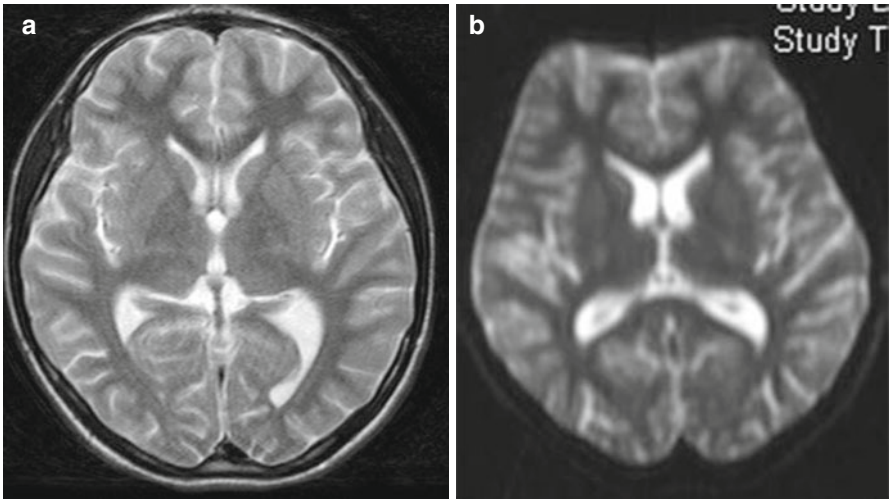

Fig. 8.5 MRI in a teenager who had attempted hanging 6 days previously. (**a**) The T2-weighted images show high signal in the posterior putamen, globus pallidus, thalami, and hippocampi which were not obvious on a further T2-weighted image 2 weeks later. (**b**) The diffusion-weighted changes 6 days post-injury are more subtle. The patient apparently made a full recovery initially developed a severe dystonic quadriparesis 1 month after the hanging

T2-weighted, diffusion and perfusion magnetic resonance imaging and proton spectroscopy may be useful but must be interpreted with caution by experts [33, 34]. Moreover, much uncertainty exists about the utility of MRI for predicting outcome in the setting of TH, as the temporal evolution of acute ischemic changes is altered by TH. Thus caution is warranted in interpreting MRI abnormalities after cardiac arrest, especially when seen on examinations performed earlier than 5–7 days after the arrest. Single photon emission computed tomography (SPECT) may be useful in demonstrating basal ganglia lesions in post-cardiopulmonary bypass chorea, but there are few data after cardiac arrest in childhood.

8.3 Recommended Emergency Interventions

8.3.1 Resuscitation

The prime aims of emergency resuscitation attempts are to restore spontaneous circulation while maintaining sufficient myocardial and cerebral blood flow to prevent irreversible ischemic damage. Most studies of CPR have been conducted in adults, in whom spontaneous circulation is often successfully restored after cardioversion of ventricular fibrillation or tachycardia. External cardiac massage (ECM), introduced in the early 1960s, almost completely replaced the previously

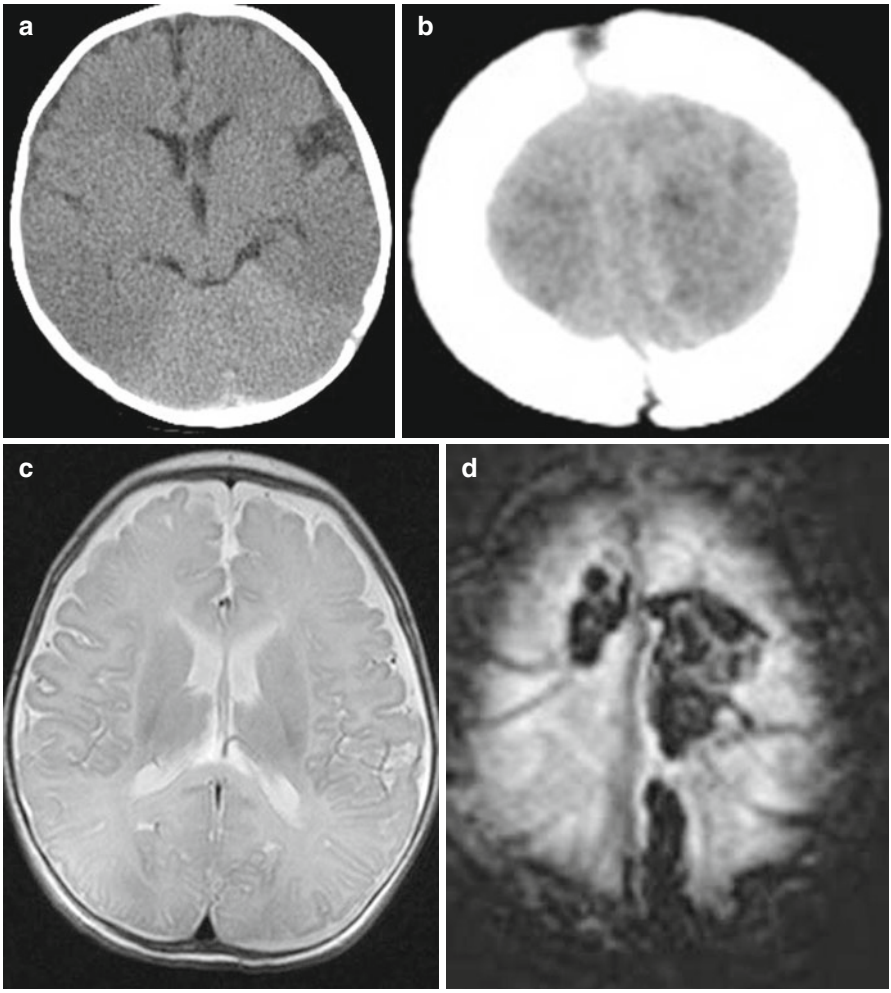

Fig. 8.6 Images from an infant aged 3 months who had an out-of-hospital cardiac arrest. (**a**) CT shows the reversal sign with lower signal in the cerebrum than the cerebellum and suggests subdural hemorrhages (**b**) which are more obvious on the T1-weighted image (**c**), which also shows ischemic change, and on the gradient ECHO image (**d**). This child had suffered non-accidental injury

standard open cardiac massage (OCM), as it was less invasive and could be performed by anybody anywhere. For children who have out-of-hospital cardiac arrests from noncardiac causes, conventional CPR by bystander is the preferable approach to resuscitation, while for arrests of cardiac causes, either conventional or compression-only CPR is similarly effective. The emphasis now is on rapid and effective chest compression with rescue breathing optional. As there is evidence for better outcome after inpatient resuscitation by a pediatric trainee, Pediatric Advanced Life Support (PALS) training should be mandatory for doctors looking after children.

8.3.1.1 Cardiac Massage to Maintain the Systemic Circulation

Restoration of cardiac rhythm with adequate output is a priority. For in-hospital arrests, higher mean arterial, coronary and cerebral perfusion pressures are generated with open cardiac massage, and it may be possible to institute emergency cardiopulmonary bypass or extracorporeal membrane oxygenation. These techniques are invasive and require a highly experienced team, although there is evidence of benefit provided there are no neurological problems.

8.3.1.2 Respiratory Function

Immediate intubation and ventilation to normoxia and normocapnia is essential. There are few data in children, but animal studies suggest a detrimental effect of exposure of the vulnerable brain to hyperoxia. Although hemoglobin oxygen saturation should be monitored and hypoxia avoided, resuscitation with 100 % oxygen is relatively contraindicated. Hyperventilation, hypocapnia, and excessive ventilation rates should be avoided during resuscitation.

8.3.1.3 Resuscitation Drugs

The drugs commonly used during cardiac arrest include the inotrope adrenaline (epinephrine), sodium bicarbonate, and calcium, but there are concerns that all three worsen outcome. The use of adrenaline was not a risk factor for death in inpatient pediatric arrest in one study [23], although it was in another [16] and has been in most studies of drowning and other causes of out-of-hospital arrest [35]. Terlipressin may be an alternative, although there is currently little evidence for an advantage in terms of outcome. In addition to long-standing concerns over the use of calcium [23], the use of sodium bicarbonate or tromethamine also appears to be a predictor of death [23].

8.3.2 Prevention of Secondary Brain Damage

Some patients recover consciousness very soon after a brief episode of cardiac arrest and they usually make a full recovery. In others, the brain may be severely and irreversibly damaged by the initial insult; most of these patients either fulfill the clinical criteria for brain stem death or have neurophysiological evidence of a poor prognosis within 24 h of the event. It is the management of the intermediate group, who remain unconscious but with some evidence of brain stem function clinically and cortical function neurophysiologically, which remains extremely controversial, particularly as some patients appear to deteriorate secondarily. While awaiting results of further studies, there are a few management strategies which can be recommended as being probably safe but

of unproven efficacy; these should preferably be reserved for the intermediate group who remain unconscious but without evidence of irreversible damage.

8.3.3 Practical Management Strategies

8.3.3.1 Management of Intracranial Hypertension (See also Chap. 11)

There are very few published data, and many groups have given up monitoring and aggressively managing intracranial hypertension in children with HIE for fear of increasing the number of children left severely handicapped or in a persistent vegetative state. However, as good outcome has been reported in some cases in whom intracranial hypertension has been vigorously prevented or managed, e.g., with surgical decompression [36], monitoring should be considered for the individual child. Intracranial pressure was monitored in 18 of the patients in the Guy's pediatric study [36] and was persistently raised (mean ICP greater than 10 mmHg) in 10 of these. The two children with good outcome and the child who made a cognitive recovery but was left with a spastic quadriparesis (probably due to a posterior fossa hematoma) all had mean ICP between 9 and 15 mmHg and maximum ICP up to 35 mmHg (i.e., above the normal range), but mean CPP was maintained above 60 mmHg and CPP never fell below 37 mmHg. In the other 15 children, either the EEG prior to ICP monitoring suggested a poor outcome or mean CPP could not be maintained above 60 mmHg and minimum CPP above 40 mmHg because of poor cardiac function or persistent intracranial hypertension. Opening, maximum and mean ICP did not predict outcome, but minimum and mean CPP did.

Appropriate candidates for ICP monitoring have been well resuscitated using modern cardiopulmonary resuscitation techniques, so that the EEG has recovered to diffuse slowing or better, despite continuing unconsciousness or sedation for ventilation. Cerebral perfusion pressure (CPP) must be frequently recorded and managed appropriately.

8.3.3.2 Management of Seizures (See also Chap. 10)

Seizures are common after cardiac arrest in children. After near-miss sudden infant death, a brief seizure may be compatible with good outcome, but status epilepticus carries a very poor prognosis [32] even if the child had recovered consciousness between the event and the onset of seizures [5]. Many children are sedated and paralyzed for ventilation after cardiac arrest and so observation of seizures may be impossible. There are few data on the prevalence of nonconvulsive seizures (NCS) or nonconvulsive status epilepticus (NCSE) in childhood hypoxic-ischemic encephalopathy. NCSE is common in neonates after asphyxia, and in comatose adults, and appears to predict death and poor outcome. In one study, 43 % of children with hypoxic-ischemic encephalopathy had a clinical seizure and 33 % had an

electroencephalographic (EEG) seizure [26], and the presence of EEG seizures predicted poor neurological outcome but not death [26].

There is a good case for giving therapeutic doses of conventional anticonvulsants, e.g., benzodiazepines, phenobarbitone, and phenytoin, to children after global ischemic insults either prophylactically or as treatment for clinical seizures or electroencephalographic discharges, particularly if the EEG background is compatible with good prognosis. Continuous infusion of short-acting benzodiazepines, such as midazolam, may be of benefit in certain selected patients with status epilepticus. Chlormethiazole is not recommended for the control of seizures after cardiac arrest, since the fluid volume is substantial and there is a significant risk of volume overload if the patient has a degree of acute renal failure. Although there are concerns about the drug's effect on the cardiac conducting system, it is probably safe to use phenytoin (loading dose 20 mg/kg, then 5 mg/kg/day in two divided doses with regular drug levels) in patients who do not have ongoing cardiac dysrhythmias provided that the drug is infused over at least 45 min. Phenobarbitone may also be effective in controlling seizures in unconscious patients and again, it may be worth pushing the drug dose towards the top end of the therapeutic range as additional sedation is not usually a problem. Thiopentone coma is relatively contraindicated, because there are significant problems with cardiac depression and with diagnosing irreversible brain damage, and this management strategy has now been largely abandoned. Other anesthetics such as etomidate and althesin either do not have a significant protective effect after ischemia or is associated with unacceptable side effects.

8.3.3.3 Hypothermia

The publication of randomized controlled trials showing benefit in terms of survival and neurological outcome for hypothermia in adults and neonates has reopened the question of whether children who have had a cardiac arrest would benefit from immediate cooling after inpatient (or out-of-hospital) cardiac arrest. Mild hypothermia has been used after cardiac arrest in children, sometimes in those predicted to do worse. At present the available data do not make the case for benefit, but it is clear that randomized trials are needed [37], and a National Institutes of Health-funded International trial began in 2011. A recent survey of pediatric intensivists in the United Kingdom found that about half did use cooling for a median duration of 24–48 h (range 4–72 h) at median target temperature of 34–35 °C (range 32–37 °C) for children who had had a cardiac arrest. More than two thirds of those using hypothermia for children targeted a temperature range higher than that applied in the published adult and neonatal studies (33 ± 1 °C), perhaps because of the previous negative experience with lower temperatures in children, e.g., after near drowning. There may be a case for selective cooling of the head or a reduction of the core temperature to 32–34 °C after cardiac arrest in some children despite the lack of controlled trials. If a cooling turban or blanket is available, hypothermia may be initiated quickly during in-hospital cardiac arrest and may be discontinued equally rapidly for clinical examinations or if there are unwanted effects.

8.4 Specific Causes of Out-of-Hospital Cardiac Arrest

8.4.1 Trauma (See also Chap. 19)

Accidental and non-accidental traumatic brain injuries are common; cardiorespiratory arrest may be secondary to the severity of the head injury, to hemorrhage from associated injuries, or to brain stem or spinal cord damage. Posttraumatic cardiorespiratory arrest is associated with a very poor prognosis in terms of survival and neurological outcome in survivors [38, 39]. In one series, 3/28 (11 %) survived to hospital discharge, 2 with respiratory arrest neurologically intact; none survived if CPR was required for >20 min [38]. In Brindis' series from California of 118 patients requiring cardiopulmonary resuscitation after trauma, 6 (5 %) survived but none was neurologically intact [39]. The prognosis may be better for those suffering penetrating, rather than blunt, trauma.

8.4.2 Near Drowning

Even in water-oriented societies, immersion accidents are relatively rare (incidence 3–6 per 100,000), but over half the children admitted to hospital survive and they often require intensive management. The prognosis for the child pulled from the water apparently dead is excellent, provided that immersion was witnessed and the time was short, bystander cardiopulmonary resuscitation is commenced immediately, transport is rapid [40], and the child gasps within 40 min of rescue and regains consciousness soon afterwards. The prognosis is much worse for the child admitted to the emergency room deeply unconscious (Glasgow coma score less than 5) with fixed dilated pupils and apnea, without a detectable pulse, and therefore requiring continuing cardiopulmonary resuscitation, especially if there is little recovery by the time of admission to the intensive care unit. In a meta-analysis [22], for this group, 23 % survived and 6 % had good neurological outcome.

8.4.2.1 Recommended Assessments After Near Drowning

Laboratory measures suggesting poor outcome after near drowning include an arterial pH of less than 7.00 and hyperglycemia. Persistent seizures are a poor prognostic sign. Several authors have found EEG to be a useful predictor of outcome, particularly if there is deterioration compared with the record performed at 24 h. Evoked potentials may also be useful and abnormal CT scan, either initially or later, predicts death or vegetative state. None of these poor prognostic indicators preclude a good outcome, although a combination makes severe handicap or vegetative survival likely, since moderate handicap is rare after near drowning. Apparently miraculous recoveries have occurred, mainly of children

who have been submerged in very cold water for long periods and present to casualty with a temperature of less than 33 °C.

8.4.2.2 Recommended Interventions in Near Drowning

Intracranial hypertension is a common but not universal feature of the encephalopathy which follows serious near-drowning incidents, although whether or not treatment prevents secondary deterioration is much more controversial [36]. Intracranial hypertension, low cerebral perfusion pressure, and low cerebral blood flow are all predictors of death but do not distinguish between intact and vegetative survival. Initial maintenance of hypothermia and slow rewarming using cardiopulmonary bypass have been used, but there is no evidence of benefit in terms of neurological outcome [41].

8.4.3 Sudden Infant Death

The risk factors for sudden infant death syndrome include sleeping in the prone position, bed sharing, maternal smoking and alcohol use, and infection or other illness. Children may be found to have died of presumed prolonged QT syndrome secondary to cardiac ion channel mutations (diagnosable on DNA from Guthrie), metabolic disease such as medium chain acyl-coA deficiency carnitine palmitoyltransferase 1A variants, or to be the victims of child abuse. Compared with the extensive literature on the epidemiology and etiology of sudden infant death (SID), there is very little data available on the prognosis for those infants who are resuscitated at the scene or in hospital ("near-miss" SID). Infants presenting in status epilepticus may have been the victims of hypoxic-ischemic events akin to "near-miss" episodes. Constantinou [5] described the clinical course in 14 patients. Half were deeply unconscious on admission and succumbed within 3 days. Five appeared conscious initially but later deteriorated with persistent status epilepticus, deep coma, and signs of brain stem dysfunction; the other two survivors were unconscious on admission but also developed status epilepticus. Overall the prognosis was extremely poor; only one child survived without severe brain damage.

8.4.3.1 Recommended Assessments After Near-Miss Sudden Infant Death

As non-accidental injury is an important cause of cardiac arrest in infancy (Fig. 8.6), it is essential to take a comprehensive history and undertake a full clinical examination, including ophthalmology to exclude retinal hemorrhages as well as imaging of the brain and a skeletal survey. Tardieu [32] found EEG to be less useful than clinical signs in distinguishing survivors with and without handicap after mainly

out-of-hospital cardiac arrest in infancy; the EEG often deteriorated in those who were not fully awake by 8 h.

8.4.4 Carbon Monoxide Poisoning

Carbon monoxide poisoning can occur in isolation, e.g., from malfunctioning heating equipment, or with smoke inhalation and burns after house fires. The majority of those with isolated carbon monoxide poisoning do well with treatment, whatever the carboxyhemoglobin on admission [42]. However, those with smoke inhalation are more likely to be unconscious on admission and have a much higher mortality despite treatment, particularly if there is also low body temperature, high carboxyhemoglobin level, and respiratory or cardiac arrest [42]. The mortality is very high if there is also cardiac arrest.

8.4.4.1 Recommended Assessments After Carbon Monoxide Poisoning

Carboxyhemoglobin should be measured on admission and after treatment and predicts death, although severity of poisoning and risk of delayed neurological sequelae are more closely associated with white cell count, C-reactive protein, and Glasgow coma score.

8.4.4.2 Recommended Interventions in Carbon Monoxide Poisoning

Normobaric oxygenation is probably adequate therapy for carbon monoxide poisoning [23], and in terms of reduction of neurological sequelae, there is little evidence for benefit for hyperbaric oxygen therapy, including those with transient or sustained loss of consciousness.

8.4.5 Electrocution Injuries

These are unusual events in childhood but can be devastating in their consequences. Small children are most at risk of electrocution in the home, while older boys are more commonly involved in high-tension electrical injuries. Neurological problems can be directly caused by the electrical injury or are secondary to the associated cardiac arrest [43]. There is also evidence for late demyelination, particularly in the spinal cord, and late extrapyramidal disorders. Atonic and myoclonic seizures are not uncommon in the long term, and there is a very high incidence of emotional disorders in adults. Children may occasionally recover after prolonged coma.

8.4.6 *Lightning*

Lightning injuries can occur at any age, but there are few published data in children. Again, the pathology, which may include hemorrhage, results either directly from the injury or as a consequence of cardiac arrest [44]. The prognosis is poor with a 30 % mortality and sequelae (not necessarily neurological) in the majority of survivors; cardiopulmonary arrest, loss of consciousness at the scene, and leg or cranial burns suggest a poor prognosis. Acutely, the neurological manifestations in children can include coma, seizures, and ataxia; changes in memory and mood can persist for long periods of time.

8.4.7 *Strangulation and Hanging*

Strangulation and hanging form <10 % of pediatric cardiac arrests, with about 0.7 deaths/100,000 children/year. They are commonly accidental in young children, although children as young as 10 have attempted suicide by hanging [45] (Fig. 8.5) and autoeroticism occurs in teenagers. Mortality is higher in those with reduced Glasgow coma score, but neurological outcome in survivors is usually good.

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Chapter 9
Neurometabolic Crisis

Linda J. De Meirleir

Abstract Unexplained signs and symptoms in an acute situation can be due to a metabolic derangement, which needs specific biochemical tests and emergency treatments. This is certainly the case in neonates and young children with an unexplained encephalopathy. Using basic tests a differential diagnosis can be made, followed by more specialized tests in blood and urine. It is extremely important to think of the different diagnostic possibilities, especially in case of metabolic acidosis, hypoglycemia, hyperammonemia, etc.

A second condition is when patients present with intractable seizures. Here also it is necessary to make the correct diagnosis and treatment.

Thirdly in case of acute ataxia some late-onset metabolic diseases should be in the differential diagnosis.

Keywords Metabolic encephalopathies • Intractable seizures • Metabolic intoxication • Metabolic acidosis • Hyperammonemia • Fatty acid oxidation defects

9.1 Introduction

This chapter will discuss clinical neurological and metabolic syndromes in which the acute presentation, diagnosis, and treatment is essential. It will only cover metabolic diseases in which emergency management is important. This chapter will not discuss the different metabolic diseases in detail, for which excellent textbooks already exist.

The focus is on three acute neurological clinical presentations: acute encephalopathy (see also Chap. 17), intractable seizures (see also Chap. 2), and acute ataxia.

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9.2 Acute Encephalopathy

9.2.1 Presenting Symptoms

A metabolic disorder should be considered in neonates and young children with overwhelming or progressive disease without a history of asphyxia and in all children with acute encephalopathy particularly when preceded by vomiting, food refusal, and increased catabolism following accidents or surgery [1]. Respiratory insufficiency, hypotonia, poor sucking reflexes, dehydration, and seizures are all possible presentations. This is also the case in children with signs and symptoms of metabolic acidosis or hypoglycemia.

In any unexplained acute encephalopathy in the neonate, small infant, and older child, one should do a basic workup, after excluding infectious diseases or intoxications. Two types of metabolic disorders can be distinguished in the acute presentation. One is of the intoxication type, where accumulation of substances will play a role in the development of symptoms. Another type is due to energy deficiency which may lead to disturbances in different organs which will then determine the clinical picture.

Most inborn errors that result in intoxication start after a symptom-free interval of a few days (related to dietary intake) while diseases related to energy deficiency start with neurological deterioration, often at birth. Results from neonatal screening might not always be available at the time of presentation.

Important data to be obtained are a previous history of death among siblings, a family history of consanguinity, and which diet was started.

9.2.2 Assessment

Basis workup in all cases of an acute encephalopathy should include:

- Electrolytes, glucose, CRP, ALT, AST, creatinine, urea, uric acid, pH, coagulation tests, and venous gases.
- Ammonia and lactate.
- Store plasma for amino acids or other.
- Store filter paper with dried bloodspots (acylcarnitines, enzymes, DNA etc.).
- Obtain urine sample perform standard strip; store sample for organic acids, orotic acid, or amino acids at −20°.

If an inborn error with a metabolic intoxication is suspected, the first steps for treatment is to stop feeding but also to avoid catabolism by giving enough calories intravenously. Further treatment depends upon the results of the basic laboratory tests.

9.2.3 Hypoglycemia

Definition: blood glucose <2.6 mmol/L (45 mg/dL) during symptomatic hypoglycemia.

In the case of hypoglycemia, further investigations are necessary including serum-free fatty acids and 3- hydroxybutyrate, acylcarnitines, insulin and cortisol,

lactate, as well as organic acids in urine, amino acids in plasma, liver function tests, ammonia, cholesterol, and triglycerides. In the newborn clinical signs and symptoms of hypoglycemia are nonspecific. Jitteriness, tremors, cyanosis, apnea, hypotonia, lethargy, feeding difficulties, and seizures are all possible signs. Less mature infants can tolerate lower levels of hypoglycemia. The most widely accepted definition of significant hypoglycemia in the newborn is a blood glucose <30 mg/dL, and <20 mg/dL in the preterm infants.

In neonates, especially non-premature babies, persistent hypoglycemia is most commonly due to hormonal disturbances such as hyperinsulinism or hypopituitarism. According to Saudubray [2] the clinical approach to hypoglycemia is based on four major clinical criteria: liver size, timing of hypoglycemia, association with lactic acidosis, and association with hyper- or hypoketosis.

In the case of hepatomegaly, defects in gluconeogenesis such as glycogen storage disease type 1, fructose biphosphatase deficiency, or glycogenosis type 3 should be considered. Respiratory chain disorders can also present with hepatic failure, hypoglycemia, and fasting lactic acidosis, such as in mitochondrial DNA depletion syndromes MPV17 or DGUOK deficiency [3].

Without hepatomegaly, disorders of fatty acid oxidation present usually without ketosis, although during crises fatty acid oxidation defects can present with microvesicular steatosis and hepatomegaly.

Ketoacidosis with hypoglycemia is seen in organic acidurias and in ketolytic defects. Adrenal insufficiency should always be ruled out in case of hypoglycemia. Congenital hyperinsulinism (CHI) leads to persistent hyperinsulinemic hypoglycemia. Recessive inactivating mutations in ABCC8 and KCNJ11 are the most common cause of CHI [4]. The duration and degree of hypoglycemia are crucial. Immediate treatment is necessary in order to prevent brain damage.

9.2.3.1 Intervention

Treatment of hypoglycemia consists as an emergency of administration of glucose IV 8–10 mg/kg/min; additional treatment depends on the diagnosis, such as MCT oil in case of a LCHAD deficiency.

9.2.4 Metabolic Acidosis

In the case of the intoxication type metabolic acidosis develops in the neonate after a symptom-free interval of a few days. Patients tend to be hypertonic with boxing movements (maple urine syrup disease) or peripherally hypotonic with increased axial tone (organic aciduria).

Metabolic acidosis is characterized by [1]

- pH < 7.20
- HCO_3^- < 10 mmol
- $PaCO_2$ < 25 mmHg

Table 9.1
Metabolic acidosis

	Ketonuria	Lactate	Anon gap	Glucose	NH_3
Diabetes	↑↑↑	N/↑	++	↑↑↑	↓
Organ acides	↑/↑↑	N/↑↑	++	VAR	N/↑
FAO	↓↓↓	N/↑↑	+	↓↓↓	N/↑
Gluconeogenesis	N/↑↑	↑↑	VAR	↓↓↓	N
Glycogenosis					
Pyruvate	N/↑↑	↑↑↑	VAR	VAR	N/↑
Respiratory chain					

In the case of metabolic acidosis one should always study the anion gap:

$(Na^+) - (Cl^- + HCO_3^-)$ which is normally 7–16 mmol/L.

In the case of acidosis with a normal anion gap the cause could be due to renal or intestinal loss of bicarbonate (diarrhea). In the case of an increased anion gap, one should look for lactate, ketones or other anions such as organic acids.

By determining blood lactate, ketones, urinary organic acids, plasma amino acids and acylcarnitines, the differential diagnosis can be made between organic acidurias, respiratory chain defects, pyruvate dehydrogenase deficiency, disorders in gluconeogenesis, fatty acid oxidation and diabetes (Table 9.1).

In the case of lactic acidosis, secondary causes must always be excluded such as sepsis, seizures, cardiac failure, shock, etc.

If there is persistent lactic acidosis together with signs of an energy deficit (hypotonia, seizures, cardiomyopathy, hepatopathy), then most likely a respiratory chain defect or pyruvate dehydrogenase deficiency can be suspected, and should be further investigated with measurement of specific enzyme activities in muscle, liver or cultured skin fibroblasts.

While ketonuria should always be considered abnormal in neonates, it is a physiological response to catabolism starting in late infancy. Physiological ketosis can be the result of prolonged fasting, vomiting, catabolism, and medium-chain triglyceride enriched feeds. In these cases the hyperketosis does not usually exceed 6 mmol/L and is usually not associated with severe metabolic acidosis or lactic acidosis. Fasting ketosis often resulting in ketotic hypoglycemia is a frequent condition in children, presenting with recurrent attacks of vomiting, triggered by a catabolic state. It is most commonly present between 1 and 8 years of age [2], often in children small for gestational age, and improves with age. It is more common in boys. Treatment consists of avoiding fasting for more than 12 h and high-calorie emergency dietary intake orally or intravenously depending upon whether the child continues to vomit. To decrease overnight fasting uncooked starch can be given before bedtime. A similar repeated ketotic vomiting phenomenon can be seen in children with severe neuromuscular disorders such as the congenital muscular dystrophies after a fast. Here also emergency recognition and glucose infusion and carbohydrate rich drinks along with preventive measures such as cornstarch before bedtime can avoid further episodes.

9.2.5 Hyperammonemia

In neonates acute hyperammonemia occurs in a number of metabolic diseases such as in urea cycle disorders and organic acidurias. The excess ammonia might injure the brain in a reversible or irreversible way depending upon the age of onset, duration, and level of ammonia. This may lead to neuronal cell loss and cerebral atrophy.

Hyperammonemia is defined as a plasma ammonia above 90 μ[mu]mol/L and above 110 μ[mu]mol/L for the neonate (μ[mu]mol/L = mg/dL × 0.59), and suspicion for a metabolic disease is >200 μ[mu]mol/L.

9.2.5.1 Clinical Presentation of Hyperammonemia in the Newborn

Initially there are nonspecific signs and symptoms such as poor feeding, somnolence, vomiting, and irritability within the first days of life followed by tachypnea and seizures leading further to hypothermia and coma.

Hyperammonemia leads to brain edema and hyperventilation and respiratory alkalosis. Levels above 350 μ[mu]mol/L lead rapidly to severe edema and high risk of herniation and death.

In the case of suspected neonatal hyperammonemia due to an inborn error of metabolism, a differential diagnosis needs to be made between urea cycle defects, organic acidurias, and fatty oxidation defects.

Tests that are necessary are an immediate repeat sample of NH_3, blood pH, blood gases, electrolytes, lactate, urea, glucose, creatinine, liver function tests, and coagulation tests; plasma amino acids, urinary orotic acid and organic acids, plasma-free carnitine, and acylcarnitines on dried blood spot. CBC which might indicate low platelets or leucopenia often seen in organic acids and should not be interpreted as sepsis.

9.2.5.2 Assessment

The causes are shown in Fig. 9.1 and include:

- Urea cycle disorders, often with respiratory alkalosis; consider also NAGS deficiency
- Organic aciduria often associated with metabolic acidosis
- Long-chain fatty acid oxidation defects, though the ammonia concentrations are generally less elevated
- Hyperinsulinism-hyperammonemia syndrome (HIHA) with moderate increase of NH_3
- Transient hyperammonemia in neonate with respiratory distress syndrome
- Pyruvate carboxylase deficiency often with acidosis

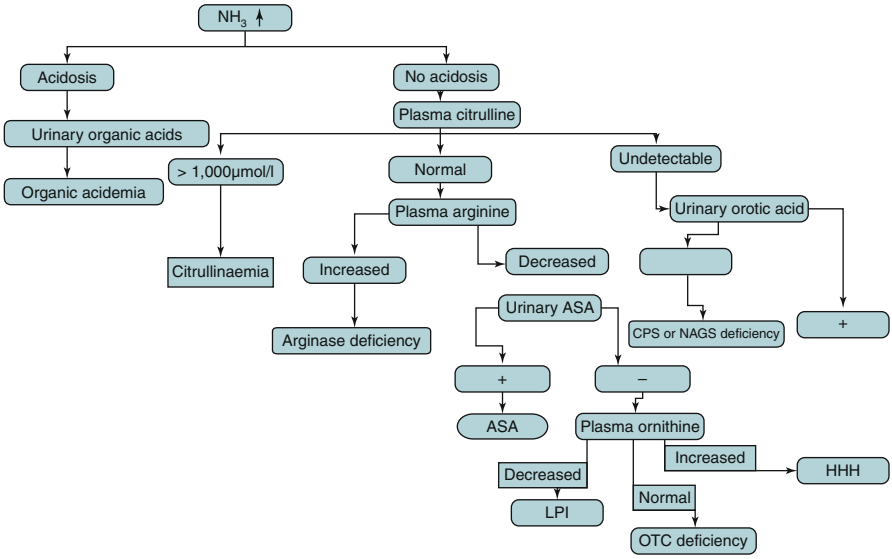

Fig. 9.1 Hyperammonemia

9.2.5.3 Intervention

Treatment of hyperammonemia is an emergency as there is a distinct correlation between outcome and duration of the neonatal coma. Also the initial or peak ammonia level may predict a poor prognosis with poor cognitive outcome if the peak ammonia exceeds 480 µ[mu]mol/L [5].

In urea cycle defects the treatment involves removal of ammonia by hemodialysis, hemofiltration, and peritoneal dialysis; using alternate pathways of elimination with benzoate and phenylacetate, adding arginine and protein restriction, but maintaining enough calories (carbohydrates and fatty acids) to avoid catabolism [6]. In the case of a suspicion of NAGSs (*N*-acetyl glutamate synthase deficiency) or CPS1 (carbamylphosphate synthase 1 deficiency), but also with other diseases associated with hyperammonemia such as in organic aciduria, a trial with Carbaglu^{R} (carbaglumic acid) 100 mg/kg/day should be started as well [7].

Insulin (0.02–0.05 E/kg/h) will inhibit endogenous protein catabolism and promote anabolism.

In certain diseases vitamin therapy could ameliorate symptoms, such as vitamin B12 in MMA, biotin in proprionic aciduria. L-carnitine should be given in the organic acidurias but is not recommended (contraindicated) for the long-chain fatty acids oxidation defects because of the risks of arrhythmogenesis [8]. In the case of a fulminating fatal encephalopathy, it is very important for diagnosis and genetic counseling to take postmortem samples of skin for fibroblast culture to be kept at room temperature in physiologic medium. Tissue biopsies such as liver and muscle need to be frozen immediately at −80 °C. In addition a portion should be taken for microscopy to be placed into in the appropriate fixative solution.

Always collect heparinized blood and EDTA blood, urine, and in some cases CSF and take a Guthrie card blood spot for acylcarnitines.

9.3 Uncontrolled Early-Onset Seizures

One should think of a metabolic cause especially in the neonate and in any young infant with unexplained and refractory seizures. In the last 10 years, a number of new gene defects have been discovered, responsible for children presenting in the neonatal and early infantile period with an epileptic encephalopathy.

9.3.1 Presentation

Epilepsy associated with inborn errors of metabolism are characterized by the following features [9]: frequent presentation in the neonatal period, infancy, or early childhood, persistent neurological impairment with developmental delay, resistance to conventional antiepileptic drugs, encephalopathy, and most often adverse cognitive outcome. Other features may include hyperexcitation, hypersalivation, and rotatory eye movements as seen in PNPO deficiency. Atypical electro-clinical presentation, atypical response to antiepileptic drugs, a mixture of generalized and partial seizures and progressive myoclonic epilepsy can be the result of an inborn error of metabolism, most notably a neurotransmitter defect. Some are treatable and these should be recognized early (Table 9.2). These include pyridoxine-responsive seizures, pyridox(am)ine-5′ phosphate deficiency, deficiency of serine synthesis, and hyperinsulinic hypoglycemia.

Table 9.2 Treatable seizures

Neonates
Pyridoxine dependent seizures
Alpha-aminoadipic semialdehyde in urine, CSF
Gene antiquitin ALDH7A1
Pyridoxal phosphate responsive seizures
Low HVA and 5HIAA; high glycine and threonine in CSF
Folinic responsive seizures antiquitin ALDH7A1
Serine biosynthesis low CSF serine
Infancy
Biotinidase: increased lactic acidosis, increase of 3-methylcrotonyl CoA and propionyl in acylcarnitines profile and most frequent increase of 3-hydroxyisovalerylcarnitine
Cerebral creatine deficiency high GAA in GAMT, low creatine; MR spectroscopy
GLUT1 deficiency low CSF glucose
Folate receptor deficiency low 5MTHF in CSF

9.3.2 Pyridoxine-Responsive or Dependent Seizures

9.3.2.1 Clinical Presentation

Typically uncontrolled seizures that can be focal, clonic, generalized myoclonic, or other forms of epilepsy [10].

This disease is now well characterized and due to mutations in antiquitin ALDH7A1 gene which encodes an alpha amino adipic semialdehyde dehydrogenase which is in the pipecolic acid pathway of the degradation of lysine. This leads to an inactivation of cofactor activity (piperidine-6-carboxylate which condenses pyridoxal phosphate) and results in accumulation of α[alpha]-amino adipic semialdehyde (α[alpha]-AASA).

9.3.2.2 Assessment

Increased levels of ⟨[αλπηα]-amino adipic semialdehyde (α[alpha]-AASA) can be found in the urine, plasma, and CSF in the patients. Other biomarker is pipecolic acid (PA), which is increased in urine, plasma, and CSF.

9.3.2.3 Intervention

In an emergency situation always give pyridoxine, 100 mg IV, followed by pyridoxal phosphate 30 mg/kg/day (orally) for 3 days (max daily 200 mg), if ineffective add-on of folinic acid.

9.3.3 Pyridoxal Phosphate Responsive Convulsions [11]

9.3.3.1 Clinical Presentation

Babies are often premature and seizures can start as early as on day 1 or even in utero. Seizures evolve into clonic seizures, status epilepticus, and myoclonia are often associated with rotatory eye movements, hyperexcitability, and hypersalivation.

The EEG can show severe burst suppression pattern or myoclonic epilepsy.

The prognosis is variable and seizures can continue even with treatment. They can also have dystonia, microcephaly, delayed myelination, and severe developmental delay.

9.3.3.2 Assessment

Biochemically one can find hypoglycemia, early acidosis, pancytopenia, and coagulopathy. There is evidence in CSF and urine of a biochemical profile consistent with

reduction aromatic L-amino acid decarboxylase with low HVA and 5HIAA, raised glycine, threonine, taurine, and histidine, and low arginine.

The diagnosis can be confirmed by searching for mutations in PNPO gene for pyridox(am)ine 5′-phosphate oxidase.

9.3.3.3 Intervention

In an emergency situation always give pyridoxine, 100 mg IV, followed by pyridoxal phosphate 30 mg/kg/day (orally) for 3 days (max daily 200 mg), if ineffective add-on of folinic acid.

9.3.4 Deficiencies in Serine Synthesis [12]

9.3.4.1 Clinical Presentation

These are often due to 3-phosphoglycerate dehydrogenase deficiency. This rare disease is characterized by congenital microcephaly, severe seizures, and psychomotor retardation.

9.3.4.2 Assessment

The diagnosis is made on the basis of decreased serine and glycine in plasma and more importantly in CSF and unrelated to the time of intake of diet.

9.3.4.3 Intervention

Treatment should start early with L-serine orally 500–700 mg/kg/day.

9.3.5 Defect in Biotinidase [13]

9.3.5.1 Clinical Presentation

Here the seizures start within the first 3 months of life; some develop myoclonic seizures and can evolve into infantile spasms.

Optic atrophy, atopic dermatitis, alopecia, and hypotonia can be present at the time of diagnosis, but it can just start as an uncontrolled seizure disorder.

9.3.5.2 Intervention

Treatment consists of lifelong biotin 5–10 mg per day.

9.3.6 GLUT 1 (Glucose Transporter 1) Deficiency [14]

This is due to mutation is SLC2A1 located on 1p35–p31.3. Three different phenotypes can be recognized [14]. The classical phenotype (84 %) with early-onset seizures (less than 2 years, 65 %) and late-onset seizures (18 %), a second nonclassical phenotype with mental retardation and a movement disorder without epilepsy (15 %), and an adult case with minimal clinical features.

The first patients described had early-onset pharmacoresistant epilepsy, with absence seizures, or myoclonic seizures leading to ataxia and microcephaly.

9.3.6.1 Assessment

The biological hallmark is the decrease of ratio CSF/blood glucose.

Cerebrospinal fluid glucose was in the study by Leen et al. [14] below 2.5 mmol/L in all patients and cerebrospinal fluid to blood glucose ratio was below 0.5 in all cases except one (range 0.19–0.52).

EEG may show 2.5–4 HZ spike waves improving on food intake [15]. Also with frequent nocturnal seizures, one should think of this disorder and do a lumbar puncture to rule out this disorder.

9.3.6.2 Intervention

Treatment currently recommended is a ketogenic diet to provide ketones to the brain as an alternative fuel.

Besides this group, which are treatable, there are a number of other severe epileptic encephalopathies due to an inborn errors of metabolism. Most frequent is the nonketotic hyperglycinemia due to a defect in degradation of glycine.

Clinical features of the disease are early-onset myoclonic encephalopathy. The disease starts within the first hours of life, coma, hypotonia, myoclonia, hiccups, ophthalmoplegia, and respiratory problems. The EEG will show a typical burst suppression pattern. The diagnosis is made by amino acid analysis with increase of glycine in blood, urine, and CSF. The prognosis is usually severe even in case of early intervention with sodium benzoate and dextromethorphan.

Other early-onset epileptic encephalopathies include mitochondrial glutamate transporter defect, glutamine synthase deficiency; but also peroxisomal disorders, sulfite oxidase and respiratory chain disorders; and defects in purine metabolism, CDG and Menkes disease. All these diseases should be in the differential diagnosis when dealing with a child with an epileptic encephalopathy. Many other genetic defects such as ARX or STXBP1 can give the same clinical presentation and present as Ohtahara syndrome, early myoclonic epileptic encephalopathy, early West syndrome, or tonic seizures [16].

Further one should think also about POLG [17] in children presenting with difficult-to-control seizures, status epilepticus partialis, and avoid by all means giving these patients valproate. Determining the alpha-fetoprotein, CSF protein, and lactate might help in the diagnosis.

9.4 Older Child with Recurrent Attacks of Ataxia

9.4.1 Presentation and Assessment

Recurrent attacks of ataxia can be a presenting sign of late-onset maple syrup urine disease or an organic aciduria, especially when associated with ketoacidosis.

Late-onset ornitine transcarbamoylase (OTC) deficiency in girls can also present with attacks of ataxia or coma due to high NH_3 [18]

Guillain-Barré-like or acute ataxia with peripheral neuropathy can be seen in boys with milder forms of PDH E1α[alpha] deficiency. Here an increase of lactate and pyruvate in plasma and CSF with normal L/P ratio is the hallmark of the disease.

9.4.2 Intervention

A ketogenic diet might prevent further episodes.

Finally attacks of ataxia can also be seen in patients with GLUT 1 deficiency, which can be diagnosed by looking at ratio of glucose in CSF/blood. Others are biotinidase deficiency, abetalipoproteinemia, Hartnup disease, and pyruvate carboxylase deficiency. Also consider acute or chronic recurrent ataxia in mitochondrial diseases (e.g., NARP, KSS, SANDO)and Refsum that can all present with ataxia due to decompensation during infections or in case of stress.

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Chapter 10
Approach to Childhood-Onset Muscle Cramps, Exercise Intolerance, and Recurrent Myoglobinuria

Ingrid Tein

Abstract The approach to an acute attack of myoglobinuria must be multisystemic. The main hazards of an attack of myoglobinuria are potentially life-threatening respiratory failure, renal failure, and cardiac arrhythmias (secondary to electrolyte abnormalities) each of which must be closely monitored until resolution of the acute catabolic crisis. There may be need for transient ventilation if there is significant weakness of the respiratory muscles and dialysis in the event of renal failure. There should be EKG monitoring for arrhythmias. Close monitoring and prompt correction of electrolyte abnormalities such as hyperkalemia and hypocalcemia are key to the prevention of arrhythmias. If renal function is normal, intravenous hydration to promote brisk diuresis should be instituted to aid clearance of the myoglobin. Bed rest to reduce further stress on bioenergetically compromised muscles should be encouraged in the acute phase. Energy substrates to bypass the biochemical pathway that is dysfunctional may need to be given intravenously, particularly if there is vomiting or gastrointestinal paresis. This chapter focuses on the clinical syndrome of acute myoglobinuria, its investigation and emergency management, and the differential diagnosis of recurrent heritable myoglobinuria based on a biochemical classification scheme. This is followed by a more specific discussion of the presenting hallmark clinical, pathological, and biochemical features; the pathway-specific diagnostic approach; and the approaches to

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management and treatment of glycolytic/glycogenolytic, fatty acid oxidation, and mitochondrial disorders. The section concludes with an algorithmic approach to the investigation of heritable recurrent myoglobinuria, childhood-onset muscle cramps, and exercise intolerance.

Keywords Myoglobinuria • Fatty acid oxidation defects • Mitochondrial disorders • Glycolytic/glycogenolytic disorders

10.1 Clinical Syndrome of Myoglobinuria and Investigations During Acute Episode

10.1.1 Presenting Features

As defined by Rowland in 1984 [1], myoglobinuria is a clinical syndrome, not just a biochemical state. If the patient is alert, there is myalgia or limb weakness. The color of the urine is usually brown, rather than red, and the urine gives positive chemical tests for both albumin and heme. On microscopy, there are few or no red blood cells. Inconstant features arising from muscle breakdown include hyperkalemia, hyperuricemia, hyperphosphatemia, and hypo- or hypercalcemia. If there is renal failure, serum potassium and calcium may rise. If the patient is comatose and if the presenting disorder is one of acute renal failure, there may be no muscle symptoms or signs.

10.1.2 Recommended Assessments

Elevated myoglobin in urine is identified by immunochemical methods with antibodies raised against purified myoglobin. Faster, more clinically relevant tests are the serum sarcoplasmic enzymes, including creatine kinase (CK) which is usually more than 100 times normal. AST from muscle may also be very elevated and is frequently mistaken for liver involvement. In case of coma and renal failure the diagnosis can be made if (a) the serum sarcoplasmic enzymes are 100 times higher than normal values and (b) there is renal failure.

Initial critical blood work, prior to giving intravenous fluids, should include serum glucose, electrolytes, BUN, creatinine, calcium, phosphorous, albumin, CK, AST, uric acid, lactate, carnitine total and free, acylcarnitines, and free fatty acid-to-ketone ratio (Fig. 10.1). Urine should be tested by hematest, and if positive, microscopy should be done to exclude more than a few red blood cells. Initial critical urine should be tested for ketones and organic acids.

If there is an elevation in serum lactic acid, pyruvate should also be measured. An elevation in the lactate-to-pyruvate ratio would suggest a defect in the mitochondrial respiratory chain. A reduction in the lactate-to-pyruvate ratio would suggest a defect in the pyruvate dehydrogenase complex.

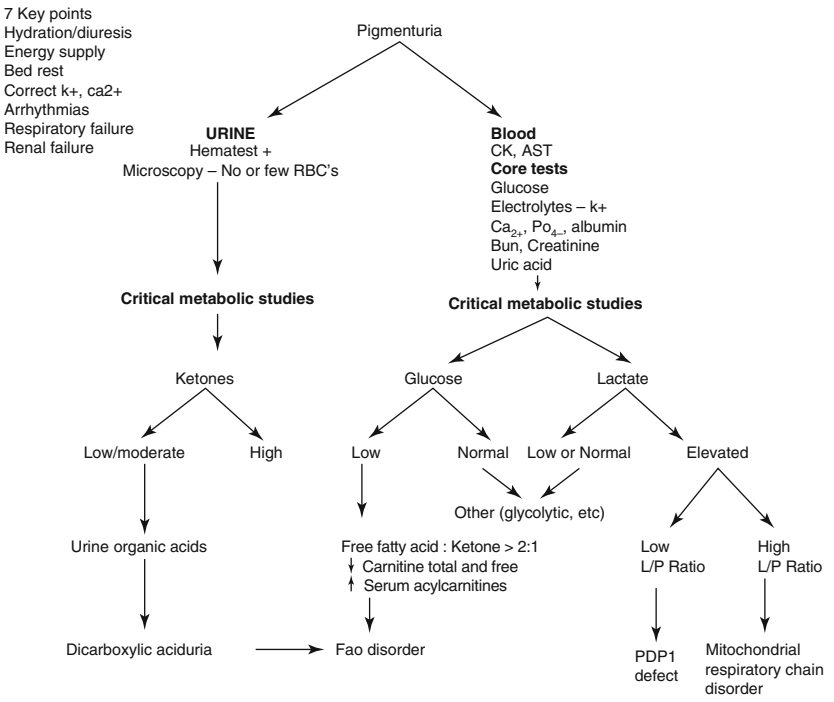

Fig. 10.1 Approach to acute attack of myoglobinuria. L/P = lactate-to-pyruvate ratio

If the serum glucose is decreased (e.g., <3 mM), it is important to determine whether there is a sufficient ketogenic response. If the urine ketones are large, this would unlikely be a defect in fatty acid oxidation (FAO). However, if the urine ketones are moderate (arising from a concentrated urine due to vomiting with dehydration) or small, a defect in FAO should be considered. The serum free fatty acid-to-ketone ratio is extremely helpful. Normally this should be 1:1; however, if the ratio is >2:1, this would be strongly supportive of a defect in the FAO pathway. In intramitochondrial ß-oxidation defects, there would likely be a decrease in serum total and free carnitine with an increase in the esterified carnitine fraction due to the accumulation of fatty acid metabolites proximal to the block which become esterified to carnitine. The serum acylcarnitine profile, which can be done on a serum sample or from dried blot spots on a Guthrie card, may provide highly useful diagnostic information regarding the chain-length specificity of the biochemical block (e.g., short, medium, or long chain) as well as the species type which may suggest the specific site of block which can then be investigated by enzyme assay in cultured skin fibroblasts, followed by molecular mutation analysis. Urine organic acids may similarly provide helpful information.

Following recovery from myoglobinuria, a prioritized series of investigations (Sect. 10.6 and Fig. 10.2) should be conducted based upon the clinical features and screening biochemical studies to identify the specific enzymatic deficiency (cultured skin fibroblasts *or* biopsied skeletal muscle as indicated for most mitochondrial disorders) as well as the genetic mutation. If one suspects a mitochondrial

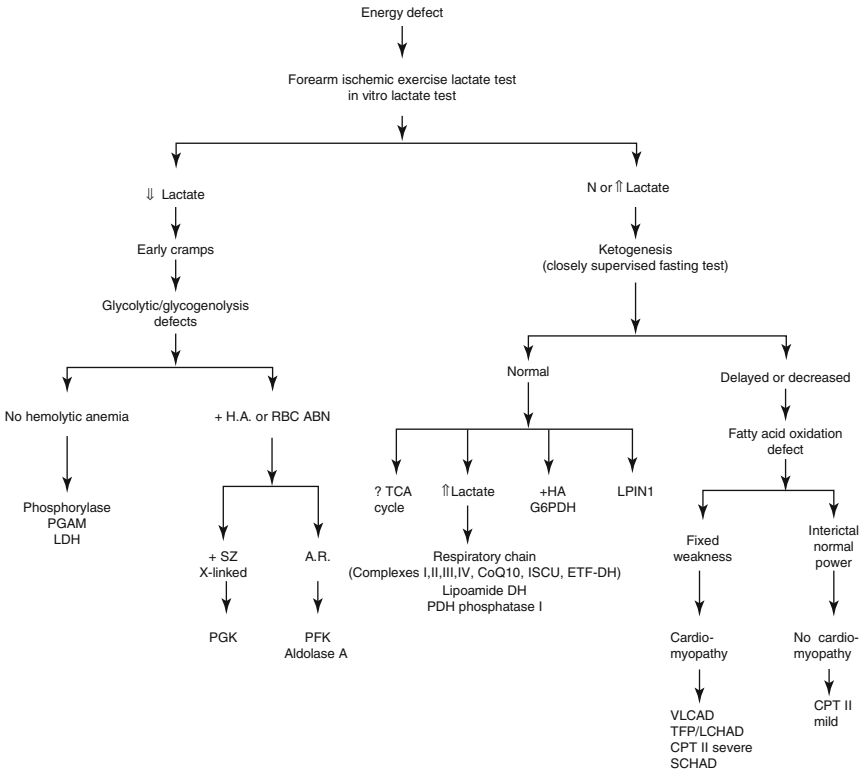

Fig. 10.2 Approach to investigation of hereditable recurrent myoglobinuria (Modified from Tein [2])

DNA depletion or deletion syndrome or muscle coenzyme Q10 deficiency, these diagnoses can only be made by muscle biopsy. Muscle biopsies should be done well after recovery from myoglobinuria to avoid false-positive defects due to necrotic muscle.

10.1.3 Recommended Interventions

The approach to an acute attack of myoglobinuria must be multisystemic. The main hazards of an attack of myoglobinuria are potentially life-threatening respiratory failure, renal failure, and cardiac arrhythmias secondary to electrolyte abnormalities each of which must be closely monitored until resolution of the acute catabolic crisis. There may be need for transient ventilation if there is significant weakness of the respiratory muscles and dialysis in the event of renal failure. There should be EKG monitoring for arrhythmias. Close monitoring and prompt correction of electrolyte abnormalities such as hyperkalemia and hypocalcemia are key to the

prevention of arrhythmias. If renal function is normal, intravenous hydration to promote brisk diuresis should be instituted to aid clearance of the myoglobin. Bed rest to reduce further stress on bioenergetically compromised muscles should be encouraged in the acute phase. Energy substrates to bypass the biochemical pathway that is dysfunctional may need to be given intravenously, particularly if there is vomiting or gastrointestinal paresis as is often seen in the fatty acid oxidation (FAO) defects. In phosphorylase deficiency, the most common glycolytic disorder, and in the FAO defects, glucose is the most effective energy substrate. Glucose is not effective in more distal glycolytic disorders as it cannot be metabolized. In FAO disorders, intravenous glucose in a balanced electrolyte solution should be given at a rate of 8–10 mg/kg/min of glucose to effectively alleviate the stress on the FAO pathway and reduce the accumulation of potentially toxic fatty acid metabolites that would accumulate proximal to the block.

10.2 Biochemical Classification and Clues to Pathogenic Mechanisms

The etiologies of myoglobinuria can be divided into hereditary and sporadic forms. Sporadic etiologies which may precipitate an attack in an otherwise normal individual can be divided into those related to exertion, crush injury, ischemia, toxins and drugs, metabolic depression or distortion, abnormalities of body temperature, infections, progressive muscle disease, and those which appear to be idiopathic. A comparison of myoglobinuria related to exertion, heat stroke, neuroleptic malignant syndrome, and malignant hyperthermia is given in Table 10.1. We will consider only the heritable causes of myoglobinuria here which predispose to recurrent myoglobinuria.

Table 10.1 Heat, fever, and myoglobinuria

	Exercise-induced myoglobinuria	Malignant hyperthermia	Malignant neuroleptic syndrome	Heat exhaustion/heat stroke
Myoglobinuria	+	+	+	+
Provoking factor	Exercise	Halothane	Neuroleptics	Exercise/exposure
Tachycardia	+	+	+	+
Acidosis	+	+	+	+
DIC	+	+	+	+
Muscle rigidity	0	+	+	0
Onset duration	Minutes	Minutes	Days	Minutes
Familial attacks	Rare[a]	Rare	None	None

Taken with permission from Rowland [3]
DIC disseminated intravascular coagulation
[a]Hereditable biochemical abnormality may be identified

The hereditary forms (Table 10.2) are particularly important because they are recurrent and suggest underlying pathogenic mechanisms. This may have implications for future treatment strategies and preventative measures in the management of both the heritable and sporadic causes of myoglobinuria. These forms may be divided into three groups based upon whether the biochemical abnormality is (1) known (2), incompletely characterized, or (3) unknown. In the first group, there are at least 27 recognized disorders, 8 affecting glycolysis or glycogenolysis, 6

Table 10.2 Heritable causes of exercise intolerance and recurrent myoglobinuria

I. Biochemical abnormality known

1. *Glycolysis/glycogenolysis*
   (1) [a]Phosphorylase [37]
   (2) Phosphofructokinase [38, 39]
   (3) [a]Phosphoglycerate kinase [40]
   (4) [a]Phosphoglycerate mutase [41]
   (5) [a]Lactate dehydrogenase [42]
   (6) Phosphorylase "b" kinase [43]
   (7) Debrancher [44]
   (8) [a]Aldolase A [45]
2. *Fatty acid oxidation*
   (1) [a]Carnitine palmitoyltransferase II [46]
   (2) Long-chain acyl-CoA dehydrogenase [70]
   (3) Very long-chain acyl-CoA dehydrogenase [47]
   (4) Medium-chain acyl-CoA dehydrogenase [48]
   (5) [a]Short-chain L-3-hydroxyacyl-CoA dehydrogenase [49]
   (6) [a]Trifunctional protein/long-chain L-3-hydroxyacyl-CoA dehydrogenase [50]
   (7) [a]Medium-chain 3-ketoacyl-CoA thiolase [51]
3. *Pentose phosphate pathway*
   (1) [a]G6PDH [52]
4. *Purine nucleotide cycle*
   (1) Myoadenylate deaminase [53]
5. *Mitochondrial respiratory chain*
   (1) [a]Coenzyme Q10 deficiency [54] due to CoQ10 biosynthetic gene defects
   (2) [a]Multiple mitochondrial DNA deletions [55]
   (3) Complex I deficiency [56]
   (4) Complex III deficiency (cytochrome b) [57]
   (5) Complex IV deficiency (Cytochrome oxidase deficiency) [58]
   (6) Cytochrome c oxidase subunit II defect [59]
   (7) [a]Iron-sulfur cluster assembly protein (ISCU) with deficiency of succinate dehydrogenase (complex II), aconitase, and complex I and complex III [4, 60]
   (8) ETF-dehydrogenase deficiency with muscle CoQ10, complexes I, II–III, IV deficiency [5]
   (9) mtDNA m.4281A>G in tRNA (Ile) with COX deficiency [61]
6. *Pyruvate dehydrogenase complex*
   (1) Pyruvate dehydrogenase phosphatase 1 (PDP1) deficiency [62]
7. [a]*Lipoamide dehydrogenase deficiency* [63]

Table 10.2 (continued)

II. Biochemical abnormality incompletely characterized
(1) [a]Impaired long-chain fatty acid oxidation [64]
(2) [a]Impaired function of the sarcoplasmic reticulum on anesthetic exposure (?) in familial malignant hyperthermia and central core disease due to RyR1 defect [65] (predisposition in Duchenne muscular dystrophy, Becker muscular dystrophy, myotonic dystrophy, myotonia congenita, Schwartz-Jampel syndrome, King-Denborough syndrome)
III. Abnormal composition of sarcolemma
(1) [a]Abnormal composition of the sarcolemma in Duchenne and Becker muscular dystrophy [66–68], LGMD21 due to mutations in fukutin-related protein gene [69]
(2) Triglyceride and membrane phospholipid biosynthesis
[a]LPIN1 – muscle-specific phosphatidic acid phosphatase [6]
IV. Biochemical abnormality unknown
(1) [a]Familial recurrent myoglobinuria
(2) [a]Repeated attacks in sporadic cases

Modified from Tein et al. [7] with permission of Elsevier Science Publishers, Amsterdam, The Netherlands. Specific references found in [1]

[a]Etiologies that have been documented to cause recurrent myoglobinuria beginning in childhood

affecting fatty acid oxidation, one involving the pentose phosphate pathway, one involving the purine nucleotide pathway, >9 involving the mitochondrial respiratory chain, 1 involving lipoamide dehydrogenase deficiency which affects several pathways, and one involving triglyceride and membrane phospholipid biosynthesis. All are autosomal recessive with the exception of PGK, G6PD, and certain forms of phosphorylase b kinase (alpha subunit) deficiencies which are X-linked. The mitochondrial defects may be either autosomal recessive, autosomal dominant, or inherited by maternal mitochondrial transmission.

It has been hypothesized that myoglobinuria in glycolytic and FAO disorders may be due to a fall in adenosine-5′-triphosphate (ATP) stores below some critical level needed to maintain the integrity of the muscle surface membrane [1]. Fuels generated from these two pathways are used to replenish phosphocreatine and phosphoenolpyruvate, high-energy phosphate compounds, which in turn are used to regenerate ATP. Dependence of skeletal muscle on different metabolic pathways depends upon the type of muscular activity [1]. Resting muscle is heavily dependent on free fatty acids and FAO. At rest, glucose utilization accounts for about 10–15 % of total oxygen consumption. Both slow and fast twitch fibers have similar levels of glycogen content at rest. In working muscle, relative utilization of triglycerides and stored glycogen versus free fatty acids and glucose depends upon the type, duration, and intensity of exercise. In moderate exercise, ATP is first regenerated from high-energy phosphates. This is followed by muscle glycogen for the first 5–10 min, indicated by the sharp rise in lactate. Lactate then falls as muscle triglycerides and blood-borne fuels from hepatic glycogenolysis are utilized. Major fuels after 90 min are free fatty acids and glucose. Free fatty acid uptake increases by 70 % in mild-moderate prolonged exercise between 1 to 4 h and after 4 h; free fatty acids are used twice as much as carbohydrates.

In the glycolytic disorders, muscle is thus most vulnerable during the initial stages of intense exercise when carbohydrates constitute the major energy source. The development of a "second-wind" phenomenon likely indicates a switch from muscle glycogenolysis (which is deficient) to hepatic glycogenolysis (which is intact) and in part to a switch from carbohydrate to fatty acid utilization [1].

Identified defects in FAO include carnitine palmitoyltransferase II (CPT II), long-chain acyl-CoA dehydrogenase (LCAD), very long-chain acyl-CoA dehydrogenase (VLCAD), short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD), medium-chain acyl-CoA dehydrogenase (MCAD), and trifunctional protein/long-chain L-3-hydroxyacyl-CoA dehydrogenase (TFP/LCHAD) deficiencies. In FAO disorders, attacks of myoglobinuria are precipitated after mild to moderate prolonged exercise (e.g., >45–60 min) when fatty acids are the key bioenergetic energy source in exercising muscle. These attacks may be further exacerbated by inadequate caloric intake as in fasting or infection with vomiting, which further limit blood glucose. In fasting, not only are muscle glycogen and blood glucose decreased, but there is defective ketogenesis due to impaired hepatic FAO. Therefore, a drop in ATP may occur. Other possible mechanisms relate to the toxicity of elevated free fatty acids arising proximal to the specific block. Excessive long-chain fatty acids, which may accumulate in long-chain fatty acid (LCFA) oxidation disorders, may have detergent properties on muscle and mitochondrial membranes leading to the potentiation of free-radical-mediated lipid membrane peroxidative injury [1]. Excessive free fatty acids and their metabolites from compensatory omega oxidation may also inhibit key metabolic pathways (e.g., gluconeogenesis, ß-oxidation, urea cycle) and thus contribute to a further decrease in ATP. Other risk factors include infection, during which metabolic processes preferentially favor FAO, which persists despite glucose delivery, thereby increasing dependence on FAO. Emotional stress has also been a recognized precipitant which may relate to catecholamine-induced lipolysis increasing the FAO stress. Cold exposure may be detrimental as cold stimulates ketogenesis in normal individuals and shivering depends upon involuntary muscle activity which is primarily dependent upon LCFA oxidation.

In the respiratory chain disorders, a drop in ATP production could again be postulated as the mechanism. Haller et al. in 1991 [1] identified a combined complex II-aconitase deficiency in muscle in a Swedish man who was strikingly similar to the large Swedish kindred described by Larsson et al. in 1964. This kindred had exercise intolerance, dyspnea, palpitations, excessive exertional rise in lactate and pyruvate, and recurrent myoglobinuria. These complex II/aconitase deficiency cases have now been identified as also having low complex I and III activities and have been attributed to a defect in the iron-sulfur cluster (ISCU) assembly protein [4]. Multiple deletions of mitochondrial DNA have been described in two brothers with recurrent exertional myoglobinuria. Coenzyme Q10 deficiency was described in two sisters with recurrent myoglobinuria. More recently an autosomal recessive isolated muscle form of CoQ10 deficiency has been described in patients with exercise intolerance, fatigue, proximal myopathy and high serum CK with severely decreased activities of complexes I and II+III, and moderately decreased complex IV, due to mutations in the electron transfer flavoprotein (ETFDH) gene which is allelic to late-onset glutaric aciduria type II [5].

Other defects in energy metabolism linked with exercise intolerance are lipoamide dehydrogenase deficiency and pyruvate dehydrogenase phosphatase I deficiency. Deficiency of lipoamide dehydrogenase is associated with recurrent myoglobinuria. It is a component of the pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and branched-chain alpha-keto acid dehydrogenase complexes. Myoadenylate deaminase and G6PD deficiencies have not been conclusively linked to a logical theory of causation as both enzymes may be absent in asymptomatic people.

In familial malignant hyperthermia (MH), there appears to be diverse underlying etiologies; however, the final triggering event appears to be a sudden increase in sarcoplasmic calcium in response to anesthetics or stress. Among these are an autosomal-dominant disorder that maps to chromosome 19q12–13.2 which involves an abnormality of the calcium-release channel in the sarcoplasmic reticulum (SR) or the ryanodine receptor. Among the genetic myopathies predisposing to MH is central core disease which is also autosomal-dominant and found to be strongly linked to MH. Further, the gene for central core disease has been mapped to the same position as MH.

In the Xp21-linked myopathies, potential membrane instability due to the missing dystrophin protein may be etiological in the mechanism for myoglobinuria. Several Becker's muscular dystrophy patients have had exertional myoglobinuria in adolescence. In Duchenne dystrophy, a predisposition to myoglobinuria has been documented with anesthesia. This reaction is distinctly different from classic MH as in Duchenne patients, the heart rate is usually decreased rather than increased and may proceed to cardiac arrest, temperature may be normal, rigidity is uncommon, and dantrolene does not alter the course of the anesthetic reaction. Duchenne patients may be protected from exertional myoglobinuria by their exercise limitation.

Recurrent myoglobinuria was described in children who presented between 2 and 7 years of age in the context of febrile illnesses. Deleterious mutations were documented in the *LPIN1 gene* which encodes the muscle-specific phosphatidic acid phosphatase, a key enzyme in triglyceride and membrane phospholipid biosynthesis [6]. Analysis of phospholipid content disclosed accumulation of phosphatidic acid and lysophospholipids in muscle of the more severe genotype which was speculated to result in myoglobinuria during stress. This disorder appears to be autosomal recessive.

There appear to be differences in the distribution of etiologies of heritable myoglobinuria in adults versus children. In a study of 100 cases of recurrent childhood-onset myoglobinuria, only 24 % of children were diagnosed biochemically, 16 with CPT II deficiency, one with SCHAD deficiency, and 7 with various glycolytic defects including 2 PPL, 1 PGK, 3 PGAM, and 1 LDH deficiency [8]. These children were divided into a type I exertional group with exertion as the primary precipitating factor (56 cases) and a type II toxic group with infection and/or fever and leukocytosis as the primary precipitants (37 cases). Type II toxic childhood group was distinguished from type I exertional childhood- and adult-onset groups by its etiologies which were limited to FAO defects and its slight female predominance in contrast to marked male predominance in the latter two groups. The type II toxic group was further distinguished by its earlier age at onset of myoglobinuria, the

Table 10.3 Differentiation between disorders of glycogen versus lipid metabolism resulting in exercise intolerance and/or myoglobinuria

	Glycolytic/glycogenolytic Phosphorylase deficiency	Fatty acid oxidation CPT II deficiency
Symptom onset in exercise	Early (first few minutes)	Late (particularly after 1 h)
Second wind	+	–
Myalgia	Cramps	Stiffness
Fixed weakness	More common	Less common
Elevated interictal CK	+	–
Abnormal forearm ischemic lactate test	+	–
Delayed ketogenesis	–	+
Muscle biopsy	± Glycogen storage	± Lipid storage

From Tein [10]. Used with permission

presence of more generalized disease (ictal bulbar signs, encephalopathy, seizures, delay), and higher mortality rate. In a study of 77 adult patients, ages 15–65 years, Tonin et al. [9] identified the enzyme abnormality in 36 patients (47 %) as follows: CPT II deficiency in 17 patients; glycolytic defects in 15 including PPL, 10; PPL b kinase, 4; PGK, 1; myoadenylate deaminase in 3; and combined CPT II and myoadenylate deaminase deficiencies in one. The most common etiology overall for recurrent myoglobinuria in both adults and children and males and females, to date, is CPT II deficiency. In adults, phosphorylase deficiency is similar in frequency to CPT II deficiency. Clinical and laboratory differentiation of classic CPT II from phosphorylase deficiency is given in Table 10.3.

10.3 Glycolytic/Glycogenolytic Defects

10.3.1 Presenting Features

The main clinical presentations and affected tissues of the muscle glycogenoses are summarized in Table 10.4 [11].

10.3.2 Recommended Assessments

A useful test for the detection of enzymatic defects in the nonlysosomal glycogenolytic pathway and in glycolysis is the "forearm ischemic exercise test" developed by McArdle in 1951 [1]. This can be successfully performed in young cooperative children even down to 7 years of age. An indwelling needle is placed in a superficial antecubital vein, and a basal lactate and ammonia are obtained without stasis. A sphygmomanometer cuff is placed above the elbow and inflated above arterial pressure. The patient is asked to rhythmically squeeze another rolled-up cuff to well

Table 10.4 Clinical presentations of muscle glycogenoses

Type	Enzyme defect	Affected tissues	Clinical presentation
II Infancy	Acid maltase	Generalized	Cardiomegaly, weakness, hypotonia, death <age 1 year
II Childhood	Acid maltase	Generalized	Myopathy simulating Duchenne dystrophy, respiratory insufficiency
II Adult	Acid maltase	Generalized	Myopathy simulating limb-girdle dystrophy or polymyositis, respiratory insufficiency
III	Debrancher	Generalized	Hepatomegaly, fasting hypoglycemia, progressive weakness
IV	Brancher	Generalized	Hepatosplenomegaly, cirrhosis of liver, hepatic failure, myopathy, cardiomyopathy, APBD
V	Muscle phosphorylase	Skeletal muscle	Intolerance to intense exercise, cramps, myoglobinuria
VII	Muscle phosphofructokinase (PFK-M)	Skeletal muscle RBC	Intolerance to intense exercise, cramps, myoglobinuria
VIII	Phosphorylase kinase	Liver	Asymptomatic hepatomegaly
VIII	Phosphorylase kinase	Liver and muscle	Hepatomegaly, growth retardation, hypotonia
VIII	Phosphorylase kinase	Skeletal muscle	Exercise intolerance, myoglobinuria
VIII	Phosphorylase kinase	Heart	Fatal infantile cardiomyopathy
IX	Phosphoglycerate kinase (PGK)	Generalized	Hemolytic anemia, seizures, mental retardation, intolerance to intense exercise, myoglobinuria
X	Muscle phosphoglycerate mutase (PGAM-M)	Skeletal muscle	Intolerance to intense exercise, myoglobinuria
XI	Muscle lactate dehydrogenase (LDH-M)	Skeletal muscle	Intolerance to intense exercise, myoglobinuria
XII	Aldolase A	Skeletal muscle RBC	Nonspherocytic hemolytic anemia, exercise intolerance, weakness
XIII	ß-Enolase	Skeletal muscle	Exercise Intolerance

Modified from DiMauro and Lamperti [11]
APBD adult polyglucosan body disease, *RBC* red blood cells

above 120 mmHg for 1–2 min of exercise, which requires constant encouragement from the observer. This can produce significant discomfort in normals and should be truncated if the patient develops an acute cramp, as myonecrosis may occur in an individual with a glycolytic disorder. After 1 min of exercise, the cuff around the arm is deflated and blood samples are sequentially obtained at 1, 3, 5, 7, 10, and 15 min. In normal subjects, there is a 3- to 5-fold increase of lactate in the first 3 min, and this declines to baseline values by 15 min. This is accompanied by a similar increase in ammonia. In individuals with a defect in glycolysis/glycogenolysis, there is an insufficient rise in lactate (less than 2-fold), and there will be a

compensatory increase in ammonia (e.g., 10-fold), which also serves to indicate sufficient effort. An insufficient lactate rise has been demonstrated in PPL, debrancher, PFK, PGK, PGAM, and LDH deficiencies, but not in acid maltase or phosphorylase b kinase deficiency. A major limitation of the test is that the rise of venous lactate in patients not having a defect in this pathway depends on the patient's ability and willingness to exercise. An insufficient effort is indicated by an insufficient rise in both lactate and ammonia.

The energy substrates used by muscle for aerobic metabolism depends upon the type, intensity, and duration of exercise as well as on physical conditioning and diet [1]. During intense exercise (close to one's maximal oxygen uptake or V02max in dynamic exercise or maximal force generation in isometric exercise), energy is derived from anaerobic glycolysis, particularly when there is a "burst" of activity with rapid acceleration to maximal exercise. At low-intensity exercise (<50 % V02max), blood glucose and free fatty acids are the primary energy source, whereas at higher intensities the proportion of energy derived from carbohydrate oxidation increases, and glycogen becomes an important fuel. At 70–80 % of V02max, aerobic metabolism of glycogen is the critical energy source, and fatigue occurs when glycogen stores are exhausted. Thus, the initial stages of intense exercise would be the time of greatest vulnerability for individuals with defective glycolysis/glycogenolysis. Patients must rest soon after the beginning of exercise due to muscle cramps, but if they continue to exercise at low intensity, they are then able to continue for a longer time which is known as the "second-wind" phenomenon. This has been attributed to a metabolic switch from carbohydrate to fatty acid utilization and by increased circulation of blood glucose from hepatic glycogenolysis in myophosphorylase deficiency, an important clue on history taking.

10.4 Phosphorylase Deficiency

10.4.1 Presenting Features

Myophosphorylase deficiency (type V glycogenosis or McArdle's disease) is a rare disease but important cause of exercise intolerance and recurrent myoglobinuria [11]. In ~50 % of patients, there are episodes of muscle necrosis and myoglobinuria after exercise, 27 % of whom develop acute renal failure. Following myoglobinuria, there is usually complete functional recovery. Fixed mild proximal greater than distal weakness is seen in about one-third of typical cases, which is more common in older patients. Exercise intolerance generally starts in childhood, but overt episodes of muscle cramping and myoglobinuria usually develop later with the diagnosis being made in the second or third decade. In some, progressive weakness begins late in life (sixth decade) with no history of cramps or pigmenturia. In four severe childhood cases, there was marked generalized muscle and respiratory weakness at or soon after birth and death in infancy.

10.4.2 Recommended Assessments

Between episodes of myoglobinuria, the serum CK is variably increased in 93 % of cases which contrasts with CPT II deficiency in which the resting CK is generally normal. EMG between episodes of myoglobinuria demonstrates fibrillations, myotonic discharges, and positive waves in up to 50 % of patients, suggesting a mild myopathy. ^{31}P-NMR spectroscopy demonstrates lack of cytoplasmic acidification during aerobic or ischemic exercise as well as a greater than normal drop of the PCr/Pi ratio.

Muscle Biopsy. On periodic acid-Schiff stain, there may or may not be focal accumulations of glycogen in the subsarcolemmal regions and between myofibrils. The phosphorylase (PPL) stain will show no staining in muscle fibers, though smooth muscle in the walls of intramuscular vessels will stain normally. DiMauro and Tsujino in 1994 [1] point out that a positive histochemical reaction may be seen in McArdle's (1) when there is residual enzyme activity and (2) when there are regenerating fibers. "False-positive" reaction in regenerating fibers is due to expression of a different isozyme in immature muscle cells. Electron microscopy shows accumulation of normal-looking glycogen ß particles under the sarcolemma and between myofibrils and myofilaments.

Biochemical Features. Muscle PPL exists as an active phosphorylated alpha form and a less active, dephosphorylated beta form. PPL activity is undetectable in most or up to 10 % of normal residual activity in the muscle of affected patients. Glycogen accumulation is moderate (about two-fold) or may be normal and is normal in structure. The majority of patients have no immunologically detectable enzyme protein in muscle by SDS-PAGE, immunoblot, and enzyme-linked immunosorbent assay (ELISA). Normal mature human muscle has a single phosphorylase isozyme, whereas cardiac muscle and brain have three different isozymes.

Molecular Genetics. The three PPL isozyme genes have been cloned, sequenced, and localized to different chromosomes. More than 100 mutations have been identified in the muscle isozyme gene, which will facilitate carrier identification. These include missense, nonsense, and splice junction mutations. The most common mutation in Europe and North America is the Arg49Stop, which accounts for 81 % of the alleles in British patients and 63 % of alleles in US patients.

10.4.3 Recommended Treatment Interventions

Most therapeutic trials have attempted to bypass the metabolic block by providing the muscle with glycolytic substrates. Efforts to raise blood glucose by oral administration of glucose or fructose have had inconsistent results and caused weight gain. Glucagon injections were impractical and had inconsistent results. Raising serum free fatty acid concentrations through the use of fat emulsions, administration of norepinephrine or heparin and fasting, increased exercise tolerance. More practical

regimens such as a high-fat, low-carbohydrate diet were not effective. Another strategy was to supply branched-chain amino acids which are taken up rather than released during exercise by McArdle muscle. However, this resulted in an impairment rather than an improvement of bicycle exercise capacity in five of six patients, possibly due to a lowering of free fatty acids by the amino acids. Slonim and Goans in 1985 [1] instituted a high-protein diet in a patient with weakness and demonstrated an improvement of muscle endurance and strength. Vitamin B_6 is another potential therapeutic aid, as overall body stores of pyridoxal phosphate are depleted in McArdle's disease due to the lack of enzyme protein to which pyridoxal phosphate is bound. One patient has been shown to have a beneficial effect with vitamin B_6 supplementation but further studies need to be done. Oral creatine monohydrate supplementation in a placebo-controlled crossover trial in nine patients alleviated symptoms and increased their capacity for ischemic, isometric forearm exercise. Another strategy has been the ingestion of sucrose prior to exercise to increase the availability of glucose [12]. In a single-blind randomized, placebo-controlled crossover study of 12 patients, sucrose ingestion prior to exercise improved exercise tolerance and sense of well-being. Aerobic training of four McArdle's patients improved peak cycle exercise capacity, circulatory capacity, and oxygen uptake [13]. Finally, a first-generation adenoviral recombinant containing full-length human myophosphorylase cDNA has been transduced into phosphorylase-deficient sheep and human myoblasts, resulting in restoration of phosphorylase activity.

10.5 Fatty Acid Oxidation Disorders

10.5.1 Presenting Clinical and Biochemical Features

Defects in FAO are important because they are potentially rapidly fatal and a source of major morbidity including recurrent myoglobinuria, progressive lipid storage myopathy, neuropathy, cardiomyopathy, recurrent hypoglycemic hypoketotic coma or Reye-like syndrome with seizures, and developmental delay. As all are autosomal recessive, there is often sudden unexpected death in siblings. Early recognition and prompt institution of therapy and preventative measures may be lifesaving decreasing morbidity. Hale and Bennett [14] suggest that there are at least four clinical and laboratory features that should lead the clinician to suspect a genetic defect in FAO as follows (Table 10.5):

1. *Metabolic Decompensation in Association with Fasting.* Children with FAO defects are most prone to decompensation during conditions that place stress on the FAO pathway for fuel generation in the context of depleted glycogen and glucose reserves. These include fasting, prolonged exercise (particularly after 1 h of mild to moderate aerobic exercise), infection with vomiting, and cold-induced shivering thermogenesis. Children are most likely to be found comatose in the early morning hours after an overnight fast. During infection, there may be

Table 10.5 Clinical features associated with specific genetic defects of fatty acid oxidation

Deficiency	Fasting disorder	Tissue involved	Hypoketotic hypoglycemia	Altered carnitine	Dicarboxylic acids	Reye-like syndrome	SIDS
LCFAUD	+	L	+	+	NR	NR	NR
OCTN2	+	H, M	+	+	NR	+	NR
CPT I	+	K	+	+	NR	+	NR
TRANS	+	H, M (Mg)	+	+	NR	+	+
CPT II (mild)	+/–	M, Mg, P	NR	+	NR	NR	NR
CPT II (severe)	+	H, M, Mg, L	+	+	NR	+	+
VLCAD/LCAD	+	H, M, Mg, L	+	+	+	+	+
Trifunctional/LCHAD	+	H, M, Mg, L, N, P, R	+	+	+	+	+
Dienoyl-CoA reductase	NR	M,D,B (H)	NR	+	NR	NR	NR
MCAD	+	(Mg)	+	+	+	+	+
SCAD	+	M, B, D, H	+/–	+	+	NR	+
SCHAD	+	H, M, Mg, L	+	+	+	NR	+
ETF and ETF/Qo	+	M, H, K, B, D	+	+	+	NR	+
HMG-CoA lyase	+	B, P	+	+	+	+	+ ?

Modified from Hale and Bennet [14]; p. 4

LCFAUD long-chain fatty acid uptake defect, *OCTN2* plasmalemmal high-affinity carnitine transporter, *CPT* carnitine palmitoyltransferase, *TRANS* carnitine acylcarnitine translocase, *LCAD* long-chain acyl-CoA dehydrogenase, *VLCAD* very long-chain acyl-CoA dehydrogenase, *trifunctional* long-chain enoyl-CoA hydratase + *LCHAD* long-chain L-3-hydroxyacyl-CoA dehydrogenase + long-chain 3-ketoacyl-CoA thiolase, *MCAD* medium-chain acyl-CoA dehydrogenase, *SCAD* short-chain acyl-CoA dehydrogenase, *SCHAD* short-chain L-3-hydroxyacyl-CoA dehydrogenase, *ETF* electron transfer flavoprotein, *Qo* coenzyme Q oxidoreductase, *HMG* β-hydroxy-β-methylglutaryl, *B* brain, *D* dysmorphic features, *H* heart, *K* kidney, *L* liver, *M* muscle, *Mg* myoglobinuria, *N* neuropathy, *P* pancreatitis, *R* retinopathy, *NR* no case yet reported

an added problem with vomiting and decreased oral intake. Children may also present with a Reye-like syndrome. Infants and younger children are at greater risk during fasting because of limited fasting adaptation capabilities; prolonged fasting for an infant <1 year of age would be 6–10 h versus 12 h for a child between 1 to 4 years of age [14].

2. *Involvement of Fatty Acid Oxidation-Dependent Tissues.* Tissues with high-energy demands that are therefore dependent upon efficient FAO include skeletal muscle, heart, and liver. With deficient hepatic ketogenesis, glucose becomes the only available fuel and therefore becomes rate limiting under conditions of FAO stress when glycogen and glucose stores have been depleted. As a result, free fatty acids, which are liberated during fasting and which cannot be metabolized due to the block in FAO, may be stored in the cytosol as triglycerides, producing a progressive lipid storage myopathy with weakness as well as a hypertrophic and/or dilatative cardiomyopathy and fatty liver with microvesicular steatosis. Increased short- or medium-chain fatty acids and, in particular, their dicarboxylic acid metabolites, from compensatory omega oxidation, may cause secondary abnormalities including an impairment of gluconeogenesis, ß-oxidation, and the citric acid cycle leading to a further decrease in cellular ATP production. In long-chain FAO disorders which are frequently characterized by recurrent myoglobinuria (CPT II, VLCAD, TFP), accumulation of long-chain fatty acids and long-chain acylcarnitines proximal to the FAO block may have detergent-like actions on muscle membranes contributing to muscle breakdown due to potentiation of free-radical-induced lipid membrane peroxidative injury [1]. Long-chain acylcarnitines also activate Ca^{2+} channels in cardiac and smooth muscle myocytes and may potentiate increased cytosolic Ca^{2+} associated with arrhythmogenesis [1].
3. *Hypoketotic Hypoglycemia.* The pattern of hypoketotic hypoglycemia reflects the accelerated rate of glucose utilization that occurs when fatty acids cannot be used as fuels and ketone bodies are not generated to spare glucose/glycogen stores. An increase in the ratio of serum free fatty acids to ketones from the normal ratio of 1:1 to >2:1 is consistent with a block in ß-oxidation.
4. *Alterations in Plasma and Tissue Concentrations of Carnitine.* In most of the intramitochondrial ß-oxidation defects, serum total carnitine concentration is decreased (<50 % of normal) and acylcarnitine fraction is increased (>50 % esterified; normal = 10–25 % in fed state and 30–50 % in fasted state) [14]. In the plasmalemmal carnitine transporter defect, total carnitine is markedly reduced (<5 %) and esterified fraction is normal [1] due to decreased renal tubular reabsorption of carnitine.
5. *Additional Laboratory Findings.* During a Reye-like syndrome, a modest hyperammonemia (100–200 µmol/L) may be seen with 3–5-fold elevations of liver transaminases [14]. In acute myoglobinuria, there are marked increases in serum CK (e.g., >100,000 U/L; normal <250). There may also be increased serum amino acids, creatinine, potassium, phosphate, and urate [8] which may have deleterious effects on the kidneys and heart. Lactic acidosis may also be noted during the acute presentation which may reflect poor perfusion or inhibition of pyruvate carboxylase by accumulated metabolites. Urine organic acids may demonstrate unusual or excessive amounts.

CPT II Deficiency. Classic CPT II deficiency is characterized by adolescent-onset recurrent episodes of acute myoglobinuria precipitated by prolonged exercise or fasting, in which power between episodes is normal and in which lipid accumulation in muscle is noted only under conditions of fasting and prolonged exercise [1]. Fasting ketogenesis is generally normal in this condition, though it may be delayed, and there is no fixed cardiomyopathy, though arrhythmias may occur during myoglobinuria. In addition, there is a severe infantile CPT II deficiency which includes recurrent Reye-like syndrome, hepatomegaly with hypoketotic hypoglycemia and elevated liver aminotransferase, cardiomegaly with arrhythmias, and elevated creatine kinase, as well as lipid storage in heart, skeletal muscle, liver, and kidney. In these cases CPT II activity in cultured skin fibroblasts was <10 % of controls in contrast to the 25 % residual activity documented in classic CPT II deficiency. The lethal neonatal CPT II deficiency with <1 % residual activity presents with a severe hepatocardio muscular phenotype with brain and renal malformations and biventricular hypertrophy [15].

VLCAD Deficiency. In a long-term follow-up study of 13 patients with VLCAD deficiency, all patients exhibited exercise intolerance and recurrent myoglobinuria triggered by strenuous exercise, fasting, cold, or fever with a mean age at onset of 10 years [1]. Muscle biopsies showed mild lipid accumulation in four. A case of perinatal onset VLCAD deficiency has been reported in a male neonate with fetal distress, neonatal asphyxia, and transient hyper-creatine kinase-emia (8,400 IU/L) followed by repeated episodes of myoglobinuria 1–2 times/year during infancy and early childhood [1].

Trifunctional Protein/LCHAD Deficiency. Recurrent myoglobinuria has been reported in TFP/LCHAD deficiency as young as 7 months of age. TFP/LCHAD deficiency may present with pigmentary retinopathy and motor-sensory neuropathy [16].

10.5.2 Recommended Assessments

1. *History and Physical Examination.* A careful history and clinical examination remain the key to investigation. The presentation may be either acute and recurrent or more chronic and slowly progressive. The acute presentation is more typical in which the child has a history of decreased oral intake during the preceding 24–36 h followed by increasing lethargy and progressive coma. The initial key investigations in a comatose child should include serum glucose and urine ketone measurements. Determination of urine ketones may be complicated because ill children are often dehydrated and will therefore have concentrated urine. If the blood glucose is above 3.3 mmol/L (60 mg/dL) and if it is accompanied by large amounts of urinary ketones, this tends to rule out a FAO disorder. However, if the blood glucose is <3.3 mmol/L and the urine ketones are trace or small in amount, this would suggest the possibility of a FAO disorder and warrants further study. Most importantly, samples from the acute presentation, particularly prior to intravenous glucose therapy, should be saved for the determination of serum carnitine total and free, serum acylcarnitines, serum

free fatty acids and ketones, and urine organic acids, acylglycines, and acylcarnitines, which may be absent at times when the child is metabolically stable. Ordinarily, the serum free fatty acid-to-ketone ratio is 1:1. In the event of a block in FAO, this ratio increases to >2:1 which is therefore a useful initial screen. Fatty acid intermediates in the serum or urine of affected children may suggest the site of defect depending upon their chain-length and species type (Table 10.6) and require specialized biomedical technology. Serum and urine specimens during the acute episode can also be used to assess integrity and hormonal regulation of the biochemical pathways involved in glucose homeostasis.

2. *Carnitine.* FAO disorders are associated with a decrease in plasma total carnitine concentration (<30 μ[mu]mol/L, normal 40–60). The lowest concentration is found in the carnitine transporter (OCTN2) defect where concentrations are usually <5 % of control. In the intramitochondrial ß-oxidation defects, the plasma total carnitine concentrations vary between 10 and 50 % of normal. In contrast, the total and free plasma carnitine concentration may be normal or increased in a child with CPT I deficiency in which the esterification of palmitate to carnitine is defective. In most FAO defects, with the exception of the carnitine transporter and CPT I defects, there is an increase in the ratio of esterified carnitine to total carnitine reflecting the esterification to carnitine of the excessive acyl-CoA's that accumulate proximal to the block in ß-oxidation. The carnitine esters can be further separated on the basis of the acid insolubility of long-chain acylcarnitine esters [14]. Separation and identification of individual acylcarnitine esters has been facilitated by fast atom bombardment-tandem mass spectrometry and isotopic exchange high-performance liquid chromatography. Specific serum acylcarnitines have been useful in the diagnosis of certain defects (e.g., octanoylcarnitine in MCAD deficiency). They are particularly helpful for long-chain FAO disorders, because they overcome the problem of the renal threshold effect whereby long-chain acylcarnitines are selectively reabsorbed at the renal carnitine transporter site at the expense of free carnitine, overcoming the problem of poor solubility of long-chain fatty acids in urine. Electrospray ionization-tandem mass spectrometry (ESI-MS/MS) is increasingly used in newborn screening programs from dried blood spots which can be used to detect FAO disorders. Stored dried blood spots are valuable for postmortem investigations to elucidate the cause of SIDS. During storage, it was found that at −18°C, acylcarnitines are stable for at least 330 days [17].
3. *Urinary Organic Acids.* Dicarboxylic acids (adipic, suberic, sebacic acids) are found in many identified intramitochondrial ß-oxidation defects. Hale and Bennett [14] point out that there are several limitations to the value of these compounds in the recognition of FAO defects. (1) These DCA may be seen in children receiving certain formulas containing medium-chain triglycerides or in children who are seriously ill (e.g., diabetic ketoacidosis) or who are receiving certain medications which interfere with FAO such as valproic acid. It should be noted that in each of these cases, the amount of ketones exceeds the amount of DCA, whereas in the intramitochondrial FAO defects, the amount of DCA equals

Table 10.6 Laboratory features associated with genetic defects of fatty acid oxidation

	Carnitine		Unique or specific metabolites		
Deficiency	Total	Free	Acylcarnitine	Acylglycine	Organic acids
LCFAUD	Low	Low	NR	NR	NR
OCTN2	Very low	Low	NR	NR	NR
CPT I	Normal/high	High	NR	NR	NR(+)
TRANS	Low	Very low	Long chain	NR	NR
CPT II (mild)	Low	Very low	Long chain	NR	NR
CPT II (severe)	Low	Very low	Long chain	NR	+
VLCAD/LCAD	Low	Low	Long chain	NR	A, Su, Se
Trifunctional	Low	Low	Long chain	NR	A, Su, Se; 3-hydroxy intermediates
Dienoyl CoA reductase	Low	Low	Decadienoyl	NR	NR
MCAD	Low	Low	Octanoyl	Suberyl, hexanoyl, phenprop	A, Su, Se
SCAD	Low	Low	Butyryl	Butyryl	A, Su, Se; ethylmalonic; methyl succinate
SCHAD	Low	Low	NR	NR	A, Su, Se; 3-hydroxy intermediates
ETF and ETF/Qo	Low	Low	Octanoyl, glutaryl, butyryl, isovaleryl	Suberyl, hexanoyl, butyryl, isovaleryl	A, Su, Se; glutaric; ethylmalonic
HMG-CoA lyase	Low	Low	3-Methylglutaryl	?	3-Hydroxy-3-methylglutaric; 3-methyl-glutaconic; 3-methyl-glutaric, A; 3-hydroxy-isovaleric

Modified from Hale and Bennet [14], p. 5

LCFAUD long-chain fatty acid uptake defect, *OCTN2* plasmalemmal high-affinity carnitine transporter, *CPT* carnitine palmitoyltransferase, *TRANS* carnitine acylcarnitine translocase, *LCAD* long-chain acyl-CoA dehydrogenase, *VLCAD* very long-chain acyl-CoA dehydrogenase, *trifunctional* long-chain enoyl-CoA hydratase + *LCHAD* long-chain L-3-hydroxyacyl-CoA dehydrogenase + long-chain 3-ketoacyl-CoA thiolase, *MCAD* medium-chain acyl-CoA dehydrogenase, *SCAD* short-chain acyl-CoA dehydrogenase, *SCHAD* short-chain L-3-hydroxyacyl-CoA dehydrogenase, *ETF* electron transfer flavoprotein, *Qo* coenzyme Q oxidoreductase, *HMG* β-hydroxy-β-methylglutaryl, *NR* no case yet reported, *A* adipic acid, *Su* suberic acid, *Se* sebacic acid, *PhenProp* phenylpropionyl

or exceeds the amount of ketones when the children are fasting. (2) These DCA are not present when children are not catabolic and are well and eating regularly or are receiving intravenous glucose at rates in excess of normal hepatic glucose production rates, thereby decreasing the dependence on FAO and the production of fatty acid metabolites. (3) Increased concentrations of DCA in the urine are generally not seen in the disorders involving the transport of fats into the mitochondria. Thus, a FAO defect can be suspected in the presence of an excess of DCA relative to ketones, but absence of DCA does not rule out a defect. Organic acid patterns may suggest the site of defect. For example, children with TFP deficiency excrete almost equimolar amounts of saturated and 3-hydroxydicarboxylic acids. However, presence of 3-hydroxy compounds also may be seen in toxic reactions with acetaminophen and intrinsic liver disease. Advances in stable-isotope dilution mass spectrometry have improved the ability to quantitate metabolites in very small quantities in plasma or urine. Useful acylglycines consistently excreted in small quantities in urine do not appear to have the same limitations of DCA and have been identified for MCAD, SCAD, ETF, and ETF-CoQ oxidoreductase deficiencies.

4. *Fasting Studies.* If the critical samples have not been taken during an acute catabolic event, a fasting study may be considered to distinguish a FAO defect from other causes of hypoglycemia. However, it must be emphasized that if a fasting study is to be undertaken, it must be done under very carefully controlled hospital conditions with continuous monitoring by physicians who are knowledgeable with respect to hypoglycemia, hypopituitarism, hyperinsulinism, and FAO disorders. It is felt by some authorities that fasting studies should *not* be performed in children with FAO disorders, because diagnostic fasting may precipitate an acute metabolic crisis, leading to morbidity or death. They suggest instead that loading tests with carnitine or phenylpropionate can be used to aid in diagnosis. As suggested by Hale and Bennett [14], there are pros and cons with each method. The reasons for a fasting study are as follows: (1) the duration of fasting tolerance can be determined under carefully controlled conditions which may provide useful information regarding the long-term management of the patient and provide guidelines for prevention; (2) the full spectrum of abnormal fasting adaptation can be studied through assessment of a number of laboratory parameters including hormonal measurements. The cardinal risk is precipitation of an acute catabolic crisis leading to morbidity and death. It would instead be preferable to collect appropriate samples, during an acute catabolic event suffered by the child.

   The primary advantage of loading tests and the measurement of specific metabolites is their safety. The disadvantages are as follows: (1) they are only useful in certain FAO defects, e.g., MCAD deficiency, thus a negative test does not exclude all FAO defects; (2) they do not evaluate fasting adaptation. The purpose of the fasting study is to identify the defective metabolic pathway through an analysis of temporal changes in substrates (glucose, free fatty acids, lactate, ketones), metabolites (carnitine, dicarboxylic acids), and relevant hormones (growth hormone, cortisol, insulin). Children must fast, only if safe, to

the point at which they have the first symptoms or have a blood glucose of <3.3 mmol/L (60 mg/dL). If at this point there is a deficient ketogenic response in the face of a significant dicarboxylic aciduria and a serum free fatty acid-to-ketone ratio of >2:1, there is strong presumptive evidence for a FAO defect.

5. *Other Studies.* Once presumptive evidence for a defect in FAO has been established, the clinical picture in combination with serum acylcarnitines, urine organic acid profiles, and urine acylglycines may suggest a specific site of defect and the chain-length specificity of the defect. Another method developed for quantitative acylcarnitine profiling by electrospray ionization-tandem mass spectrometry in human skin fibroblasts, using unlabelled palmitic acid as substrate, has revealed pathognomonic acylcarnitine profiles in a variety of short-, medium-, and long-chain FAO defects.

   (a) *Fatty Acid Oxidation Studies.* A screening tool, if the defect is expressed in cultured skin fibroblasts, is measurement of the oxidation rates of [1–^{14}C]-labelled palmitate (C16), octanoate (C8), and butyrate (C4) in fibroblasts to establish chain-length specificity.
   (b) *Enzymatic Assays.* Depending upon the suspected site of defect, a direct enzymatic assay may then be performed in cultured skin fibroblasts or biopsied muscle.
   (c) *Uptake Studies.* For the carnitine transporter (OCTN2) defect, diagnosis is confirmed by in vitro studies of carnitine uptake in cultured skin fibroblasts which show negligible uptake of carnitine in affected patients. Heterozygotes may demonstrate normal Km values but reduced Vmax values of 13–44 % of control suggesting a decreased number of normally functioning transporters. This is the most sensitive study for detection of carriers as their serum carnitine may be normal.
   (d) *Molecular Studies.* Molecular characterization of specific defects includes Western blotting to determine whether the defects are cross-reacting material positive suggesting a kinetic deficiency or whether they are cross-reacting material negative suggesting decreased enzyme production. Western blotting has also been used in the determination of the amounts of the alpha and ß-subunits of ETF. Most of the genes are known which has led to discovery of specific mutations leading to development of molecular probes.

10.5.3 Recommended Treatment Interventions

Mainstay of therapy is avoidance of precipitating factors. Recommendations in long-chain FAO defects have been made by consensus [18]. General strategies follow next.

Avoidance of Precipitating Factors. Avoidance of precipitating factors, such as prolonged fasting, prolonged aerobic exercise (>30 min), and cold exposure resulting in shivering thermogenesis, is key. Prolonged fasting would be 6–10 h for the

infant younger than 1 year of age or 12 h for the child between 1 and 4 years of age during a state of well-being. Fasting time would be even shorter in the context of illness. In the event of progressive lethargy or obtundation or an inability to take oral feedings because of vomiting, the child should be taken immediately to the emergency room for intravenous glucose which should be provided at rates sufficient to prevent fatty acid mobilization (8–10 mg/kg/min) [14]. This regimen should be continued until the catabolic cascade has been fully reversed and the child is able to take oral feedings. It is wise to avoid prolonged exercise (>30 min) as during this time there is increased fat mobilization. A high-carbohydrate load prior to exercise is advisable with a rest period and repeat CHO load at 15 min. Avoidance of cold exposure is key.

High-Carbohydrate, Low-Fat Diet. In general, it is advisable to institute a high-carbohydrate, low-fat diet with frequent feedings throughout the day, which would be commensurate with the special nutritional needs of the child given his or her age. This goal is best achieved with the aid of a metabolic dietitian, aiming toward approximately 60 % of calories from carbohydrate sources, 15 % from protein, and approximately 25–30 % from fat. Monitoring of essential fatty acid (EFA) levels is important to ensure that the child is receiving adequate EFA, as this may require supplementation in a fat-restricted diet. Augmentation with EFA (1–2 % of total energy intake) is used to reduce the risk of EFA deficiency [18, 19]. Flaxseed, canola, walnut, or safflower oils can be used. An older child should have three meals per day with three equidistantly placed intermeal snacks, including a bedtime snack. In younger children, oral or nasogastric tube feeds of an appropriate formula is indicated. In HMG-CoA lyase deficiency, a high-carbohydrate, low-fat, low-protein diet with leucine restriction should be instituted.

In symptomatic VLCAD deficiency, long-chain fat content of the diet is suggested to be 25–30 % of total energy [18, 19]. Since the predominant clinical symptoms in VLCADD patients are episodic muscle pain and myoglobinuria suggesting muscular energy deficiency, it is recommended that the diet be enriched in medium-chain triglycerides (MCT) to provide 20 % of total energy from MCT. Increased MCT (or carbohydrate) prior to exercise is also recommended (e.g., 0.25–0.5 g MCT/kg).

For TFP deficiency, long-chain fat intake should be as low as possible in both asymptomatic and symptomatic patients [18, 19]. In newborns, a special infant formula low in LCT and high in MCT is important with EFA supplements. In view of the high mortality rate, dietary treatment in patients detected by newborn screening should be initiated immediately after screening results are available, even before confirmation of diagnosis. With institution of solid food, it is recommended that the fat content is 25–30 % of total energy, with 20–25 % as MCT and 5–10 % as LCT.

Uncooked Corn Starch. To delay onset of fasting overnight, nightly institution of uncooked corn starch, in doses similar to those used in the treatment of glycogen storage disease (1–2 g/kg body weight/day as a single nighttime dose), will prolong the postabsorptive state and delay fasting. Cornstarch provides a sustained release source of glucose from the gastrointestinal tract, thereby preventing hypoglycemia and lipolysis. Cornstarch is usually initiated at 8 months of age when pancreatic

enzymes are first able to function at full capacity for appropriate absorption. Initial recommended doses are 1.0 g/kg/day which can be gradually increased to 1.5–2.0 g/kg/day by age 2 years as needed. This may result in excessive weight gain. Routine use is not recommended but is part of oral prophylactic and emergency management [18, 19].

Specific treatments for individual FAO disorders include the following:

Medium-Chain Triglyceride (MCT) Oil. MCT oil as a nutritional source could be useful in long-chain FAO disorders as medium-chain fatty acids would circumvent the block in long-chain FAO. MCT oil could be started at a dose of 0.5 g/kg/day divided in three daily doses and could be increased up to 1 or 1.5 g/kg/day as tolerated. The major side effect is diarrhea. Usefulness of this approach may be limited as excess MCT would ultimately be stored as long-chain fats in adipocytes. Furthermore, the success of MCT oil supplementation in LCHAD deficiency has been highly variable [1]. When a high percentage of energy from fat is provided by MCT oil, patients are at risk for EFA deficiency and they should be supplemented with EFA (1–2 % of total energy intake).

Riboflavin. Certain cases of multiple acyl-CoA dehydrogenase deficiencies (e.g., ETF or ETF-CoQ-linked deficiencies) respond to riboflavin. The dose is about 50 mg three times a day for infants and young children and 100 mg three times a day for older children [1].

Carnitine. The essential indication for carnitine therapy is the carnitine transporter (OCTN2) defect, characterized by carnitine-responsive cardiomyopathy and very low plasma and tissue concentrations of carnitine (generally <5 % of normal) [1]. All 22 affected patients treated with high-dose oral carnitine supplementation demonstrated a dramatic improvement in their cardiomyopathy and myopathy within the first few weeks of therapy, as well as a reduction of heart size toward normal within a few months of therapy. In addition, three children with significant failure to thrive before therapy demonstrated a marked improvement in growth after therapy. Of 19 patients treated with carnitine therapy for 5–20 years, 18 continued to be healthy. Thus, in the OCTN2 defect, high-dose oral carnitine supplementation at 100 mg/kg/day in four divided daily doses is critical and lifesaving, significantly reversing the pathology in this otherwise progressive and lethal disease. Furthermore, early carnitine therapy from birth prevents the development of the clinical phenotype [20].

In intramitochondrial ß-oxidation defects with secondary carnitine deficiency, the results of carnitine therapy have been highly variable and insufficiently evaluated. Theoretically, carnitine has been given to limit the intracellular concentrations of potentially toxic acyl-CoA intermediates within the cell through transesterification and to thereby liberate CoA, a critical intracellular cofactor [14]. However, there has been no objective prospective study to prove that carnitine administration has had a beneficial effect, including the study of a patient with MCAD deficiency. Furthermore, there is increasing evidence to suggest that carnitine administration may have deleterious effects in long-chain FAO disorders. In these disorders there is an accumulation of long-chain acyl-CoAs proximal to the metabolic block, which

on esterification become long-chain acylcarnitines. Excessive palmitoylcarnitine may have detergent effects on membranes and arrhythmogenic effects as previously discussed [1]. This warrants further study.

Specific Therapies for LCHAD/TFP Deficiency. Oral prednisone has been shown to lead to a dramatic reversal of the limb-girdle myopathy and marked reduction in the episodic myoglobinuria in one boy with myoneuropathic LCHAD deficiency [1]. Several children with LCHADD who had associated pigmentary retinopathy were shown to have a deficiency of the $(n-3)$-polyunsaturated fatty acid, docosahexaenoic acid (DHA), and supplementation with DHA led to some improvement in visual function. Daily oral administration of a cod liver oil extract containing high amounts of DHA led to a marked clinical and electrophysiological recovery of the progressive peripheral sensorimotor axonopathy in one boy with myoneuropathic LCHADD [1]. The recommended dose of DHA supplementation in TFP complex including LCHADD by a European consensus panel is 60 mg/day in children weighing <20 kg and 120 mg per day in children >20 kg body weight [18, 19]. Higher amounts of DHA were used to reverse the neuropathy [1].

Triheptanoin. Use of the anaplerotic odd-chain triglyceride, triheptanoic acid, has been reported to be of value in long-chain FAO defects [1]. In three VLCAD deficient patients fed controlled diets in which the fat component was switched from medium-even-chain triglycerides to triheptanoin, there was rapid clinical improvement including resolution of chronic cardiomyopathy, myoglobinuria, and weakness for >2 years in one child and of myoglobinuria and weakness in the others. More studies need to be done.

Peroxisome Proliferators Activated Receptor (PPAR) Agonists. The PPARs upregulate mitochondrial FAO. Bezafibrate, a hypolipidemic agent, activates PPARδ and PPARα. It increases palmitate oxidation in fibroblasts from patients with mild myopathic phenotypes of CPT II or VLCAD deficiency but has no effect in cells with severe mutations [21]. One of the reported adverse effects is drug-induced increased CK; however, reports of bezafibrate-induced myoglobinuria are rare and only reported in patients with renal insufficiency who tend to accumulate the drug. Djouadi and Bastin [21] recommend that FAO tests in patient fibroblasts may offer a reliable way to assess drug responsiveness and, in combination with clinical, biochemical, and molecular analysis, should provide a rational framework for patient stratification in future clinical trials.

10.6 Mitochondrial Encephalomyopathies

10.6.1 Presenting Clinical Features

Mitochondrial diseases are clinically heterogeneous. Pure myopathies may vary in age at onset, course, and distribution of weakness. Patients may also have exercise intolerance and premature fatigue. A number of distinct clinical syndromes have

been described, e.g., Kearns-Sayre, MERRF, and MELAS syndrome, each due to distinct mutations in mtDNA. Common features to all three include short stature, dementia, sensorineural hearing loss, lactic acidosis, and ragged red fibers (RRF) on muscle biopsy. In children, given the earlier age of onset and generally more severe clinical phenotype, there may be a number of overlap syndromes, e.g., MELAS/Kearns-Sayre syndrome. The prevalence of mtDNA point mutations that cause disease is estimated as 1/5,000–1/10,000 and the frequency of mtDNA mutations amongst healthy subjects as 1/200 [22]. Mutations in *POLG*, the gene coding for the catalytic subunit of the mtDNA polymerase, polg, have been recognized as a major cause of human disease, possibly accounting for up to 25 % of all patients with mitochondrial diseases with variegate phenotypes including fatigue, muscle weakness, and muscle pain [23].

10.6.2 Morphologic Features

Ragged red fibers (RRF) or ultrastructural alterations of mitochondria in muscle biopsy specimens provides an important diagnostic clue; however, as pointed out by DiMauro [24], there are important limitations as follows: (1) RRF or ultrastructural mitochondrial abnormalities can be seen in disorders of nonmitochondrial etiology such as muscular dystrophies, polymyositis, and some glycogenoses, in which they likely represent secondary changes; (2) many primary mitochondrial diseases such as enzyme defects in metabolic pathways other than the respiratory chain, e.g., PDHC, CPTII, ß-oxidation defects do not have RRF. Though RRF are usually present in defects of mtDNA which affect the respiratory chain, there are also exceptions such as Leber's hereditary optic neuropathy (LHON) in which the mitochondrial changes are subtle, without RRF. Further, RRF may depend on the threshold effect (% mutant mtDNA) and on the stage of disease. Two other useful stains are succinate dehydrogenase (SDH) and cytochrome oxidase (COX) stains. RRF are often COX-negative, though not all COX-negative fibers are RRF. COX-negative RRF are seen in progressive external ophthalmoplegia and mtDNA deletions and in MERRF (myoclonus epilepsy with RRF) but not MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes) syndrome which has COX-positive RRF. E/M may show increased mitochondrial population (pleoconial myopathy), increased size (megaconial myopathy), abnormal cristae, and osmiophilic or paracrystalline inclusions which are deposits of mitochondrial CK. There may also be lipid and glycogen storage signifying a defect of terminal oxidation.

Genetic Classification. Mitochondria are the only subcellular organelles with their own DNA (mtDNA) which are capable of synthesizing a vital set of proteins. Human mtDNA is a small (16.5 kb), circular, double-stranded molecule that has been completely sequenced and encodes 13 structural proteins, all of which are subunits of respiratory chain complexes, as well as 2 rRNAs and 22 tRNAs needed for translation. Unique features of mtDNA are as follows [24]: (1) Its genetic code differs from that of nuclear DNA (nDNA), (2) it is tightly packed with information

as it contains no introns, (3) it is subject to spontaneous mutations at a higher rate than nDNA, (4) it has less efficient repair mechanisms than nDNA, (5) it is present in hundreds or thousands of copies per cell, and (6) it is transmitted by maternal inheritance. In the formation of the zygote, mtDNA is contributed only by the oocyte. If there is a mutation in some mtDNA in the ovum or zygote, this may be passed on randomly to subsequent generations of cells, some of which will receive few or no mutant genomes (normal or wild-type homoplasmy), others will receive primarily or exclusively mutant genomes (mutant homoplasmy) and others will receive a mixed population of mutant and wild-type mtDNAs (heteroplasmy). There are important implications from maternal inheritance and heteroplasmy, as follows [24]: (1) inheritance of disease is maternal as in X-linked traits, but both sexes are equally affected, (2) phenotypic expression of a mtDNA mutation will depend upon the relative proportion of mutant to wild-type genomes with a minimum critical number of mutant genomes being necessary for expression (threshold effect), (3) at cell division, the proportion may shift in daughter cells (mitotic segregation) leading to a corresponding phenotypic change, and (4) subsequent generations are affected at a higher rate than in autosomal-dominant diseases. The critical number of mutant mtDNAs needed for the threshold effect may vary depending upon the vulnerability of the tissue to impairments of oxidative metabolism, as well as on the vulnerability of the same tissue over time which may increase with aging. The majority of mitochondrial proteins, however, are encoded by nDNA, synthesized in the cytosol, and then imported into mitochondria. This transport of proteins requires a complex series of posttranslational events and translocation machinery involving synthesis of larger precursors in the cytosol, amino terminal leader peptides which function as address signals and recognize specific mitochondrial membrane receptors, translocation across the mitochondrial membrane, and cleavage of the leader peptides with assembly of mature peptides at their final intramitochondrial location. Genetic classification of mitochondrial diseases is given in Table 10.7 [25].

Defects of mtDNA can be divided into mutations in mitochondrial protein synthesis genes and mutations in mitochondrial protein-coding genes. Protein synthesis gene defects may include duplication/deletion as seen in Kearns-Sayre and Pearson marrow-pancreas syndrome, mutations in tRNA as seen in MELAS and MERRFS, and defects in rRNA. Single deletions are usually sporadic and duplications ± single deletions are rare and usually maternal. Mutations in protein-coding genes affect 13 of 82 structural proteins (7 for complex I, 1 for complex III, 3 for complex IV, and 2 for complex V) and may be multisystemic (e.g., LHON, NARP, MILS) or tissue specific. To date over 120 point mutations have been documented in mtDNA.

The majority of mitochondrial diseases are due to defects in nDNA and many are autosomal recessive in inheritance though some are autosomal dominant or X-linked. Nuclear gene defects are generally more severe, uniform, and earlier in onset than mtDNA defects. Diseases due to mutations in nDNA include mutations in genes encoding subunits of the respiratory chain, mutations in genes encoding ancillary proteins needed for proper assembly of the respiratory chain (e.g., SURF1, SCO1, SCO2, COX10, and COX15 which are involved in the assembly of complex IV),

Table 10.7 Genetic classification of mitochondrial respiratory chain (RC) diseases [24, 25, 26, 27]

Defects of mitochondrial DNA
1. Mutations in mitochondrial protein synthesis
   A. mtDNA rearrangements
      (a) Single deletions (usually sporadic)
      (b) Duplications or duplications/deletions (maternal transmission)
   B. mtDNA point mutations (maternal transmission)
      (a) tRNA genes
      (b) rRNA genes
2. Mutations in protein-coding genes
   A. Complex I (ND) genes
   B. Complex III—cytochrome b
   C. Complex IV (COX I, II, III)
   D. Complex V (ATPase 6) genes

Defects of nuclear DNA (Mendelian transmission)
1. Defects of the respiratory chain subunit genes—complex I, II, III
2. Defects in respiratory chain assembly ancillary proteins
   A. Complex I, e.g., *NDUFA12L*, *ACAD9*
   B. Complex III, e.g., *BCS1L*
   C. Complex IV, e.g., *SURF1*, *SCO2*, *LRPPRC*
   D. Complex V, e.g., *ATPAF2*
3. Defects in Coenzyme Q10 biosynthesis (*CABC1*, *COQ2*, *COQ8*, *ADCK3*, *PDSS1*, *PDSS2*)
4. Defects of intergenomic signaling required for mtDNA integrity and replication
   A. Multiple deletions of mtDNA—*POLG1*, *ANT1*, *PEO1*, *ECGF1*, *POLG2*, *TYMP*
   B. Depletion of mtDNA—*TK2*, *DGUOK*, *POLG1*, *SUCLA2*, *SUCLG1*, *MPV17*, *RRM2B*, *PEO1*, *TYMP*
5. Defects of mitochondrial transport machinery—*TIMM8A*, *SLC25A3*, *ABCB7*
6. Defects in mtDNA translation—*GFM1*, *MRPS16*, *TSFM*, *TUFM*, *PUS1*, *DARS2*
7. Alterations mitochondrial membrane lipids in which RC is embedded—*TAZ*
8. Alterations in mitochondrial fission and fusion—*MFN2*, *OPA1*, *DLP1*
9. Defects in mitochondrial apoptosis—*FASTKD2*

Modified and updated from Vu et al. [28]

defects of intergenomic signaling (e.g., multiple mtDNA deletions, mtDNA depletion), defects of mitochondrial protein importation (e.g.,TIMM8A mutations in Mohr-Tranebjaerg syndrome), alterations of lipid milieu of the inner mitochondrial membrane (e.g., TAZ gene mutations resulting in Barth Syndrome), and alterations of mitochondrial motility or fission (e.g., OPA1 gene). Structural nuclear genes encode all subunits of complex II and most subunits of complexes I, III, IV, and V as well as CoQ10 and cytochrome c. Multiple deletions of mtDNA may be due to defects of thymidine phosphorylase, adenine nucleotide translocator 1, and polymerase gamma (POLG) genes.

Exercise Physiology. Alterations of oxidative metabolism can be detected by standard exercise physiology tests. The most useful indicator of a patient's capacity for oxidative metabolism is their maximal oxygen uptake [24]. Typical physiologic responses in patients with defects in oxidative metabolism are as follows: (1) Increase of cardiac output during exercise is greater than normal relative to the rate

of oxidative metabolism. (2) Oxygen extraction per unit of blood remains almost unchanged from rest to maximal exercise, leading to a gross mismatch between oxygen transport and utilization. In patients with heteroplasmic mtDNA mutations, there is an inverse relationship between the proportion of skeletal muscle mutant mtDNA and peak O_2 extraction during exercise [29]. (3) Ventilation is normal at rest but increases excessively relative to oxygen uptake. (4) Venous lactate, which is usually elevated at rest, increases excessively relative to workload and oxygen uptake. Mitochondrial function in muscle in vivo can be quantitatively evaluated using ^{31}P-NMR. The ratio of phosphocreatine (PCr) to inorganic phosphate (Pi) can be measured in muscle at rest, during exercise, and during recovery. In mitochondrial defects, PCr/Pi ratios are lower than normal at rest, decrease excessively during exercise, and return to baseline values more slowly than normal.

10.6.3 Selected Mitochondrial Diseases: Presenting Clinical and Biochemical Features

Coenzyme Q10 (CoQ10) Deficiency. Two sisters developed exercise intolerance and slowly progressive weakness of axial and proximal limb muscles with sparing of facial and extraocular muscles. Both had episodic myoglobinuria associated with seizures or infections. Family history suggested autosomal recessive inheritance. Muscle biopsies revealed excessive lipid and mitochondria in type I fibers. Biochemical analysis suggested a muscle (5 % normal) and probably brain-specific isozyme defect of CoQ10 and CoQ10 replacement therapy improved both muscle and brain function.

Primary CoQ10 deficiency can cause at least five major syndromes [30]: (1) encephalomyopathy characterized by recurrent myoglobinuria, brain involvement, and RRF; (2) severe infantile multisystemic disease including retinitis pigmentosa, optic nerve atrophy, bilateral sensorineural hearing loss, progressive ataxia, nephrotic syndrome, and cardiomyopathy; (3) cerebellar ataxia. This is the most common phenotype with epilepsy as the most common associated feature, but pyramidal signs, mental retardation, myopathic weakness, and delayed motor milestones are other associated symptoms and signs [30]. Muscle morphology does not show RRF and lipid storage myopathy, and CoQ10 is moderately reduced in skin fibroblasts (4) Leigh syndrome with growth retardation, ataxia, and deafness, (5) isolated myopathy. In this phenotype, there is subacute onset of exercise intolerance and proximal limb-girdle weakness at variable ages with lipid storage and RRF in muscle as well as increased serum lactate and CK. In all patients with different phenotypes, there were reduced activities of complex I + III and II + III, with normal activities of isolated complex I and III [30]. The diagnosis is critical given the significant clinical response to CoQ10. The different clinical phenotypes appear to encompass both primary and secondary forms [31]. Primary CoQ10 deficiency is

due to biosynthetic defects which have been associated with the earliest and most severe variants of CoQ10 deficiency [31]. Three genes *PDSS1, PDSS2,* and *COQ2,* of the nine genes in the CoQ10 biosynthetic pathway, have been implicated. All patients with different forms of CoQ10 deficiency have shown clinical improvement with oral CoQ10 which requires high doses and long-term administration. Its oral bioavailability is poor due to extreme hydrophobicity. Muscle abnormalities improve clinically and biochemically; however, cerebral symptoms are only partially improved which could be due to presence of irreversible brain damage before therapy or poor penetration of CoQ10 across the blood–brain barrier [30].

The isolated myopathic form of coenzyme Q10 deficiency may be caused by mutations in the ETF-dehydrogenase gene and can be treated with CoQ10 and riboflavin [5]. These patients present with exercise intolerance, fatigue, proximal myopathy and high serum CK, lipid storage myopathy, subtle signs of mitochondrial myopathy, and severely decreased activities of respiratory chain complexes I and II + III, moderately decreased complex IV, and significantly decreased CoQ10 in muscle. Late-onset glutaric aciduria type II and the myopathic form of CoQ10 deficiency may be allelic diseases.

Complex IV Deficiency. Cytochrome oxidase (COX) deficiency has a myopathic form and a multisystemic form, dominated by encephalopathy [25]. There are two forms of myopathy, both of which are present soon after birth with severe diffuse weakness, respiratory distress, and lactic acidosis but with very different outcomes. The fatal infantile myopathy often has associated renal disease with De Toni-Fanconi syndrome and results in death before 1 year of age. Autosomal-recessive inheritance is suggested by pedigree analysis, and immunocytochemical studies have documented a selective defect of COX subunit VIIa in four patients. Benign infantile myopathy presents with severe weakness and frequently ventilator dependence and gavage feedings in early life. Subsequently there is spontaneous improvement and a return to normal by 2 or 3 years of age. There is a lack of both subunit VIIa and subunit II on muscle immunocytochemistry in the benign form, with a spontaneous recovery toward normal COX activity both histochemically and biochemically. The principal molecular basis of this disorder is a maternally inherited homoplasmic m.14674T > C mt-tRNA(Glu) mutation in 17 patients from 12 families [32]. Tissue-specific mechanisms downstream of tRNA(Glu) may explain the spontaneous recovery.

mtDNA Depletion. mtDNA depletion, which results from defects of intergenomic signaling, is usually characterized clinically by congenital or childhood forms of autosomal recessive myopathy or hepatopathy [24]. Although skeletal muscle and liver seem to be the main target tissues, other tissues are often affected in both conditions, including kidney and the central nervous system. mtDNA depletion should be considered in children with the spinal muscular atrophy phenotype but without mutations in the SMN gene. The decrease in mtDNA is documented by densitometry of Southern blots and confirmed by immunocytochemistry with anti-DNA antibodies and by in situ hybridization. In severe cases, depletion of muscle

mtDNA varies between 83 and 98 %. Mutations in two genes, both of which are involved in mitochondrial nucleotide homeostasis, have been associated with mtDNA depletion syndromes, even though they do not account for all cases. Mutations in the gene encoding thymidine kinase 2 are frequently documented in patients with myopathic mtDNA depletion.

POLG. Mutations in *POLG* cause mtDNA depletion or multiple secondary mutations of mtDNA [23] and have been identified in a wide range of mitochondrial diseases including isolated clinical syndromes with fatigue, muscle weakness, and muscle pain. Over 100 different *POLG* mutations have been described. Some behave as both dominant and recessive alleles and certain patients have three or four mutations within the same gene and polymorphic genetic variants (which occur in up to 4 % of the population) which appear to modulate the phenotype. Recessive mutations tend to cause mtDNA depletion and are present in childhood, whereas dominant mutations tend to cause adult-onset disease with multiple secondary deletions of mtDNA. Thus, depletion, multiple deletions, and multiple different point mutations may be present in varying degrees with different *POLG* mutations. Defined clinical syndromes described in patients with POLG mutations may also include CPEO, infantile SMA, MERRF, MELAS, MNGIE, mitochondrial recessive ataxia syndrome (MIRAS), or sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) presentations. It has been recommended that POLG should always be considered in patients with (1) PEO with a positive family history and/or multiple mtDNA deletions in skeletal muscle biopsy; (2) ataxia with an axonal sensorimotor neuropathy, particularly if there is epilepsy; and (3) all children with unexplained encephalopathy, especially if there is evidence of liver dysfunction [23]. In patients with well-defined clinical syndromes that are consistent with POLG mutations, it is recommended to check for two common pathogenic alleles A467T and W748S in blood DNA. In those who do not have a well-recognized POLG-related syndrome but have suspected mitochondrial disease or features that form part of the classical POLG syndromes, a systematic approach is preferable which begins with a tissue biopsy from a clinically affected organ which must be frozen (skeletal muscle or liver). The aim is to look for biochemical evidence of mitochondrial dysfunction and mtDNA studies on frozen affected tissues for depletion or multiple mtDNA deletions which should lead to *POLG* sequencing. Genetic counseling is a challenge.

10.6.4 Recommended Therapeutic Approaches in Mitochondrial Diseases

Overall the therapy of mitochondrial respiratory chain disorders is highly inadequate. The therapeutic approaches are comprehensively reviewed in DiMauro and Mancuso [33]. Palliative therapy includes anticonvulsants, treatment of endocrinopathies, and surgical procedures, e.g., cochlear implants for hearing loss, surgery

for cataracts and ptosis, pacemakers for cardiac conduction blocks, and liver transplantation for liver failure if other organs are relatively spared. Valproic acid should be avoided in Alper's disease and otherwise only be used with extreme caution and in association with L-carnitine, as it inhibits cellular carnitine uptake [1]. Other strategies include removal of noxious metabolites including lowering lactic acidosis. Though dichloroacetate (DCA) lowers serum lactic acid, a double-blind, placebo-controlled, randomized, crossover trial of DCA in a uniform cohort of MELAS patients with the A3243G mutation had to be terminated due to significant peripheral nerve toxicity [34]. Thus, DCA should not be used long term in mitochondrial patients prone to peripheral neuropathy. Attempts to bypass respiratory chain blocks through the administration of electron acceptors have been disappointing. There may be future strategies through genetic engineering. Cofactor and metabolite supplementation has been the mainstay of therapy, particularly in disorders of primary deficiencies, e.g., CoQ10 deficiency [30] and OCTN2 deficiency [20]. Other agents include riboflavin, thiamine, folic acid, and creatine. Antioxidants and reactive oxygen species scavengers are an area of increasing interest, particularly in complex I and III deficiencies where there is excess generation of oxygen free radicals. Agents used have included vitamin E, CoQ10, idebenone, and dihydrolipoate. Aerobic endurance and resistance exercise and physical therapy help to prevent deconditioning and disuse muscle atrophy and have been shown to improve exercise tolerance in patients with mtDNA mutations [35, 36]. Gene therapy is a highly challenging area because of heteroplasmy and polyplasmy, but approaches have been developed to decrease the ratio of mutant to wild-type mitochondrial genomes (gene shifting through exercise), converting mutated mtDNA genes into normal nuclear DNA genes and importing cognate genes from other species [33]. Preventive therapy through genetic counseling and prenatal diagnosis is important for nuclear DNA-related disorders [26].

10.7 Summary of Diagnostic Approach to Investigation of Recurrent Myoglobinuria

Based upon the clinical features and screening biochemical tests, a practical approach can be derived for the prioritized investigation of recurrent myoglobinuria (Fig. 10.2). If there is a history of true muscle cramps within the first minutes of high-intensity exercise or of a "second-wind" phenomenon, this would suggest a glycolytic or glycogenolytic disorder. Alternatively, if there is a history of muscle stiffness after mild to moderate prolonged exercise (e.g., >1 h) or of myoglobinuria precipitated by fasting or cold exposure, this would suggest a defect in FAO. The first clinical test would be an in vivo forearm ischemic lactate test. In the young child in whom this is not possible, an in vitro lactate test may be performed on the muscle biopsy to test the integrity of the glycolytic pathway. If lactate production is insufficient (less than a 3–4-fold rise) this would suggest a block in the glycogen

pathway. Defects in glycolysis/glycogenolysis can be divided into two groups, those in which there is an associated hemolytic anemia such as PGK, PFK, and aldolase A deficiency and those without hemolytic anemia, e.g., PPL, PGAM, and LDH deficiency. PGK can be further distinguished from PFK and aldolase A, as PGK is X-linked and may have associated seizures, whereas PFK and aldolase A are autosomal recessive. The forearm ischemic lactate test can also be used to assess whether there is an appropriate rise (3–4-fold) in ammonia. If ammonia production is insufficient, this would suggest a defect in the purine nucleotide cycle.

If there is adequate lactate production, the next important question relates to whether there is any evidence for deficient ketogenesis. If ketogenesis appears normal, the considerations include a defect in the pentose phosphate pathway (G6PD deficiency) which may be distinguished by the presence of hemolytic anemia. Other considerations would include the mitochondrial encephalomyopathies secondary to defects in the respiratory chain or mitochondrial DNA, which may be suspected if there are marked elevations of serum lactate (>2-fold) and certain characteristic clinical features such as failure to thrive, short stature, and sensorineural hearing loss or perhaps a maternal pattern of inheritance. If the attacks of myoglobinuria occur in early childhood and are primarily precipitated by fever, a mutation in LPIN1 should be considered. Defects in the tricarboxylic acid cycle could theoretically result in deficient energy production and myoglobinuria, though no such defects have been identified to date.

If there is evidence of delayed or deficient ketogenesis, a defect in FAO should be suspected. The most common defect is the classic “adult” myopathic form of CPT II deficiency with adolescent-onset recurrent myoglobinuria, normal power, and normal CK between episodes and no associated cardiomyopathy or overt liver disease. This contrasts with the fixed lipid storage myopathy and cardiomyopathy seen in LCAD/VLCAD, LCHAD/TFP, and SCHAD deficiencies. The common “adult” myopathic form of CPT II deficiency contrasts with the rare “infantile” hepatic form of CPT I deficiency which presents with recurrent hypoglycemic hypoketotic coma and seizures in which there are no muscular manifestations. “Infantile” CPT II deficiency presents with fasting hypoketotic hypoglycemic encephalopathy, elevated CK, cardiac arrhythmias, and cardiomegaly with a residual CPT II activity of 10 % in cultured skin fibroblasts in contrast to the 25 % residual activity in “classic” adult CPT II deficiency. Lethal neonatal CPT II deficiency with null mutations (<1 % activity) presents with dysmorphic features, hepatocardiomuscular symptoms, hyperammonemia, dysmorphic features, microcephaly, brain and renal malformations, and biventricular hypertrophy [15].

Careful consideration of the history and physical exam, followed by selected, prioritized screening biochemical investigations, should allow the clinician to reach a presumptive diagnosis, to be confirmed by specific investigations, including a skin and/or muscle biopsy as indicated and subsequent enzymatic and genetic studies.

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Chapter 11
Management of Seizures and Status Epilepticus

Suresh Pujar, James J. Riviello Jr., and Rod C. Scott

Abstract Convulsive status epilepticus (CSE) is a common emergency in childhood and is associated with substantial morbidity and mortality. There is a lack of consensus on the management of CSE in children, mainly due to regional variations in the availability and licensing of drugs used in treatment of CSE and also due to insufficient evidence base particularly for drugs used to treat refractory CSE. In this chapter, we discuss the rationale for early treatment of seizures, available treatment options, and present a stepwise treatment algorithm for the management of CSE in children.

Keywords Seizures • Status epilepticus • Refractory • Management • Protocol

11.1 Introduction

Convulsive status epilepticus (CSE) is the most common medical neurological emergency in childhood and is associated with substantial morbidity and mortality [1]. Although the etiology of CSE is the primary determinant of subsequent morbidity and mortality, the duration of the CSE may also have an influence

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on the outcome [1]. Therefore, there is universal consensus that CSE in childhood needs to be treated early as this may help to prevent adverse outcomes.

11.2 Definition of CSE

The conventional definition of CSE is "a seizure lasting more than 30 min, or intermittent seizures lasting more than 30 min without a return of normal function in between" [2]. The 30-min duration is meant to demarcate the transition point when SE becomes established and also when seizure-induced neuronal injury begins to occur [2–4]. However, more recently there has been a move towards an "operational definition" of CSE, and clinicians around the world agree that patients with a seizure lasting for longer than 5 min should be treated as if they were in established CSE [2].

The majority of generalized seizures last for less than 5 min and seizures lasting for more than 5–10 min are less likely to self-terminate [2, 3, 5]. In a study of new-onset seizures in children, the longer a seizure lasted, the less likely it was to stop spontaneously within the next few minutes [5]. This "self-sustaining" characteristic of prolonged seizures has also been demonstrated in animal models, and the evidence suggests that this is due to endocytosis of inhibitory $GABA_A$ receptors and recruitment of the excitatory AMPA and NMDA receptor subunits at the synaptic membrane, thereby, facilitating excitation and progression of seizure activity [4]. Another distinguishing feature of CSE is time-dependent development of pharmacoresistance. Several studies have shown that seizures are more likely to terminate if treatment is administered earlier rather than later [6]. In a prospective study of CSE in children, for each minute delay from the onset of CSE to arrival at the emergency department, there was a 5 % (with 95 % confidence interval of 3–6 %) cumulative increased risk of CSE lasting longer than 60 min [7]. Data from animal models suggests that the time-dependent pharmacoresistance is due to internalization of inhibitory $GABA_A$ receptors, reducing the potency of drugs such as benzodiazepines [4]. All of these lines of evidence suggest that early appropriate treatment of CSE is required.

Sometimes seizures do not terminate after initial treatment (refractory CSE). CSE is considered to be refractory if an episode of CSE continues after the administration of one first-line and one or two second-line drugs or if a seizure lasts longer than 1–2 h [8].

11.3 Rationale for Early Treatment

Due to methodological limitations, it is difficult in humans to establish the independent role of CSE on outcomes, as these outcomes are usually confounded by other variables such as the cause of CSE. Nevertheless, it is possible that epileptic discharges occurring over a long period of time can cause neuronal injury. There is growing evidence from animal and human studies that prolonged seizures result in neuronal injury and increase the risk of epilepsy and adverse cognitive and behavioral outcomes [1, 4, 8]. There is also evidence to suggest that early

treatment of seizures may avoid hospitalization and results in better outcome [6]. An association between longer duration of CSE and increased short-term mortality has also been reported, although a significant association is seen mostly in adults [1, 3, 8].

11.4 Stages of CSE

Based on the duration of the seizure, CSE can be divided into sequential stages [9]. The knowledge of the stage of CSE is useful in guiding management of prolonged seizures:

- Incipient CSE—seizure duration less than 5 min
- Impending or early CSE—seizure duration between 5 and 30 min
- Established or late CSE—seizure duration between 30 and 60 min
- Refractory CSE—seizure duration more than 60 min

11.5 Treatment Protocols

The purpose for having a written treatment protocol for CSE with a clear structured time frame is to ensure timely, appropriate management and prevent errors in the stressful environment of a medical emergency. This is particularly useful for junior medical staff, who are likely to be inexperienced in managing CSE. Despite having standardized protocols for management of CSE, several studies have shown that the protocols are often not followed, resulting in longer CSE and higher rates of admission to intensive care units [10]. The main issues identified were [1] giving inadequate doses of benzodiazepines, particularly rectal diazepam; [2] treating with more than two doses of benzodiazepines; and [3] delay in initiating second-line treatment and/or anesthetic intervention [10].

Although it would be ideal to have a universal protocol for management of childhood, this has not been possible mainly due to variations in availability and licensing of drugs used in treatment of CSE in different parts of the world [11]. Emergency departments could develop their own protocol derived from evidence-based guidelines and adapted according to regional needs and drug availability. Also, individuals susceptible to repeated episodes of CSE should have individualized treatment protocols, based on their past experience, so that ineffective treatment and undesirable outcomes are avoided.

11.6 Principles of Treatment

The management of a child with CSE can be broadly divided into [1] initial stabilization and evaluation [2], seizure termination, and [3] diagnosis and treatment of the underlying cause.

11.6.1 Initial Stabilization and Evaluation

As with any other medical emergency, the initial stabilization of a child presenting with a prolonged seizure involves monitoring and ensuring adequate airway, breathing, and circulation (the ABC protocol). In the pre-hospital setting, basic life support should be administered by the first respondent (parent/teacher/paramedic) and child maintained in recovery position (a three-quarter-prone position) to ensure airway patency. Vital parameters should be monitored continuously and temperature checked. Hyperthermia is not uncommon during CSE, but may also indicate a febrile illness, and a CNS infection should be strongly considered. A brief history should be taken and a quick examination performed to confirm diagnosis and rule out a nonepileptic seizure or a movement disorder or drug-induced or metabolic encephalopathy.

Assessment and management of the airway can be particularly challenging in a patient with ongoing seizure. Arterial blood gas analysis can provide useful information in this situation. Despite periods of apnea and cyanosis occurring during the tonic or clonic phase of seizures, most patients breathe sufficiently as long as the airway remains patent. Maintaining adequate airway may require use of oropharyngeal or nasopharyngeal airway devices, and rapid sequence intubation should be considered in case of respiratory insufficiency or if Glasgow coma scale score is less than 8. Patients should be given 100 % oxygen to correct hypoxia.

If rapid intravenous access is difficult, an intraosseous line should be considered. A bedside blood glucose measurement should always be done to exclude hypoglycemia, and investigations sent to the lab to measure blood glucose, electrolytes, calcium, magnesium, drug screening for accidental or deliberate overdose, and drug levels if patient is on regular antiepileptic medication.

11.6.2 Seizure Termination

The goal of treatment for CSE is to [1] terminate all seizure activity as soon as possible [2], prevent recurrence of seizures, and [3] treat complications both of CSE and of the treatment administered [12]. Ideally, this is achieved by using a drug that is easy to administer, has immediate onset of action and long half-life, has no serious adverse effects on cardiorespiratory function, and has minimal effect on level of consciousness. Unfortunately, none of the currently available drugs fulfills all these criteria.

11.6.2.1 Drugs Commonly Used in the Treatment of CSE in Children

Drugs commonly used in treating CSE in children, their mode of administration, dose, and common side effects and precautions are listed in Table 11.1. A brief description of the different classes of medications used in treatment of CSE is presented in this section.

Table 11.1 Drugs commonly used for treatment of prolonged seizures/convulsive status epilepticus in children

Drug	Route of administration	Dose	Common side effects/ precautions
Pre-hospital/out-of-hospital treatment			
Midazolam	Buccal	0.15–0.3 mg/kg	Sedation, respiratory depression
	Intranasal	0.15–0.3 mg/kg	
	Intramuscular	0.2 mg/kg	
Diazepam	Rectal	0.5 mg/kg	Sedation, respiratory depression
Lorazepam	Intranasal	0.1 mg/kg	Sedation, respiratory depression
First-line treatment			
Lorazepam	Intravenous	0.1 mg/kg	Sedation, respiratory depression
Diazepam	Intravenous	0.2–0.3 mg/kg	Sedation, respiratory depression
Midazolam	Intravenous	0.15–0.2 mg/kg	Sedation, respiratory depression
Second-line treatment			
Phenytoin	Intravenous	20 mg/kg (rate 1 mg/kg/min, a repeat dose of 10 mg/kg may be considered)	Cardiac arrhythmias, hypotension, thrombophlebitis
Fosphenytoin	Intravenous	20 mg PE/kg (rate 2–3 mg PE/kg/min, a repeat dose of 10 mg PE/kg may be considered)	Cardiac arrhythmias, hypotension
Phenobarbital	Intravenous	15–20 mg/kg (rate 2 mg/kg/min)	Sedation, respiratory depression, hypotension
Sodium valproate	Intravenous	20–40 mg/kg (rate 5 mg/kg/min)	Hepatotoxicity, encephalopathy Avoid in metabolic disorders
Levetiracetam	Intravenous	30–60 mg/kg (rate 5 mg/kg/min)	Consider in liver disease/ metabolic disorders
		High dose: >150 mg/kg/day	Adjust dose in renal impairment
Treatment of refractory CSE			
Midazolam	Intravenous	Bolus 0.2 mg/kg, f/b infusion at 0.05–2 mg/kg/h	Respiratory depression, hypotension Breakthrough seizures
Very high-dose phenobarbital	Intravenous	Bolus 20 mg/kg, dose increased to reach a level of 70–344 μ[mu]g/mL	Respiratory depression, hypotension
Thiopental	Intravenous	Bolus 5 mg/kg, f/b infusion at 3–5 mg/kg/h	Respiratory depression, hypotension, cardiorespiratory arrest, ileus, immunosuppression Prolonged mechanical ventilation

(continued)

Table 11.1 (continued)

Drug	Route of administration	Dose	Common side effects/ precautions
Pentobarbital	Intravenous	Bolus 5–15 mg/kg, f/b infusion at 0.5–5 mg/kg/h	Respiratory depression, hypotension, cardiorespiratory arrest, ileus, immunosuppression Prolonged mechanical ventilation
Propofol	Intravenous	Bolus 1–2 mg/kg, f/b 1–2 mg/kg/h (max 5 mg/kg/h)	Avoid in children under the age of 16 years due to risk of propofol infusion syndrome Not to be used with ketogenic diet
Isoflurane/ desflurane	Inhalation	1–5 %	Respiratory depression, hypotension Seizure recurrence during tapering

PE Phenytoin equivalent, *f/b* followed by

Benzodiazepines

Benzodiazepines act at $GABA_A$ receptors and inhibit neuronal transmission. They are considered as first-line drugs for treatment of CSE due to their efficacy, safety, and availability in IV and also non-IV (per rectum, buccal) formulations which are easy to administer in out-of-hospital settings. They are most effective early during CSE, and their efficacy is reduced as the seizures progress due to internalization of $GABA_A$ receptors.

Phenytoin/Fosphenytoin

Phenytoin acts by slowing the recovery of voltage-activated sodium channels, thus decreasing the repetitive action potentials in neurons. Phenytoin should not be infused at a rate greater than 50 mg/min, as hypotension may occur due to the propylene glycol diluent. Also, because of the high pH of phenytoin solution (approximately 12), thrombophlebitis is very common and extravasation may result in extensive tissue necrosis. Fosphenytoin, the water-soluble prodrug of phenytoin, can be infused at rates faster than phenytoin and is less toxic to the tissues. Fosphenytoin however does not reduce the risk of the cardiac side effects.

Barbiturates

Barbiturates primarily act at $GABA_A$ receptors to increase chloride conductance across the neuronal membrane and inhibit neurotransmission. Phenobarbital is often

used as a second- or third-line therapy for CSE. The risk of respiratory depression is increased when phenobarbital is administered following benzodiazepines.

Thiopental and pentobarbital (a metabolite of thiopental) are barbiturate anesthetics effective in treatment of refractory CSE. Their dose can be titrated to achieve burst suppression and are nearly always effective in stopping seizures. However, they are often associated with significant side effects such as ventilator-associated pneumonia, intestinal ileus, bowel ischemia, and cardiorespiratory arrest.

Sodium Valproate

Sodium valproate, a broad-spectrum anticonvulsant, acts through several mechanisms including modulation of sodium and calcium currents and increase of inhibitory GABA transmission. The main advantage of valproate is low risk of hemodynamic instability even at high rates of infusion. Valproate is hepatotoxic and should be avoided in children with suspected metabolic disorders.

Levetiracetam

Levetiracetam, like valproate, is a broad-spectrum anticonvulsant with multiple sites of action including calcium channels, glutamate receptors, and GABA modulation. As it is primarily excreted by renal route, dose modification is required in renal impairment.

Propofol

Propofol is an IV anesthetic agent with potent anticonvulsant properties. It acts through direct activation of $GABA_A$ receptors, although it also affects sodium and calcium currents to reduce cortical excitability. The most serious side effect of propofol therapy is "propofol infusion syndrome (PRIS)," characterized by metabolic acidosis, arrhythmias, hypotension, rhabdomyolysis, renal failure, and sometimes death. The risk of PRIS is increased in children receiving infusion rates exceeding 5 mg/kg/h for longer duration, and when used in combination with ketogenic diet.

There are therefore many drugs which can be used for the treatment of CSE. However, it is insufficient to simply be aware of the medications. It is also essential to establish a system that allows appropriate use of anticonvulsants in both pre-hospital and hospital settings (see Fig. 11.1).

11.6.2.2 Pre-hospital Treatment

In the large majority of children, an episode of CSE starts in the community [7, 13]. The median seizure duration prior to hospital arrival and treatment is 45–68 min in

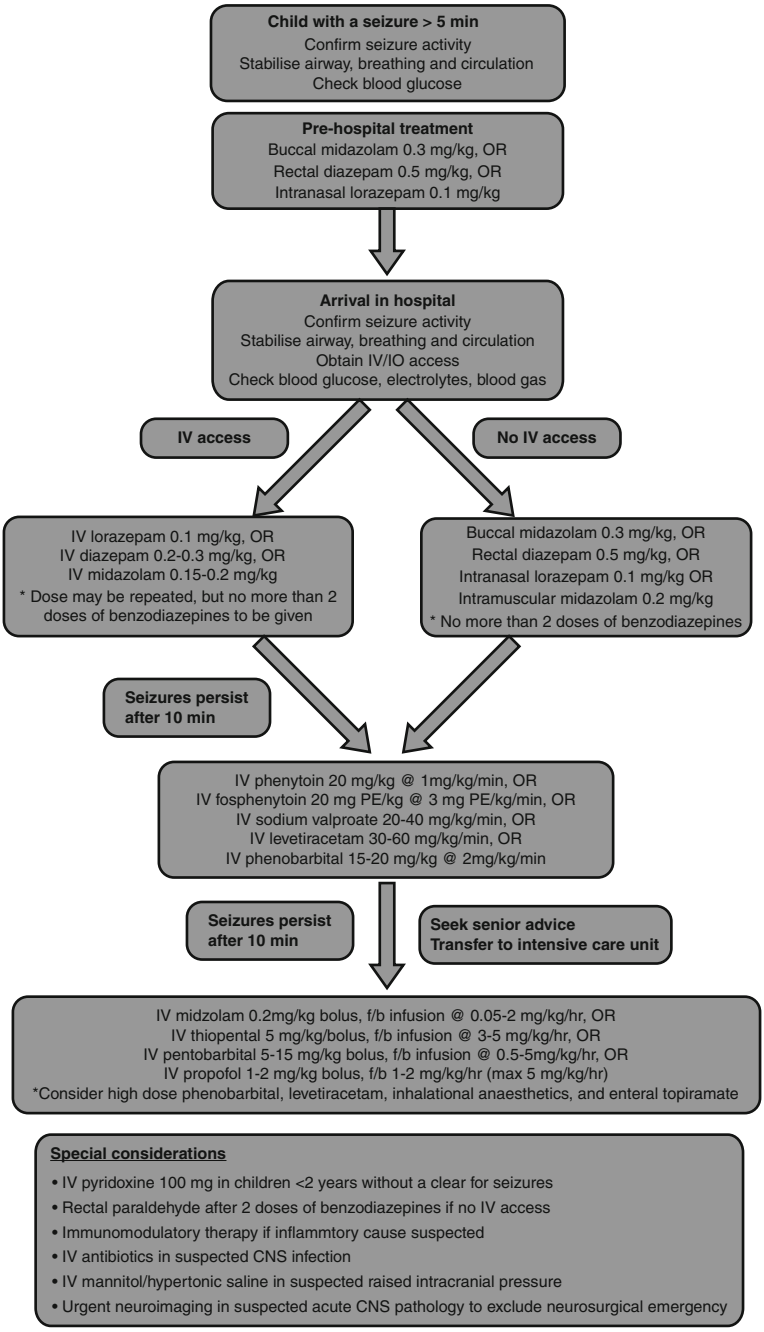

Fig. 11.1 Treatment algorithm for the management of convulsive status epilepticus in children

resource-rich countries and is substantially higher in resource-poor countries [7, 13–15]. Delaying treatment until the child reaches a hospital will increase the duration of CSE, increasing the risk of pharmacoresistance, brain injury, admission to the intensive care unit, and the associated morbidity and mortality. In addition, early out-of-hospital treatment of seizures often results in early termination of seizures and may avoid hospitalization [6].

There is now consensus among clinicians that pre-hospital treatment of prolonged seizures is important and it is recommended that pre-hospital treatment be included in all CSE treatment protocols [16]. A common reason for lack of efficacy of pre-hospital treatment is administration of lower-than-recommended dose of medication [7]. Increasing awareness among paramedical staff and parents may result in improved efficacy of pre-hospital treatment and avoid hospitalization.

Benzodiazepines are recommended for pre-hospital treatment due to their proven efficacy and availability of preparations suitable for non-intravenous mode of administration. Diazepam administered via intravenous (IV) or per rectal (PR) route has traditionally been the first-line drug used in treating prolonged seizures and has proven efficacy in terminating seizures [17]. However, IV access is often difficult in an out-of-hospital setting, and PR administration may be difficult in certain circumstances (e.g., child in a wheelchair) or socially unacceptable in public places.

Several studies have shown that buccal midazolam is at least as effective as, or even superior to, PR diazepam in terminating prolonged seizures with comparable side effect profile and reduced risk of seizure recurrence [17]. Intranasal (IN) lorazepam, IN midazolam, PR lorazepam, clonazepam as oral disintegrating tablet or wafer, and intramuscular (IM) midazolam have also been proven to be safe and effective in terminating prolonged seizures and therefore considered if buccal midazolam is not available in out-of-hospital setting [6, 18, 19].

11.6.2.3 In-Hospital First-Line Treatment

Although IV lorazepam and IV diazepam are equally effective in terminating seizures in children, IV lorazepam has longer duration of action and is associated with fewer adverse events and therefore recommended as the first-line drug when IV access is available [7, 18]. IV midazolam has also been shown to be safe and effective in terminating seizures in children [6]. If there is difficulty in obtaining IV access, drugs used in pre-hospital setting should be used in order to avoid delay in treatment.

A repeat dose of benzodiazepine may be administered if necessary, but consideration should be given to pre-hospital treatment and a child should not receive more than two doses of benzodiazepines as this increases the risk of respiratory depression [7]. As benzodiazepines have a relatively short duration of action, this should be followed by a loading dose of phenytoin or fosphenytoin to reduce the risk of seizure recurrence [20].

11.6.2.4 Second-Line Treatment

Phenytoin is the most commonly used second-line therapy if there is no response to benzodiazepines [6, 10]. Although IV phenytoin is successful in terminating benzodiazepine-resistant seizures in a considerable proportion of children, it cannot be infused rapidly and is associated with significant side effects. Therefore, some prefer using fosphenytoin, a water-soluble prodrug of phenytoin, whose efficacy is comparable to that of phenytoin, but can be infused more rapidly, and with fewer side effects [6, 20].

Phenobarbital, routinely used as the first-line therapy for neonatal seizures, is sometimes recommended as the second-line and often as third- or fourth-line therapy for CSE in older children [6, 10]. Although the anticonvulsant effect of phenobarbital is similar to benzodiazepines and phenytoin, its major limitation is potential for respiratory depression, especially if given after benzodiazepines [6, 10, 20].

IV sodium valproate has been shown to be a safe and effective alternative second-line therapy for prolonged seizures in children. Several case series and open-label studies in children and adults report a success rate of 65–100 %, with minimal side effects [6]. Although there are no prospective comparative studies, the reported success and better safety profile has led to IV valproate being included in CSE treatment protocols in children [6].

Like IV sodium valproate, IV levetiracetam has increasingly been used for treatment of prolonged seizures in children, and the available evidence, mainly from case series, suggests that IV levetiracetam may be safe and effective in treating prolonged seizures and repetitive seizures in children [6]. Recent reports suggest that higher doses of IV levetiracetam (150 mg/kg/day or greater) could be used safely to control seizures in children where conventional doses (40–60 mg/kg/day) are ineffective [21]. IV Lacosamide has been shown to be safe and effective in treatment of refractory status epilepticus in adults, but its use in children has not yet been reported [22].

11.6.2.5 Treatment of Refractory CSE

About 10–40 % of seizures fail to respond to first- and second-line therapy, and the morbidity and mortality associated with refractory CSE is considerably higher compared with CSE responsive to therapy [8, 12]. Children with refractory CSE require close monitoring and prompt treatment of complications and therefore should be managed in intensive care units. Continuous electroencephalography (EEG) may be required to monitor seizure activity and response to treatment.

The currently available therapeutic options for managing refractory CSE include IV infusion of anesthetic doses of midazolam, barbiturates (thiopental, pentobarbital, and very high-dose phenobarbital), propofol, and less commonly, ketamine and inhalational anesthetics. There is no strong evidence to recommend one therapy over the others, as there are no randomized controlled trials comparing their outcomes. In addition to clinical seizure termination, often the aim of treatment is to achieve EEG burst suppression and maintain for 12–48 h prior to tapering [8].

However, it is unclear whether burst suppression alone improves seizure control or outcomes.

A meta-analysis of treatment of refractory CSE in children showed that midazolam may be a good choice for initial treatment [23]. In addition to its efficacy, its short duration of action and titratability and low rate of adverse effects make it the preferred benzodiazepine for continuous IV infusion [8, 12, 20]. Although treatment with midazolam is generally effective and well tolerated, there is increased propensity for breakthrough seizures, often necessitating change of treatment [12, 24].

Thiopental and pentobarbital (a metabolite of thiopental) are highly effective in termination of refractory CSE, achieve burst suppression on EEG, and have lower rate of breakthrough seizures [8, 12, 24]. However, they are associated with potentially fatal side effects. Pentobarbital is often preferred over thiopental due to its better side effect profile [20]. There are also reports of safety and efficacy of very high-dose phenobarbital (doses up to 80 mg/kg) in refractory CSE [25].

The efficacy of propofol in terminating refractory seizures is comparable to thiopental, and due to its short half-life, recovery is rapid even after prolonged use [8, 12]. However, the most significant drawback is the liability to cause a potentially fatal propofol infusion syndrome which, although more common in adults, is seen in children also and therefore not approved for use as a sedating agent in children under the age of 16 years.

Inhalational anesthetics, isoflurane and desflurane, at concentrations of 1–5 % have been reported to be effective in refractory CSE in children not responding to IV anesthetics [26]. They have rapid onset of action, safe, and can be titrated to achieve and maintain burst suppression. Their main side effect is hypotension requiring IV fluids and vasopressors in all patients, and there is propensity for seizure recurrence upon withdrawal requiring addition of other anticonvulsants.

11.6.2.6 Other Therapies to Be Considered

Pyridoxine

In children under the age of 2 years, the possibility of pyridoxine-dependent seizures should be considered, and a trial of up to five IV 100 mg bolus doses of pyridoxine attempted [27]. The IV trial should be done under EEG and cardiorespiratory monitoring as pyridoxine administration in responsive children may result in EEG suppression and apnea requiring resuscitation.

Enteral Topiramate

There are several reports of efficacy of topiramate in controlling seizures resistant to anesthetic drugs and breakthrough seizures during tapering of anesthetic agents [8]. The dose of topiramate is rapidly increased over 72 h and adjusted according to the response. Though well tolerated, patients should be monitored for development of metabolic acidosis.

Ketamine

Ketamine, a noncompetitive NMDA receptor antagonist, acts independently of a GABA pathway and therefore may be effective in late stages of refractory CSE. Although shown to be effective in treating refractory seizures, it has the potential of causing NMDA antagonist-mediated neurotoxicity and therefore needs further evaluation [8]. Ketamine increases intracranial pressure and therefore should not be used in states of raised intracranial pressure.

Immunomodulatory Therapy

Immunomodulatory therapy (corticosteroids, adrenocorticotrophic hormone (ACTH), IV immune globulin, and plasmaphoresis) should be considered early in CSE due to suspected inflammatory conditions such as anti-NMDA receptor antibody encephalitis, Hashimoto encephalopathy, Rasmussen encephalitis, and limbic encephalitis with antibodies to $GABA_B$ receptor, GAD, or VGKC [8, 26].

Ketogenic Diet

There are a few reports of efficacy of ketogenic diet (KD) in CSE refractory to conventional anticonvulsants [8, 26]. KD has been reported to be particularly effective in treatment of pharmacoresistant status epilepticus associated with fever-induced refractory epileptic encephalopathy in school age children (FIRES) [28]. An underlying metabolic disorder should be ruled out before initiating KD and should not simultaneously be used with propofol, as propofol may impair fatty acid oxidation and result in fatal complications.

Hypothermia

There is evidence from animal studies that hypothermia may be beneficial in reducing seizures and have neuroprotective effect [26]. In spite of proven benefit of hypothermia in neonates with hypoxic ischemic encephalopathy, and in adults after cardiac arrest, there are only a few reports of its use in CSE [26].

Surgery

Both resective and disconnective surgery may be considered in carefully selected cases of refractory CSE [29]. The surgical procedures include focal cortical resections, hemispherectomies, multiple subpial transections, and rarely, corpus callosotomy and vagal nerve stimulation implantation. Resective surgery may yield immediate and long-term benefit in cases of definite localization.

11.6.3 Diagnosis and Treatment of the Underlying Cause

A diagnostic evaluation with a good history and brief examination should be performed simultaneously with treatment of seizures. Investigations should be performed to diagnose easily correctable metabolic conditions such as hypoglycemia, electrolyte imbalances, and hypocalcemia. Drug screening should be performed for accidental or deliberate overdose and drug levels if patient is on regular antiepileptic medication.

The rate of CNS infection was 12.8 % in a review of 1,859 children presenting with CSE and 20 % in children with first ever febrile CSE (12 % acute bacterial meningitis) [30, 31]. CNS infection should be especially considered in febrile children younger than 2 years and treated with IV antibiotics (cefotaxime, acyclovir, and erythromycin). Lumbar puncture should be delayed until the child is stabilized.

Urgent neuroimaging may be necessary if there is suspicion of an acute CNS pathology such as hemorrhage, space occupying lesion, or if a clear cause for CSE is not known, especially to exclude need for urgent neurosurgical intervention [31]. Neuroimaging should only be performed after the seizure is controlled and the patient is stabilized. If there is suspicion of raised intracranial pressure, mannitol 0.25 g/kg, or hypertonic saline (3 %) 3 ml/kg, should be considered.

11.6.3.1 Special Consideration

West Syndrome

West syndrome (WS) is a common epileptic encephalopathy with onset in infancy and characterized by frequent epileptic spasms, psychomotor regression and a distinct EEG pattern (hypsarrhythmia) [30]. The prognosis is poor in the majority with persistent seizures, profound psychomotor impairment, and behavioral comorbidities. However, better outcomes have been reported with early control of spasms and resolution of hypsarrhythmia, and therefore, it is recommended that effective therapy should be initiated soon after the onset of symptoms [30].

Corticosteroids are often recommended as the first line therapy in WS. They are highly effective for the treatment of spams in WS with response rates between 60 and 80 % [30]. Adrenocorticotropic hormone therapy (ACTH) has been shown to be effective both at low dose (20–40 units/m^2 per day) and high dose (150 units/m^2 per day), and there is insufficient evidence to define the optimum ACTH dose and duration of treatment for treatment of spams. There is also some evidence for high dose oral steroids to be as effective as ACTH and with reduced side effects [30]. Vigabatrin is very effective for the treatment of spasms associated with tuberous sclerosis, and is therefore recommended as first line therapy for this condition. Vigabatrin is also effective in treating spasms due to other causes, but is often used as second line therapy due to potential retinal toxicity reported with its prolonged

use [30]. A trial of pyridoxine could be considered if there is no response to standard therapy, or if the clinical picture is suggestive of pyridoxine dependency. Antiepileptic drugs (e.g., nitrazepam, topiramate, sodium valproate), and ketogenic diet have been reported to be beneficial in some refractory cases of WS. Children with resectable brain pathology and seizures refractory to medical treatment may benefit from early epilepsy surgery.

11.7 Conclusion

CSE is a common emergency in childhood and is associated with substantial morbidity and mortality. Early intervention results in better response to treatment and outcome. Management of refractory CSE is often challenging and is associated with significant side effects and requires intensive care. Therefore, pre-hospital treatment should be included in all CSE treatment guidelines and protocols in order to reduce the chance that CSE becomes refractory. The current evidence supports the use of benzodiazepines as the first-line therapy. Limited data has demonstrated that IV valproate and levetiracetam are effective and safe in treatment of CSE in children. Prospective studies are needed to determine the roles of currently available medications as second-line therapy and for refractory CSE.

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Chapter 12
Management of Increased Intracranial Pressure

Bengt Gustavsson

Abstract This chapter discusses the intracranial pressure (ICP) in the growing child and young adult. The purpose is to give the reader a condensed view of possible causes, symptoms, and the basal initial management in general and at different ages in the child with a pathological high intracranial pressure.

Keywords Intracranial hypertension • Management • Children • Cerebral perfusion pressure • Cerebrospinal fluid • Meningitis

12.1 Introduction

The intracranial pressure (ICP) is dependent on three compartments inside the fixed volume of the cranium: volumes of the brain, blood, and cerebrospinal fluid (CSF), respectively. Brain tissue occupies about 80 % of the total intracranial volume. The remaining 20 % are evenly shared by blood (in arteries and veins) and CSF (in the ventricles, the basal cisterns, and the subarachnoid space). Since these volumes are not compressible, ICP is normally measured by assuming that it is evenly distributed among all intracranial compartments, including the intradural space of the spinal canal. This also assumes that the CSF circulation is constant without any obstruction.

The normal intracranial pressure increases with age (Table 12.1), partly because the cranial bones that cover the brain will be more rigid as the fontanels and the sutures close with age. As the child gets older, the calvarial bone and meninges increase in size as the brain matures; also the volumes of blood and cerebrospinal fluid (CSF) increase as the child grows. After the fontanels are closed, the intracranial volume becomes constant. This means that if one intracranial component increases in volume, it can be compensated by a decreased volume in one or both of

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Table 12.1 Intracranial pressure at different ages

Age	Normal range (mmHg)
Adults and older children	<(5) 10–15
Young children	3–7
Term infants	1.5–6

Depending on the child's position, mental/clinical status, and eventual sedative [1]

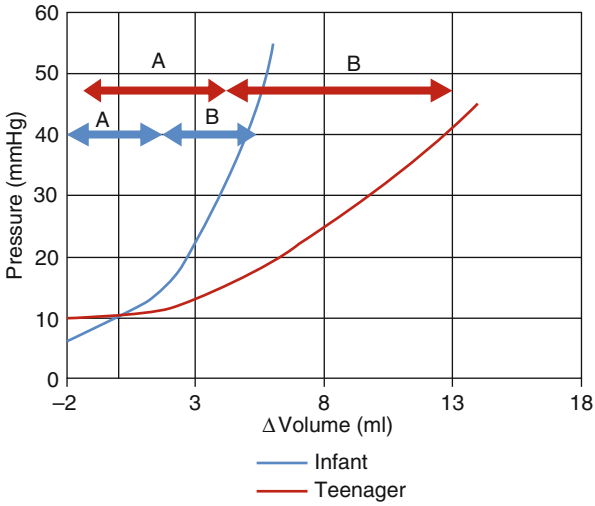

Fig. 12.1 Pressure-volume curves in an infant and a teenager, illustrating less compliance for the same volume in the infant. A = Interval with good compensatory reserve; B = interval with poor compensatory reserve (Modified from Refs. [2, 3])

the other intracranial components (Monro-Kellie doctrine). A delayed reaction of this compensatory reserve results in an immediate, within minutes, increased ICP in the case of introduction of an extra volume. This can be illustrated by the pressure-volume curve (Fig. 12.1).

The pressure-volume curve is significantly steeper in infants than in older children, partly due to their relatively smaller intracranial volume. In the presence of other intracranial masses (obstructive hydrocephalus, cysts, tumors), the intracranial volume can increase rapidly, resulting in a growth curve deviating from the normal head circumference growth chart. The growth could be detected in a few days in infants and in weeks or months in children up to about 5 years of age, without other obvious symptoms of raised ICP.

A sufficient cerebral blood flow (CBF) is critical for the homeostasis of the brain, the survival of nerve cells, and the protection of normal brain functions. There is a risk that ICP elevated above normal may decrease the CBF significantly and cause cerebral ischemia and eventually brain infarction.

However, measuring overall CBF is difficult at bedside, and it is even more complicated to measure CBF in the areas of the brain that are at risk for ischemia (the penumbra zones), that is the brain tissue surrounding a damaged brain or the part of the brain compressed by, e.g., an expansive pathological process.

CBF depends on both the cerebral perfusion pressure (CPP) and the vascular resistance.

Cerebral perfusion pressure (CPP) is determined by the mean arterial pressure and the ICP:

$$CPP = mean\,arterial\,blood\,\,pressure - ICP$$

$$\left(mean\,arterial\,\,pressure = diastolic\,blood\,\,pressure + \left[1/3\,of\,\,systolic\,BP - diastolic\,BP\right]\right)$$

It is worth to stress that values of CPP might differ between neurosurgical centers, depending on the choice of zero level for ICP measurements as well as for the invasive blood pressure. It is not defined where to locate the pressure dome for zero levels of ICP and arterial blood pressure (ABP). If the zero level for measure of ICP as well as for ABP is done at the level of foramen of Monro, the pressure measured, mean carotid pressure, is at least independent of positioning of the patient.

The cerebral autoregulation will modulate the CBF to be the same, despite a fairly wide variation of the systemic blood pressure. Normal CPP in adult is >50 mmHg and in the premature born infant, it is possibly around 35 mmHg [4]. The ICP can probably be significantly increased for days or even weeks for some patients, without risk for brain damage as long as the CPP stays within acceptable limits [5].

12.1.1 Symptoms

Symptoms of raised ICP are not specific. The symptoms can be very diffuse and difficult to pick up in the emergency room or at the outpatient clinic. Infants can have raised ICP without noticeable symptoms, except for the head circumference crossing percentiles on the growth chart. Headache, nausea, and vomiting in the mornings are the prevailing symptoms, such as in, e.g., children with brain tumors [6], especially in combination with visual symptoms. Visual problems occur frequently in the case with raised ICP but may not be apparent until examined (Table 12.2).

If increased ICP cannot be controlled, it can be life threatening due to herniation of the temporal lobe (uncal, tentorial herniation) or the whole brain down the posterior fossa and the foramen magnum (brainstem herniation) (see also Chap. 1, Table 1.7 for differentiation of symptoms). Intracranial bleedings, cerebral infections, and obstructive hydrocephalus, including shunt dysfunction, can cause just as acute changes of the intracranial content as traumatic brain injury and necessitate emergent actions to secure the supply of oxygen and energy to the brain.

Other mass lesions might evolve more slowly and cause an increasing flora of symptoms over days, weeks, and years. Abscesses, tumors and arachnoid cysts, global or focal cerebral edema after ischemic, toxic, infectious, or inflammatory events, and systemic diseases are other possible causes for raised ICP (Table 12.3).

The increment of ICP that can be tolerated by the individual child can vary significantly. While most patients will suffer from a herniating brain if the ICP is

Table 12.2 Clinical symptoms of raised intracranial pressure

Common symptoms
Vomiting, especially cascade-like; typical: vomiting in the mornings
Double vision, blurred vision, papilledema
Neck stiffness, torticollis (tilted head and possible decreased motion)
Irritability or personality changes
Focal neurological deficit
Note for infants and small children:
Full or bulging fontanel
Widened sutures of the skull bone
Prominent veins in the scalp
Increasing head circumference—change of percentiles
Sunset phenomena
"Failure to thrive"
Stomach ache

Table 12.3 Possible causes of raised ICP

Primary intracranial
With mass effect compressing the normal brain:
Hydrocephalus—shunt dysfunction
Tumors
Cysts
Cerebrovascular causes (bleedings, thrombosis, and embolus (arterial or venous))
Abscess (not necessary followed by fever and elevated CRP)
Edema, focal or general
Without mass effect:
Infections (meningitis, encephalitis, Reyes syndrome)
Epilepsy
Benign intracranial hypertension
Systemic pathology with influence
Diabetic ketoacidosis
Hypertensive encephalopathy
Toxic substances (e.g., lead)
Renal failure (hemodialysis, hemolytic-uremic syndrome)
Liver encephalopathy
Burns
Hypoxic-ischemic catastrophe
Cardiac arrest
Near drowning

>50 mmHg, in our department we experienced a 2 years old child, under ICP monitoring, was seen playing in his bed with this high ICP. The child did not even have papilledema. Another of our patients, an adolescent, suffered from severe headache, chronic papilledema, and decreasing visual acuity with similar high ICP.

It is reasonable to expect a higher ICP with a body weight above normal due to an increased intra-abdominal and in turn intrathoracic pressure, although this has

Table 12.4 Symptoms and findings in highly increased intracranial pressure—threatening brainstem herniation!

Decreased level of consciousness (GCS < 15)
Dilated pupils/sluggish or no light reaction, focal neurological deficits
Yawning, spontaneous hyperventilation
Ophthalmoplegia, diplopia or difficulties to accommodate
Decerebrate rigidity/opistotonus, positive Babinski sign
Increased blood pressure/bradycardia, irregular or superficial respiration (*Cushing's triad*)
Death
Hypotension is not caused by raised intracranial pressure!

not been confirmed. Other conditions resulting in raised pressure in the intracranial draining veins can result in increased ICP, for example, venous outflow obstruction due to stenosis of the jugular foramen or intracerebral venous thrombosis.

Analyzing intracranial pressure wave forms caused by the systolic blood pressure is important. The shape and the amplitude give information about the cerebral compliance [7]. These pressure waves should be present to confirm that the monitoring equipment is working well. It should, however, be noted that the pressure waves can be absent in a child with open fontanel or missing a significant bone flap (e.g., after hemicraniectomy).

12.1.2 Extracranial Symptoms Due to Increased ICP

- Increased BP and bradycardia as in Cushing's triad (Table 12.4).
- Neurogenic pulmonary edema can be caused by a sudden increased ICP resulting in an increased alveolar permeability and edema. This is an emergency state with high risk of upcoming herniation of the brain, requiring both symptomatic and causative treatments.

12.2 Causes of Raised ICP

Causes of raised ICP can be divided into processes in the already existing intracranial components, the brain, the blood, and the CSF, or other space-occupying lesions.

12.2.1 Brain

Stroke and trauma are the most common causes for expansion of the whole or parts of the brain. Both bleedings and infarctions can cause important mass effects inside or outside the brain thereby abruptly increasing the risk for life-threatening (malignant) ICP. Inflammatory changes and toxins can also cause brain swelling. The peak swelling usually is reached on day 3–5.

12.2.2 Brain Edema

Increased brain volume due to increased water content within the brain tissue itself is a common and important cause for raised ICP. Focal edema can result in focal symptoms without a significant increase of the ICP. In the clinical situation, it might not be possible to differentiate between cerebral edema and increased cerebral blood volume, as sometimes seen, e.g., in epilepsy, defect autoregulation caused by asphyxia, brain injury, or as a result of toxins [8].

Brain edema could be divided into five different types:

- Vasogenic edema—increased permeability of plasma proteins through the walls of the endothelial cells of the capillaries to the extracellular space. It might be induced by inflammatory processes like infections, tumors, infarcts, bleedings, or other vascular processes. Most likely it is observed during the first hours after a traumatic brain injury or an epileptic status. Disruption of the blood brain barrier occurs and can be measured by calculating the albumin CSF/albumin blood ratio.
- Cytotoxic edema—leakage of intracellular metabolites to the extracellular space due to dysfunction of the cell membrane and the ion pumps within it. Cytotoxic edema is usually induced by lack of energy present in hypoxic/ischemic conditions or by toxins. The leakage of intracellular metabolites might progress to neuronal cell death. Cytotoxic edema is often seen in conjunction with vasogenic edema.
- Hypoosmotic edema—decreased osmolarity in the plasma will result in accumulation of water in the astrocytes. This condition is usually caused by hyponatremia.
- Hydrostatic edema—defect autoregulation resulting in increased intravascular pressure that transmits to the capillaries, followed by leakage of water to the extracellular space. This type of edema is caused by hypertension and is possibly present also in some traumatic brain injuries.
- Interstitial edema—transependymal resorption of CSF from the ventricular system to the extracellular space (periventricular) caused by hydrocephalus with elevated intraventricular CSF pressure.

Steroids are effective mainly on vasogenic edema. Drainage of CSF will decrease the interstitial edema.

12.2.3 Sinus Thrombosis

Sinus thrombosis is much less frequent than cerebral infarcts. CT angiography or magnetic resonance angiography (MRA) will demonstrate if there is any blood flow in the sagittal or transverse sinuses or bridging veins. Most common causes:

- Septic (otitis, sinusitis, meningitis, septicemia)
- Aseptic (dehydration, cardiac failure, hematologic diseases or coagulopathies, anemia, nephrotic syndrome, pregnancy, anticonception medication, diabetes, trauma, ulcerous colitis)
- Unknown

12.2.4 Idiopathic Intracranial Hypertension (IIH)

Idiopathic intracranial hypertension (IIH), also called benign intracranial hypertension or pseudotumor cerebri, is a condition with raised intracranial pressure of unknown cause without an expansive intracranial process or impaired CSF circulation. On imaging the ventricles are normal or slightly smaller in size. IIH is more common in girls and obesepersons. In children with IIH, weight or sex is not different than in the normal pediatric population. Headache is the most common symptom with or without visual problems such as reduced visual acuity or blurred vision due to papilledema, impaired eye movements, and visual field defects [15]. There is no consensus on a specific level of ICP to define the condition. However, most centers would agree that the lumbar pressure should be more than 20 cm H_2O [9].

The treatment is symptomatic and depending on severity of symptoms. Most often the initial treatment will be an attempt to decrease the CSF production with oral medication (e.g., acetazolamide 30–100 mg/kg/day or furosemide 2–4 mg/kg/day). In the case of a severe papilledema, an opening of the optic sheet along the intraorbital part of the optic nerve is an option. CSF drainage via lumbar puncture on a regular basis or by a shunt will often decrease the pressure permanently.

12.2.5 Hydrocephalus

12.2.5.1 Obstructive Hydrocephalus

Obstructive hydrocephalus is caused by an obstruction of the CSF pathways, in turn caused by malformations, tumors, bleedings, or infections, mostly occurring at the foramen of Monro, the aqueduct, or foramina of Luschka or Magendie. This can be acute and life threatening as in the case of a foramen Monro cyst.

12.2.5.2 Communicating Hydrocephalus

Communicating hydrocephalus can be caused by increased CSF production or a defective absorption. The first cause is extremely rare, even in the case of choroid plexus tumors.

As opposed to IIH, the communicating hydrocephalus most often is revealed on CT or MRI. The ependyma in the ventricular wall is a semipermeable membrane. This is a prerequisite to force the brain parenchyma to be compressed even at a low level of pressure difference between the ventricular compartment and the brain tissue. Therefore the ventricles can become larger than normal.

12.2.5.3 Patients with Hydrocephalus Treated with Shunt Systems

Children with hydrocephalus treated with shunts, regardless of type and location of the distal end, are at risk for shunt malfunction. Symptoms of shunt dysfunction

Table 12.5 A child with a suspected shunt dysfunction can preferably be dealt with according to the algorithm

Variations over the day—morning headache?
Headache initiated by effort
Light/sound hypersensitivity
Signs of infections
Tick bites
Hereditary
In infants and small children, signs of headache could be diffuse, such as general impact, abdominal pain, irritability, and ophthalmoplegia
Shunt dysfunction
Underdrainage—symptoms as having raised intracranial pressure
Over function—relief of symptoms lying flat

For symptoms possible related to brain tumors at different ages, see also www.headsmart.org.uk

can be of both the acute type as well as the slowly increasing type. A child with a suspected shunt dysfunction can preferably be dealt with according to the algorithm (Table 12.5). However, since symptoms of shunt dysfunction could be diffuse, it is wise to be generous in admitting the child to hospital for observation! History and imaging are the cornerstones for the diagnosis. Most shunts are possible to palpate for test of function—indicative but not fully reliable. Radiological imaging, frequently as a CT scan, is the gold standard to rule out the ventricular size, extra- or intracerebral fluid collections or bleedings, and the location of the ventricular catheter. If signs of a malfunctioning shunt are detected, then the whole shunt system has to be visualized to reveal eventually a broken shunt or displaced shunt. An ultrasound of the abdomen might visualize cysts or abscesses in this compartment. It is crucial to compare current imaging with baseline imaging performed at a significant time after shunt insertion when the child was doing well.

12.2.5.4 Signs of Underdrainage

Same signs and symptoms as in raised ICP (Table 12.2) and also:

- Increased head circumference?
- Swelling at the operative sites (skull, neck, or abdomen)?
- Adjustable shunt? If so, check pressure level (device or x-ray (fluoroscopy)).
- Abdominal pain? Abdominal swelling? Ultrasound visualized cysts or fluid collections?
- Rule out infection (neck stiffness, photophobia, increased CRP) eventual lumbar puncture, or tap from the shunt system (after consulting a neurosurgeon!). Signs of other infections than shunt infection?
- Shunt dome stiff at palpation and fill immediately (suggestive of blocket shunt valve or peritoneal catheter). Shunt dome easy to compress but refill very slowly, > 1 min (suggestive of blocked ventricular catheter). Does pumping relieve symptoms?
- Neuroradiology (ultrasound or CT scan—shunt scan (complete system) if signs of underfunction on CT scan)

12.2.5.5 Signs of Overdrainage

- Decreased or not increasing head circumference
- Headache, lethargy, or irritability in the afternoon or in upright position
- Less symptoms lying down
- Shunt dome easy to compress but takes more than 30 s to fill again
- Extracerebral fluid collections on CT

12.2.5.6 Patients that Have Undergone Third Ventriculostomy

- Same signs and symptoms as in raised ICP (Fig. 12.1) and also:
- Swelling at the operative site in the scalp
- Infection? As above
- Flow void absent on MRI?

Overdrainage is extremely rare.

12.2.6 Arachnoid Cysts

This is a common incidental finding and is congenital, supposed to be a duplication of the arachnoid membrane, filled with CSF due to a valve effect. There is rarely acute acute symptoms but should be evaluated by pediatric neurologist or neurosurgeon.

There is a risk of bleeding in the cyst or in the subdural space, even with minor trauma.

12.2.7 Pathological Processes

If a pathological process causes raised ICP or not is dependent on size, localization, and at what rate the process increases in size.

12.2.8 Infections

12.2.8.1 Bacterial Meningitis

Consider if the critical ill child with decreased level of consciousness (GCS less than 15) also might have raised ICP! Measure lumbar pressure when doing lumbar puncture and, if elevated, discuss with a neurosurgeon. The child might be helped by an extraventricular drainage (EVD).

Frequent use of EVD in an adult series of unconscious (GCS < 8) patients suffering from bacterial meningitis showed a reduction in mortality from 30 to 10 % as compared to matched historical data (Glimåker et al, submitted).

12.2.8.2 Intracranial Abscesses

Intracranial abscesses are seen as a circular contrast-enhancing process on CT. Infection parameters including CRP might be normal. In children spread of an infection per continuitatum, sinusitis or mastoiditis, a defect immunological response, or septic emboli in the case of VOC, is the most common underlying cause. It can be seen even with normal body temperature and CRP.

12.2.8.3 Acquired Cysts

Cryptococcal fungal infections may cause raised ICP with or without ventricular dilatation on imaging of the head. These infections are mainly seen in patients with AIDS [10].

Neurocysticercosis and echinococcal parasites are endemic parasites (Eastern Europe, Asia, Central and South America, and Africa, respectively, Uruguay, Australia, and New Zealand) producing cysts but occasionally cause raised ICP due to obstruction of CSF pathways or creating absorption problems. The cysts are visualized on neuroimaging as calcifications, ring enhancing cysts, or edema (CT or MRI).

12.2.9 Brain Tumors

Symptoms depending on tumor location, type, and age of the patient. Thirty five to fifty percent of patients have symptoms or signs of ophthalmological problems. The majority of symptoms are caused by hydrocephalus and raised ICP. See [6, 11].

12.2.10 Craniostenosis

Craniostenosis means lack of growth of the calvarium due to stenotic sutures not allowing enough space for the growing brain. This can result in slowly increased ICP in the small child. Loss of skull growth is mainly seen in syndromic craniosynostosis, that is, craniosynostosis, that involves more than one suture and is often hereditary. Craniostenosis is also seen in rare cases of cardiac malformations and blood diseases due to increased production of blood cells in the calvarium.

Craniostenosis may be rarely seen after previous surgery for simple craniosynostosis.

Differential diagnosis is a familial (genetic) small skull in an in other ways healthy child. It is often easy ruled out by measure of the parents' head circumference.

12.2.11 Secondary Causes in Patients Previously Treated for Intracranial Processes

Children previously treated for an intracranial infection (e.g., meningitis), brain injury, tumor, or cerebral vascular insult should be checked for recurrence, progress, or impaired CSF circulation with imaging. The underlying disease and presenting symptoms are indicative for level of priority.

12.3 Recommended Assessments

The assessments can be done according the suggestions in the algorithms in this chapter.

At presentation in the emergency room, the patient with impaired level of consciousness is preferably examined according to the ATLS scheme (Table 12.6) [12].

The rather diffuse symptoms of severely raised ICP have to be considered (Table 12.4).

Patient history and result of the neurological examination (Sect.s 1.7.3) will give information on how to plan further investigations and treatment of the patient. Some of the alternatives are summarized in Fig. 12.2.

The above figure shows the most crucial parameters up front but also the parameters that have to be followed with a high frequency until the patient has been stabilized and at possibly lower frequency when the diagnosis has been

Table 12.6 Examining and stabilizing a patient according to the ATLS-concept

(A) Airway (and spinal control)
(B) Breathing
(C) Circulation
(D) Disability
(E) Environment/exposure
Acker et al. [12]
The unconscious patient, GCS ≤ 8, should be intubated and ventilated! Investigate for neurological, cardiological, or other cause for the present condition
Perform parallel investigation of both metabolic/toxic causes and possible intracranial space-occupying lesions (acute CT scan. Question: Signs of brainstem herniation/raised ICP?)

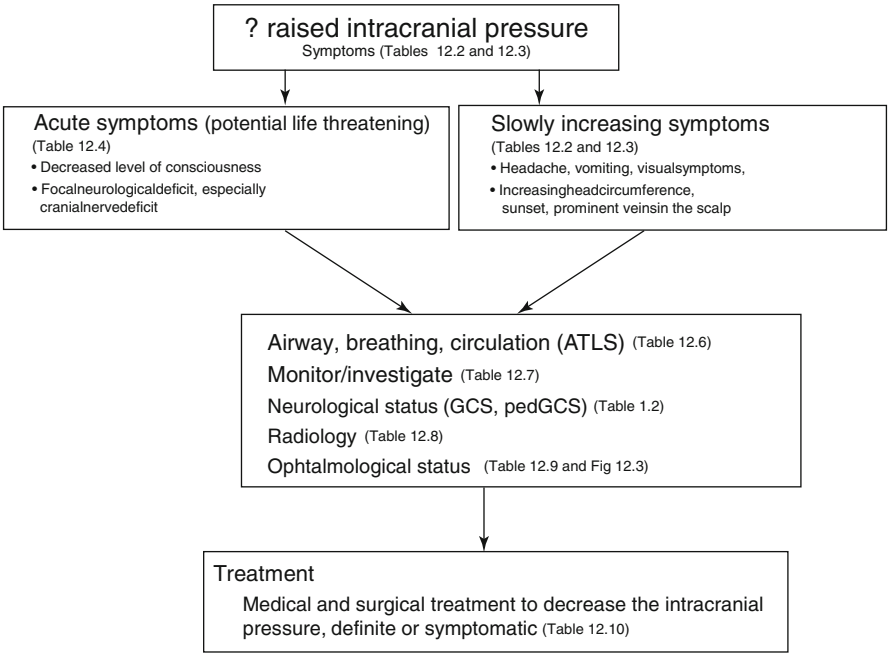

Fig. 12.2 Algorithm suggesting dividing patients with raised intracranial pressure according to the severity and how to investigate the possible child with raised ICP

Table 12.7 Monitoring

Vital functions: heart rate, blood pressure, oxygen saturation (pulse oximetry)
Neurological status: level of consciousness—Glasgow Coma Scale (GCS, pediatric GCS), pupil reactions and paresis schedule (Grassé & reversed Barré)
Frequency: depending on the child's condition and findings from the examination, every 15 min to each hour
The child should be monitored by nursing staff on a frequent basis, before the assessment of a physician and until the results of the investigations exist and a treatment plan has been established. Monitoring is crucial to be able to pick up any changes indicative to how urgent the situation is and could give important clues for further investigations and diagnosis
The child should be kept without food and drinks until a treatment plan has been established! (Is there a need for sedation for investigation or treatment?)

established. Monitoring of vital functions and level of consciousness is performed by the nursing staff, and any deviations immediately reported to the physician in charge (Table 12.7). An important note is that the GCS and pediatric GCS always give the scores for the best response. Thus, a patient can be both hemiparetic and might have a dilated pupil and still get the same score as without these signs.

Again depending on age and findings, further examination of the child will include a radiological investigation. Table 12.8 will give some clues which type of investigation to choose.

Table 12.8 Radiological investigations to consider in the child with possible raised ICP

Ultrasound (USD) could be used in the child with an open fontanel. It should mainly be seen as a screening method for intracranial processes. The greatest advantage being that the child does not need any sedation for the procedure. However, USD is dependent on the experience of the investigator and is not suitable for finding lesions in the subdural space or posterior fossa
Computed tomography scan (CT) is the investigation of choice in most acute situations. It is available in most hospitals around the clock. It is fast; the average investigation will take 5–10 min. Most intracranial lesions will be found (bleedings, ischemia/infarcts, mass lesions, dilated ventricular system, calcifications). How well an infarct or a bleeding is visualized is dependent on time from the event. Blood in the ventricular system can be rinsed away in hours. Bony structures are well seen
Small children (6 months–4 years) might need sedation
The use of contrast medium will give even more information. Pathological processes with a defect blood brain barrier will show up (tumors, old bleedings, infections). Imaging of the vascular system (CT angiography) could reveal vascular pathology (sinus thrombosis and vascular malformations). Impaired renal function or allergy to the contrast medium might be a contraindication to giving contrast
CT scan with bone window and 3D reconstruction is superior to skull x-ray to find closed sutures. The radiation dose is significantly less than for a CT of the brain tissue
Magnetic resonance tomography (MRI) is the best imaging technique to reproduce the brain parenchyma
This is the method of choice to visualize the posterior fossa
Obstruction of CSF pathways could be shown using flow sequences
Ischemia could be visualized early on diffusion sequences
MR angiography (MRA) can show vascular malformations and thrombosis in arteries or veins
Use of gadolinium contrast will visualize leakage in the case of an abnormal blood brain barrier (tumors, old bleedings, infections, inflammatory processes)
It might be possible to differentiate between an abscess and contrast-enhancing lesions of other origin
Due to the investigation takes fairly long time ($\geq$ 45 min) and produces a significant noise; children between the ages of 6 months and 5–6 years old need proper sedation or even full anaesthesia
Plain skull x-ray could be used to check for open sutures. However, it is not as good as 3D CT
Indirect signs on raised ICP could be seen (digital impressions, copper beaten appearance) but are not equal with pathological raised ICP
There is no need for sedation

Table 12.9 Ophthalmological examination

Visual acuity, pupillary reaction, eye movement, inspection of fundi, and test of the visual field (possible from school age in most cases)
Normal findings of fundi do not exclude raised ICP
Papillary edemas usually take days to develop and can take several weeks to disappear
Suspect non-accidental trauma if retinal hemorrhages are found

Abnormalities of the ophthalmological status are common in this group of patients. Table 12.9 and Fig. 12.3 will give a very condensed information on what examinations to do and possible findings. Check that ophtalmological signs are in chapter 5 there is a more complete discussion of the subject.

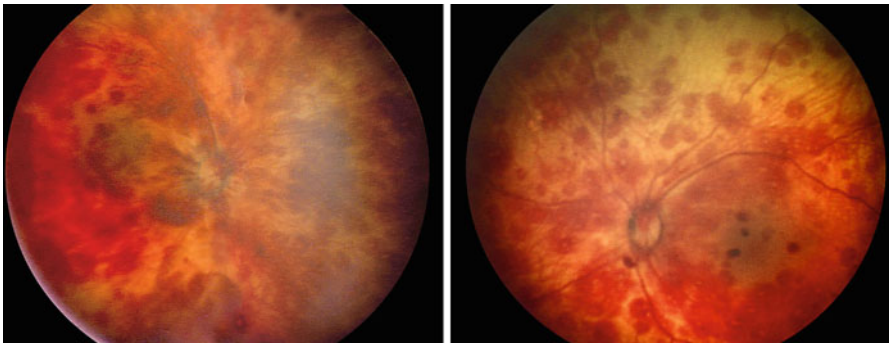

Fig. 12.3 Widespread retinal hemorrhages (Photo courtesy of Dr. L. Jakobson. See also Chap. 5, Fig. 5.4)

12.4 Recommended Interventions

Knowledge on the management of raised ICP is mainly derived from treating traumatic brain injuries in adults and children. Raised ICP is one of the most important issues in this group of patients. In a child with brain injury, the ICP can change acutely within minutes and meticulous monitoring of the ICP is therefore crucial.

As in the case with head trauma, children found to have a level 8 or less of consciousness according to GCS should be intubated and mechanically ventilated as soon safely possible.

Values recommended in the text of Table 12.10 can be seen as goals for the treatment.

In some situations hyperventilation can be of importance to control the ICP. Hyperventilation causes vasoconstriction of the arteries of the brain and results in less blood volume intracranially, and this can result in lower ICP since the brain gets more space. However, the vasoconstriction also means less blood flow and increases the risk of brain infarction due to ischemia in areas of the brain with already compromised blood flow. By measuring the oxygen content in venous blood from the jugular bulb, it is possible to keep the ventilation at a level with less risk of ischemia. Patients with raised ICP sometimes spontaneously hyperventilate to very low levels of pCO_2 in an attempt to lower the ICP.

Both hyperventilation and the use of mannitol might have to be slowly reduced in order not to get rebound effects.

12.4.1 Methods to Measure ICP

At present there are no reliable noninvasive methods (transcranial Doppler, neuroradiology, tympanic membrane displacement, optic sheath diameter, fundoscopy, VEP) [1].

Table 12.10 Treatment of raised ICP

Treat the primary cause first! To avoid future neurological deficits, it could be necessary to perform temporary procedures to lower the intracranial pressure (hyperventilation, osmotic therapy, ventricular drainage), before more definite/etiologic treatment can be given
The goal for all treatments of raised ICP is to maintain normal homeostasis for the brain by maintaining an adequate blood flow to support metabolism in all parts of the brain (often simplified by calculation of the cerebral perfusion pressure, CPP)
Cerebral perfusion pressure (CPP) = medium arterial pressure—ICP. The lower limit for CPP is thought to be 40 mmHg for infants and small children and 50–60 mmHg for older children and adults. (see also Sect. 12.1)
It is way more important first to establish a normal circulation and try to treat the cause of a possible raised intracranial pressure rather than to put in an intracranial pressure monitor
Monitoring and basal treatment in the intensive care unit
General care (pain relief, IV fluids, use *hyper*osmolar fluids, *not* hypoosmolar fluids, monitor circulation to be at an adequate level, seizure control)
Do not lower the blood pressure routinely—the patient might need it for an adequate perfusion pressure of the brain!
Saturation of oxygen (> 95 %)
Ventilation—normoventilation (pCO_2 4.5–5.0 kPa)
Circulation (systolic blood pressure > 90 mmHg, normovolemia, S-Na > 140 mmol/L)
Intracranial pressure (ICP) <10–15–20 mmHg (age dependent)
Cerebral perfusion pressure > (35)40–60 mmHg (age dependent)
B-glucose 4–8(10) mmol/L
Normothermia, <37.5 °C
Catheter to the jugular bulb if hyperventilation is needed to avoid cerebral ischemia
Medical treatment
Hyperventilation (pCO2 < 4.5 kPa)
Hypertonic saline 3 % (5–10 mL/kg 5–10 min duration. Serum sodium level <160 mmol/L)
Mannitol 20 % (0.2–1(2) g/kg intravenously, 10–60 min duration). Could be repeated if S-Na >140 mmol/L and S-osmolality < 320. If S-Na is <140 mmol/L, restituate sodium level first!
Do not forget to put in a urinary catheter!
Betamethasone (Betapred) 0.125 mg/kg in two doses a day (bid) against tumor edema. Combine with Sucralfate or omeprazole to avoid peptic ulcers
Surgical treatment
Intracranial pressure monitoring/extraventricular drainage for monitoring and drainage of CSF
Evacuation/drainage of intracranial expansive process (extirpation of tumor, bleeding, drainage of CSF)
Create space for the swollen brain (drain CSF, hemicraniectomy, lobe resection)

12.4.2 Lumbar Puncture (LP)

Intracranial expansive processes have to be ruled out. If fundoscopy shows papilledema, LP is contraindicated, unless CT or MRI does not show any signs of herniation of the brain! Lumbar pressure is not reliable if CSF compartments do not communicate freely. Coagulopathy is a relative contraindication.

The lumbar pressure depends on the following:

- Patient position, preferable lying on the side. Lying with bent or straight legs does not give any clinically important difference in lumbar pressure [13].

- Mental status, the child must be calm.
- Sedation might increase ICP 5–10 mmHg [4].

Lumbar puncture is used to monitor the cerebrospinal pressure at a single occasion. Always measure the initial pressure.

12.4.3 Invasive ICP Monitoring

Coagulopathy is a relative contraindication.

Indications could be:

- Diagnostic—in order to establish the diagnosis of raised ICP.
- Management of raised ICP—monitor the patient with obvious signs of, or at risk for, raised ICP and treatment—by draining CSF to lower the ICP and evaluate the effect on symptoms.

Most neurosurgical centers would use invasive ICP monitoring in an unconscious child, GCS < 8, with possibly elevated ICP.

12.4.3.1 Localization of the ICP Monitor

Intraventricularly by an extraventricular drainage is the gold standard for localization of the monitor. Great advantages are the possibility to drain CSF to lower the ICP and to have an easy access for CSF analysis.

Intraparenchymal localization, due to less infection risk, is the best choice for prolonged diagnostic measures.

Elevation of the patients head will give a lower ICP but does not increase CPP[14].

12.4.3.2 Surgical Treatment to Reduce ICP

Most effective is to remove the expansive process that causes the raised ICP (tumor, abscess, bleeding, or excessive CSF).

Extraventricular drainage can be used as a quick rescue before a more radical operation.

It is also possible to create space for the intracranial content by reducing brain volume (resection of pathologic brain tissue) or by removal of skull bone and opening of the dura to let the brain expand, hemicraniectomy.

12.5 Conclusion

Children with slowly increasing intracranial pressure (ICP) can be a challenge to diagnose in the emergency room. Diagnosis may be difficult because the symptoms at start are nonspecific for pathologic ICP. The physician has to think about the possibility of increased ICP, e.g., in the unusual case of a toddler complaining about stomach ache in the morning. The suspicion has to be based on a combination of the history of the patient, clinical findings on observation and examination, and followed by imaging of the neuroaxis.

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Chapter 13
Management of Migraine and Other Headaches

Jens Böhmer and Alyssa A. LeBel

Abstract Headache is a common symptom in childhood and adolescence. Primary headaches, including migraine and tension-type, are most frequent, especially in adolescence, often occur together in an individual, and are readily differentiated from secondary headaches (such as traumatic, neoplastic, or infectious headache) by history and targeted physical examination. A prompt and definitive diagnosis of a primary headache disorder facilitates effective treatment. Migraine variants and "periodic syndromes" are more likely in children, including paroxysmal torticollis and vertigo, cyclic vomiting syndrome and abdominal migraine, and confusional migraine. A rare genetic syndrome, familial hemiplegic migraine, is associated with a neuronal channel defect, suggesting a role for sodium and calcium channel dysfunction in the pathophysiology of some migraine presentations. Chronic daily headache and analgesic overuse headache are increasingly recognized in pediatrics.

Treatment of all primary headaches include both pharmacologic and nonpharmacologic modalities, including education, lifestyle modification, cognitive-biobehavioral therapy, and adjustment of unrealistic expectations. Reports of

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controlled clinical trials have increased the choice of treatments for acute and chronic headaches in pediatrics. However, drug therapy for pediatric headaches remains primarily based on adult studies.

Keywords Pediatric headache • Migraine • Tension-type headache • Complicated migraine • Prophylactic treatment of migraine • Aura • Childhood periodic syndromes • Chronic daily headache

13.1 Introduction

13.1.1 General Introduction

Headache as a common complaint in childhood is a frequent cause of visit to the emergency department [1]. There has been a great effort to develop classification systems to help diagnose childhood headache (see Chap. 3); however, clear borders between the different headache entities do not exist in reality, especially in children. In fact, many children present with mixed forms of different primary headaches (i.e., tension headache and migraine). When migraine is diagnosed, it is of great importance to point out that cure is not a realistic aim. Migraine has usually come to stay, but the severity and frequency of the attacks can be strongly influenced by lifestyle changes and abortive and preventive medication [2].

Tension-type headache does not differ significantly in its presenting symptoms in childhood from those in adulthood and comprise bilateral headache of milder severity than migraine, without associated autonomic symptoms or aura. Migraine with aura was previously called “classic migraine.” It represents 20 % of all migraine cases and consists of two distinct phases, both of which can be present to a variable degree. The first is a depression of neuronal activity, spreading from back to front over the cortex in a slow pattern, 3 mm/min, combined with decreased blood flow. This is the aura that most commonly involves visual symptoms, both “plus symptoms” (sparkles, colors, hallucinations, micropsia) and “minus symptoms” (blurred vision, hemianopsia, transient blindness, blind spots) that the child may describe. The second phase is the headache with the same features as in migraine without aura.

Migraine without aura is more common and sometimes challenging to diagnose. The severity of headache, the family history, and associated symptoms (especially nausea and vomiting that are not typical for other primary headaches) as well as the relapsing course with attacks after symptom-free intervals help secure the diagnosis. Migraine with aura is easier to diagnose as primary migraine, but more difficult to differentiate from serious secondary headaches in the first attack, since the aura represents a neurological deficit. The absence of warning signs in the neurological examination; the reversal of aura symptoms, usually within minutes; and a positive family history help avoid unnecessary investigations, such as EEG and CT.

However, there is the infrequent possibility that migraine-like headache can be due to a serious underlying disorder (see Chap. 3). The importance of an accurate physical and neurological examination cannot be overemphasized.

13.1.2 Classification

Migraine is one of the primary headaches for which the International Headache Society has developed and revised a classification system (see Chap. 3) [3]. When used in children, it proves to be somewhat rigid; both regarding the times of an attack (that can be as short as 20 min in a younger child) and the mixed forms of headache that many young patients experience.

13.1.3 Epidemiology

Migraine affects even small children <5 years with a prevalence rate of approximately 2–4 %, with a slight male preponderance. During school years, the rates rise to about 10 % without sex differences. From adolescence into adulthood, there is a clear female predominance (at least 2:1), and migraine may affect 20–30 % of the population.

Migraine often persists beyond childhood; at least 50 % of pediatric migraineurs continue with their disease into late adulthood. Boys have a much higher likelihood to become migraine-free than girls.

It has been speculated whether children and adolescents with migraine show a different psychological profile; systematic reviews do, however, not report more psychological dysfunctioning or more psychiatric comorbidities in this group [4]. The most common finding in children and adolescents with migraine is that they tend to have little or nearly no leisure time that is not already scheduled.

13.1.4 Pathophysiology

13.1.4.1 Genetics

Migraine is a disease with a strong genetic background that puts the individual at risk for developing attacks. Twin studies indicate a 60–70 % genetic influence. Migraineurs with aura seem to have a higher genetic burden than those without aura. Usually one of the parents has or has had migraine (90 % of the cases); a negative family history should raise suspicion whether the diagnosis is correct. Mutations in several ion channels and ion pumps have been linked to certain migraine variants, such as familial hemiplegic migraine. Several of those channels are also found to be

mutated in epilepsy syndromes such as the Dravet syndrome, providing evidence for commonalities of migraine and epilepsy. The involvement of channels and pumps shows the importance of balanced neurotransmission. Polymorphisms play a substantial role, however, complicating the risk prediction for the individual. Environmental factors contribute significantly, necessitating that patients identify and avoid their personal risk factors. It is speculated that early-onset disease reflects increased genetic susceptibility to environmental triggers [5, 6].

13.1.4.2 The Attack

Migraine was classically believed to be primarily a vascular disease, but other theories have developed, with the theory of a cortical spreading neuronal depression explaining the aura phenomenon as the scientifically most recognized. Notably, the stereotyped, transient disturbance of brain function that an aura represents cannot be sufficiently explained by vascular theories alone. The aura resembles epileptic seizures, with the main difference being that the brain disturbance in a seizure spreads faster and lasts shorter. The theory of cortical spreading depression describes waves of depolarization that spread on the cerebral cortex in a creeping pattern, with a comparably low speed of about 3 mm/min. This wave, believed to be triggered by brainstem-derived circuits, usually starts in the occipital cortex and then spreads frontally, thus explaining the most common aura symptoms of the visual system. The neuronal and glial cells initially depolarize for seconds, as well, followed by neuronal silence that lasts several minutes. These neurophysiological changes may reflect the sensory symptoms of the aura. At the same time and probably initiated by those changes, there is vasoconstriction in the areas of aura, followed by vasodilatation as the aura subsides. This stimulates pain-sensitive structures within the vessels and initiates headache [7].

13.1.5 Triggering Factors

The factors that commonly can trigger a migraine attack are very diverse and may not always be completely identified during an initial consultation: it is more important to put the patient in charge of finding out patterns that worsen or improve their headache. Headache diaries are of great importance. Nevertheless, the most common trigger factors should be discussed and include external or internal stress (family, peer group, school), especially the time after a stressful period, e.g., after a school week, and physical exercise. Dietary factors include certain cheeses, chocolate, red wine and caffeine, and many more, including skipped meals. Changes in sleep pattern as well as too much or too little sleep can provoke attacks. Hormonal changes, most commonly menstruation, as well as minor head trauma are other common trigger factors. Dehydration as a trigger of migraine is common especially during summer. Lack of exercise or overtraining can worsen migraine.

13.2 Migraine

13.2.1 Presenting Symptoms of Migraine

13.2.1.1 Migraine with Aura

Factors that can help in distinguishing migraine with aura from stroke are the presence of "plus symptoms" (stroke is more commonly associated with deficits) as well as the slowly evolving course of aura. The aural symptoms usually repeat in a stereotyped fashion in the individual. Most commonly, aura resolves within minutes to a few hours, but symptoms of 24–72 h duration may occur. Aural symptoms can furthermore affect the sensory and/or motor system (hemiplegic/hemisensory migraine), the brainstem and cerebellum (basilar migraine), or the oculomotor nerves (ophthalmoplegic migraine). The aura can even disturb body image and time sense and lead to confusion and amnesia (Alice-in-wonderland syndrome/acute confusional migraine).

It may be preceded by a prodromal phase that can last for up to 3 days, during which the individual can sense an impending attack (behavioral changes, fatigue, and adephagia). Brain function during this period is reduced as measured by neuropsychological testing and functional imaging. Commonly, the aura subsides within 60 min, and headache develops as cerebral vasoconstriction is followed by dilatation. The headache is never maximal at onset but evolves in both quality (dull in the beginning, then pulsating) and severity. It is located around and behind the eyes, the forehead, and the temples. The younger the child, the more common that the headache is bilateral. Older children describe typical unilateral pain that can change side between attacks. A child experiencing a migraine attack has moderate to severe pain and associated symptoms (nausea, vomiting, photo/phonophobia), looks ill, and wants to lie down and sleep (which terminates the attack). Headache lasts between minutes in the young child, some hours in most patients, and up to 2 days in extreme cases. Migraine is not a disease of constant headache but of attacks that repeat and that can occur in clusters (e.g., during times of increased demands in school).

13.2.1.2 Migraine Without Aura

Initially called "common migraine," migraine without aura accounts for approximately 80 % of migraine cases. One individual may have episodes of both migraine with and without aura. It has to be emphasized that aura symptoms have to be specifically asked for, especially in the young child. In a typical attack of migraine without aura, a prodromal phase up to several days (the individual senses the forthcoming attack) is followed by headache that evolves slowly and then becomes more intense and pulsating. At the same time, the child looks sick and has associated symptoms such as nausea, vomiting, photophobia, and pallor. Exercise worsens the headache, and sleep terminates it. The headache can improve and then aggravate again during a longer attack.

13.2.1.3 Complicated Migraine

Hemiplegic/Hemisensory Migraine

Symptoms that antedate or accompany the onset of migraine symptoms (headache and/or vegetative symptoms such as pallor, nausea, vomiting, photophobia) include unilateral motor weakness (hemiplegia/hemiparesis), which may affect speech, and/or sensory symptoms (paresthesia, hyperesthesia, allodynia), which may persist hours after that the headache has disappeared. This headache variant has a strong heritance (autosomal dominant) and increases the risk for stroke. The treatment consists of NSAID/acetaminophen and antiemetics, as triptans (and ergotamine) are contraindicated due to their vasoconstrictive effects.

Basilar Migraine

Believed to derive from vertebrobasilar vasoconstriction, basilar migraine has concerning symptoms, such as (occipital) headache, diplopia, vertigo, tinnitus, or ataxia, dysarthria, altered consciousness, or syncope. Pathologies of the posterior fossa and the inner ear, as well as cardiac anomalies and intoxications, need to be ruled out.

Ophthalmoplegic Migraine

Ophthalmoplegic migraine is a very rare disease consisting of unilateral headache, paresis of the ipsilateral ophthalmic nerve (pupillary defects and ptosis), and possibly even monocular blindness. Sometimes the abducens or trochlear nerves are involved.

Acute Confusional Migraine

Acute confusion migraine is most common in very young children and presenting with acute episodes of confusion, unresponsiveness, dysarthria, and disorientation. Headache and/or nausea and vomiting can be present or absent.

Status Migrainosus

A migraine attack that last longer than 72 h is called status migrainosus in adults; according to the adapted criteria for children, this would imply duration of more than 48 h. However, some authors recommend referring to pediatric status migrainosus in an attack lasting more than 24 h. Intermittent disruption (sleep, medication)

is possible. Status migrainosus is commonly provoked by extensive use of over-the-counter analgesics, a fact that has to be taken into consideration when considering abortive treatment. When the aura lasts longer than expected, migraine infarction (stroke) needs to be excluded (see Chap. 15). If the headache of a migraine attack does not improve on simple analgesics and triptans, inpatient treatment with intravenous agents should be considered. There is no evidence that one agent would be superior to any other, treatment is dependent on local preferences. Ketorolac intravenously is used successfully in children as well as dihydroergotamine (DHE) (nasal, oral, and intravenously), as single drugs or in combination with oral antiemetics such as metoclopramide, even though newer studies favor the use of ondansetron, given the higher likeliness of extrapyramidal-motoric side effects (even life-threatening dystonic reactions are seen) of metoclopramide in children compared to adults. Ondansetron has neither any known interactions with other drugs (it is metabolized through several cytochrome P450 enzymes of the liver) and is not sedating. Another dopamine-receptor antagonist, prochlorperazine, has shown to be successful when used intravenously, with limitations of recurrence of headache and the risk for dyskinesias. Even intravenous dexamethasone has shown to be effective as an add-on treatment in adults with refractory migraine and could be taken into consideration. Opiates show limited effect in adults and are not recommended for use in children. Intravenous fluids are commonly given and are certainly indicated in cases of heavy vomiting, but there are no studies supporting the effect.

13.2.1.4 Childhood Periodic Syndromes

Formerly known as migraine equivalents, the childhood periodic syndromes are believed to be precursors to migraine, as such they appear in the International Classification of Headache Disorders. Headache is usually not present. Features they share with migraine are heredity, episodic presentation with acute illness between symptom-free intervals, as well as the therapeutic regime that stresses reassurance and avoidance of trigger factors. Acute and preventive medication used for more common migraines is also prescribed, yet on a strictly empiric level. Since the presenting age is younger, a high suspicion for secondary causes is needed and the diagnosis—as opposed to that of migraine—is one of exclusion, often requiring neuroradiology and EEG [4].

13.2.1.5 Benign Paroxysmal Torticollis of Infancy

Manifesting between 2 and 8 months of age with a female predominance, the child presents with episodic torticollis, i.e., tilting of the head to either side, sometimes accompanied by ataxia and vomiting as well as other dyskinetic symptoms as dystonic posturing of the trunk. Attacks can last hours to days and resolve usually before school age (Table 13.1).

Table 13.1 ICHD-II diagnostic criteria for benign paroxysmal torticollis of childhood

A. Episodic attacks, in a young child, with all of the following characteristics and fulfilling criterion B:
(a) Tilt of the head to one side (not always the same), with or without slight rotation
(b) Lasting minutes to days
(c) Remitting spontaneously and tending to recur monthly
B. During attacks, signs of one or more of the following:
(a) Pallor
(b) Irritability
(c) Malaise
(d) Vomiting
(e) Ataxia
C. Normal neurologic examination between attacks
D. Not attributed to another disorder

Table 13.2 ICHD-II diagnostic criteria for benign paroxysmal vertigo of childhood

A. At least five attacks fulfilling criterion B
B. Multiple episodes of severe vertigo, occurring without warning and resolving spontaneously after minutes to hours
C. Normal neurologic examination and audiometric and vestibular functions between attacks
D. Normal EEG

13.2.1.6 Benign Paroxysmal Vertigo of Childhood

This disorder usually presents at preschool age, equally in girls and boys, with sudden onset of ataxia, mostly manifesting with the child being scared or refusing to walk. Nystagmus and vegetative symptoms are common, especially vomiting. Benign paroxysmal positional vertigo needs to be ruled out (see Chap. 6). Episodes usually last seconds to minutes, rarely hours, and tend to occur in clusters. They may decrease in frequency and intensity and will eventually resolve within months to years (Table 13.2).

13.2.1.7 Abdominal Migraine

This entity presents with sudden-onset abdominal pain of non-colicky quality that is usually located around the umbilicus and that is accompanied by migraine-like vegetative symptoms such as pallor. Prodromal and/or aura-like phenomena occur. Headache is not present or at least not dominant. Anorexia is common; nausea and vomiting happen but to a lesser extent. The age of onset is school age with a female predominance. It is very uncommon to debut in puberty. Attacks occur with weeks to months in between. It is a diagnosis of exclusion. An important difference from inflammatory bowel diseases or recurrent abdominal pain syndrome is the absence of diarrhea and constipation. The child is otherwise and between the attacks healthy but may suffer from migraine headache as other family members typically do.

Table 13.3 ICHD-II diagnostic criteria for abdominal migraine

A. At least five attacks fulfilling criterion B–D
B. Attacks of abdominal pain lasting 1–72 h (untreated or unsuccessfully treated)
C. Abdominal pain has all of the following characteristics:
1. Midline location, periumbilical or poorly localized
2. Dull or "just sore" quality
3. Moderate or severe intensity
D. During abdominal pain, at least two of the following:
4. Anorexia
5. Nausea
6. Vomiting
7. Pallor
E. Not attributed to another disorder

Attacks tend to be provoked by trigger factors such as stress or lack of sleep. The attacks cease in most cases but can continue into adulthood. Most children with abdominal migraine later develop common migraine headache. Therapeutic strategies do not differ from those of migraine headache, with emphasis on avoidance of triggering factors, rest and/or oral analgesics during attacks, and careful identification of those in need of prophylactic treatment (Table 13.3).

13.2.1.8 Cyclic Vomiting Syndrome

This is an entity that can manifest in all ages but that is most often diagnosed at the age of 5, including a delay of 2–3 years due to diagnostic uncertainties. It consists of a repetitive and stereotyped (but with great individual differences) pattern of nausea and vomiting that is typically preceded by a prodromal phase of several hours, followed by severe vomiting (6 to >10/h) and signs of extreme discomfort (nausea, abdominal pain, pallor, photophobia, apathy). This phase lasts most commonly 24 h and is followed by a recovery phase of usually about 6 h until the patient is restored to full health. Important differences as compared with migraine headache attacks are the signs of a stress reaction during the vomiting phase (e.g., tachycardia, high blood pressure, low-grade fever, and neutrophilia). Also, the patient might not only be apathetic and sick but also oppositional, demanding, and irritated. Triggering events should be found, and the family history is usually consistent with migraine. Most children have no further episodes after 10 years of age, yet most ultimately develop migraine headache. The syndrome is very difficult to diagnose. There may be absence of findings on the general and neurological examination, a nonprogressive course, as well as negative results of laboratory studies and gastroenterologic procedures. A trial of prophylactic migraine medication is indicated. Of great importance is the presence of the prodromal phase that allows abortive medication with oral analgesics, a triptan, and/or antiemetics. During the attack, fluid loss due to excessive vomiting commonly requires intravenous replacement and control of serum electrolytes (Table 13.4).

Table 13.4 ICHD-II diagnostic criteria for cyclical vomiting

A. At least five attacks fulfilling criteria B and C
B. Episodic attacks, stereotypical in the individual patient, of intense nausea and vomiting lasting from 1 h to 5 days
C. Vomiting during attacks occurs at least 4 times/h for at least 1 h
D. Sign-free between attacks
E. Not attributed to another disorder

13.2.2 Diagnosis of Migraine

There are two main goals in diagnosing pediatric migraine: first, to give a diagnosis to patient and parents. This alone will guarantee a higher likeliness of appropriate treatment. Caregivers are commonly so worried about malignancies or stroke as the reason of their child's headache that they will not listen until they are reassured (which, unfortunately, sometimes even requires neuroimaging in absence of warning signs). Teenagers will not adhere to the designated treatment if they are not convinced by what their doctor explains to them.

Second, the patients requiring prophylactic treatment, including those in need of detoxification due to excessive use of over-the-counter analgesics, need to be identified and referred to appropriate centers. There is clear evidence showing that the earlier the diagnosis, the earlier the treatment, the better the outcome. See Chap. 3 for diagnostic criteria and differential diagnosis of headaches.

13.2.3 Recommended Treatment of Migraine

13.2.3.1 Abortive Treatment

Abortive treatment of migraine primarily consists of classical over-the-counter analgesics, mainly ibuprofen and acetaminophen, both of which have shown to be superior to placebo. Furthermore, there are migraine-specific drugs, namely, the triptans and ergotamine, as well as drugs that address migraine-specific comorbidities, i.e., nausea and vomiting. Only nasal sumatriptan has enough evidence to be recommended to the pediatric population in Europe (over 12 years). It is very important to keep in mind that migraine attacks tend to be shorter the younger the patient is—it is not uncommon that attacks in schoolchildren last for only 30–60 min, making medication difficult or unnecessary. At the same time, children in a migraine attack have an imperative need to sleep—putting them to bed terminates the attack (see Table 13.5) [9–13].

13.2.3.2 Prophylactic Treatment

The preventative treatment of migraine should be discussed early whenever there are signs and symptoms such as chronic or frequent and severe episodes of pain,

Table 13.5 Abortive treatment

Simple analgesics	
Acetaminophen	15 mg/kg po/pr/iv, max 60 mg/kg/day
Ibuprofen	10 (–15) mg/kg po/pr, max 40 mg/kg/day
Acetylsalicylic acid	>12 years: 500 (–1,000) mg po, max 3 times/day
Antiemetics	
Metoclopramide	<6 years: max 0.5 mg/kg/day
	6–14 years: 5–10 mg, max 3 times/day
	>14 years: 10–20 mg, max 3 times/day
Ondansetron	0.1 mg/kg iv (max 4 mg), max 8 mg/day
Migraine-specific analgesics	
Sumatriptan nasal spray	>12 years: 10 mg, max 20 mg/day

disruptive to the child's normal routine. As a general rule, the number of schooldays the child misses should not exceed one per month. Other reasons to consider prophylaxis are severe attacks (e.g., lasting >1 day), inefficiency or contraindications for abortive treatment (e.g., dyspepsia or hemiplegic migraine), and, most of all, analgesic overuse. The number of days when the individual medicates against migraine should not be more than 9 days/month for simple analgesics and 6 days/month for triptans. If those numbers are exceeded, withdrawal is warranted: this can include preventive medication as well as medical certificates for both child and caregiver to stay at home during the expected 2–3 weeks' time of initial worsening.

Once the headache and/or aura symptoms are considered to have a severe impact on the child's life and are not controlled by simple lifestyle changes (i.e., identification of trigger factors) and abortive medication, referral to a specialist in a tertiary center for childhood headache is warranted.

There are a number of medications that are commonly and successfully used for the prophylaxis of migraine, though none of them was initially developed for this purpose. Most belong to the groups of antihypertensive agents, antiepileptic drugs, and antidepressants. No agent is superior to another; it is more the individual that leads to the drug of choice: beta-blocking agents such as propranolol should be considered if no history of asthma is present and if the child does not tend to have hypotension (that relative contraindication is doubted by several authors, though). Antidepressant agents (e.g., amitriptyline) can help if migraine has negative effects on the mood and sleep. Valproate and topiramate, of the group of antiepileptic drugs, show good effects; the former is better if no problems with obesity exist, the latter tends to work better with pronounced aura and may be associated with weight loss.

The treatment has to be reevaluated regularly: efficacy cannot be expected within the first weeks, and a goal of complete resolution of migraine is unrealistic. Treatment is usually sustained over a period of 6–12 months but might have to be continued even longer.

However, nonpharmacologic treatments remain the mainstay of treatment for recurrent and chronic headaches, including regular sleep, a well-balanced diet, excellent hydration, and regular exercise. Attention must also be given to the patient's possible school and family stress and relationships with peers. Adjuvant

biofeedback, cognitive-biobehavioral therapy (CBT), physical therapy for neck and shoulder muscle spasm and general reconditioning, and massage therapy may be considered.

13.3 Other Types of Headaches

13.3.1 Tension-Type Headache

Tension-type headache is one of the primary headaches that presents with similar features in children as in adults, that is, bilateral headache of mild to moderate severity, of pressing, non-pulsating character that lasts between hours to days and that is not accompanied by classical migraine features such as nausea, vomiting, pallor, or aura phenomena. Stress is a common trigger and patients often have an increased tenderness on palpation of the neck and scalp muscles. See Chap. 3 for the diagnostic criteria. There is no good evidence for treatment options in children and adolescents, but simple over-the-counter analgesics are commonly used with good effect. Importance has to be given to the comorbidity with migraine and to the risk of abusive drug use.

13.3.2 Secondary Headaches

Secondary headache is defined as headache in the presence of another disorder known to be able to cause headache. There should be evidence of a close temporal relationship or another causal relationship to the headache; headache should be resolved or greatly reduced within 3 months by treating the underlying disorder.

Secondary headaches need to be recognized and often, reassurance is curative to the worried patients and their parents. Treatable underlying disorders need to be dealt with (see Chap. 3). Nevertheless, the headache itself needs to be taken care of with simple analgesics in adequate dosages, as long as no complicated headache like chronic daily headache is suspected.

13.3.2.1 Chronic Daily Headache Syndrome

There are different definitions of the chronic daily headache (CDH) syndrome in the pediatric population. A simple and feasible approach is to define every headache that occurs for more than 4 h a day, more than 15 days per month in at least a month as CDH. The International Classification of Headache provides criteria for four types of CDH: transformed migraine, chronic TTH, new daily persistent headache, and hemicrania continua. CDH comprises about one third of all headache patients referred to a pediatric neurologist (prevalence of 1 % in the general population). Most commonly, it occurs in teenage girls. The headache can be primary or

secondary (for the differential diagnosis, see Chap. 3), this chapter dealing with the primary type. It usually has the characteristics of a primary headache such as migraine or TTH, very often of both, and may interfere strongly with the patient's life (preventing school attendance). Most patients have a known recurrent headache disorder (migraine or TTH); an external factor such as analgesic overuse or stress (e.g., in the beginning of the new school year) or a (often rather mild) head trauma transforms it into CDH. Genetic factors may contribute to chronification and there is strong correlation with psychiatric diseases (depression and anxiety disorders), necessitating a multidisciplinary approach with drugs being only part of the treatment. Referral to a headache expert is always warranted. Management can require prophylactic drugs as well as an inpatient course (see status migrainosus). Girls, those presenting in a young age (<13 years) and those with a psychiatric disorder are at high risk for persistence and need to be followed throughout adolescence and later referred to an adult neurologist [14, 15].

13.4 Conclusion

Headache is very common in childhood and adolescence, even though visits for the primary reason of headache represent not more than 1–2 % of the visits to the ED. Most commonly, those patients suffer from a benign secondary headache. The absence of red flags in history and the physical examination supports refraining from unnecessary investigations. Of great importance is the recognition of those that really need to be taken care of: migraineurs and especially all those that already have developed a chronic daily headache [16]. Most commonly, the referral to a pediatric neurologist (or a pediatrician interested in headache) is the right choice, but in acute exacerbations of all different types of headache, an inpatient course might be necessary to step out of the vicious circle. The minute a primary headache disorder is suspected, responsibility of identifying triggering factors should be shared between doctor and patient, who also has to be advised to keep a diary of their headache including the intake of analgesics. It needs to be mentioned that many patients that seek to the ED for a primary headache have already had it for some days—including trials of different analgesics—representing a difficult-to-treat group per se.

Furthermore, the doctor has to have knowledge about the periodic syndromes of childhood (see above), all of which most probably represent migraine equivalents to prevent patients from years of investigations without proper treatment.

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Chapter 14
Central Nervous System Infections (Bacteria and Parasites)

Charles R.J.C. Newton

Abstract Infections of the central nervous system (CNS) are common in children and should be investigated and managed promptly, since delay may result in significant morbidity or mortality. This chapter provides an approach to a child with neurological features associated with infections and then discusses the most common infectious disease syndromes likely to be encountered in practice, e.g., meningitis. It also includes those infections that are not found in many neurological text books, e.g., tetanus, but which need to be considered in the differential diagnosis of other neurological conditions.

Keywords Central nervous system infections • Bacteria • Fungi • Parasites

14.1 Introduction

Infections of the central nervous system (CNS) are common in children and can mimic many other neurological conditions. Suspicion should be aroused in any child who presents with neurological features in conjunction with a history of fever or recent travel. Prompt assessment and investigation are required, since the child can deteriorate rapidly. Initial management is often empirical, based upon the epidemiology of infections in the area, since delay often leads to significant morbidity or mortality.

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14.2 Approach to the Febrile Child with Neurological Symptoms

Fever is the cardinal feature of infection, but not all children with CNS infections present with fever. A history of fever in the presence of neurological symptoms, which include many nonspecific features (e.g., vomiting, diarrhea, lethargy), should arouse suspicion of CNS infection. In these circumstances, history should focus on:

- Potential sources of infections, i.e., contact with adults and children with infections, pets, travel, and history
- Evolution of the illness: how quickly has the illness developed
- Appearance of complications
  - Impaired consciousness
  - Seizures

Examination should concentrate on:

- Identifying potential sources of infection, e.g., ears
- Assessing levels of consciousness
- Looking for evidence of focal neurological deficits

Management needs to include immediate assessment of the cardiovascular and neurological status of the child, to determine if there is adequate oxygenation and cardiac output, and provide a baseline from which to monitor changes in cardiac, respiratory, and neurological status. Supportive care is important. In particular:

- Maintaining blood pressure to ensure adequate cerebral perfusion.
- Managing fluids.
- Correction of hypoglycemia and electrolyte disorders.
- Respiratory support may be needed.
- Immediate administration of antimicrobials, usually starting with an empiric regimen including a broad-spectrum antibiotics (e.g., cephalosporin), an antiviral (e.g., acyclovir), and an agent to treat *Mycoplasma* sp.
- Detection and treatment of:
  - Seizures
  - Raised intracranial pressure

Immediate investigations should include:

- Complete blood count (CBC) and differential.
- Nonspecific tests for infections, e.g., C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR).
- Blood glucose.
- Electrolytes, urea or creatinine, and liver enzymes.
- Assays of coagulation in those with hemorrhages or petechiae.
- Cultures of blood and urine and any other fluids which are thought to be involved, e.g., nasopharyngeal aspirates.

Table 14.1 Lumbar puncture

Indications
1. Signs of meningitis
2. Impaired consciousness
3. Seizures
Contraindications
1. Raised intracranial pressure, suggested by the following signs:
Impaired level of conscious or agitation
Brainstem signs of herniation, particularly diplopia, abnormal pupillary responses
Motor posturing
Papilledema
Papilledema is not a sensitive sign for RICP and is often a late sign of RICP in meningitis
Bulging fontanelle in the absence of other signs of RICP is not a contraindication to LP
2. Signs of space occupying lesion
Focal neurological signs
Focal seizures
3. Cardiovascular compromise/shock
4. Respiratory compromise
5. Bleeding diathesis
6. Skin infection over the site of the LP
7. Febrile child with purpura where meningococcal infection is suspected. Give antimicrobials immediately
Complications
1. Failure to obtain or blood stained CSF (common)
2. Post-dural puncture headache up to 5–15 %
3. Transient/persistent paresthesia/numbness (very uncommon)
4. Respiratory arrest from positioning (rare)
5. Spinal hematoma or abscess (very rare)
6. Tonsillar herniation (extremely rare in the absence of contraindications above)

- Blood should be taken for serological assays.
- Lumbar puncture (Table 14.1) should be considered any children with:
  - Signs of meningitis
  - Seizures—if not typical of febrile seizures [1]
  - Impairment of consciousness
- Emergency neuroimaging should be considered in children with:
  - Impaired level of consciousness
  - Focal neurological deficits
  - Suspicion of raised intracranial pressure

Further investigations will be directed by possible etiologies.
When performing a lumbar puncture (LP), the following should be considered:

- Measure opening pressure using a manometer or an iv "giving set" and a tape measure.
- Take cerebrospinal fluid (CSF) in appropriate tubes for

Table 14.2 Interpretation of CSF usually immediately available

	White cell count		Biochemistry	
	Neutrophils	Lymphocytes	Protein	CSF: Blood ratio
Condition	$\times 10^6$/L	$\times 10^6$/L	g/L	
Normal neonate	0	<20	<1.0	>0.6, or CSF glucose >2.5 mol/L
Normal child	0	<5	<0.4	>0.6, or CSF glucose >2.5 mol/L
Viral meningitis	<100	10–1,000	<1.0	>0.6
Acute bacterial meningitis	Usually >100	50–1,000	>1.0, but may be normal	<0.4 but may be normal
Tuberculosis meningitis	Usually <100	10–1,000	1.0–5.0 but may be normal	<0.3 but may be normal
Fungal meningitis	May occur early in the illness	5–100	>1.0	>0.4
Encephalitis	<10	>20	>0.4	>0.6
Neuroborreliosis	<10	100–500	0.5–1.5	>0.4

  - Microbiology investigations (microscopy, culture, and sensitivity)
  - Glucose (with paired plasma sample)
  - Lactate
  - Protein

- Other CSF investigations include
  - Rapid antigen testing for *S. pneumoniae, N. meningitidis,* and *H. influenzae*
  - Polymerase chain reaction (PCR) for

    Bacteria (*S. pneumoniae, N. meningitidis, H. influenzae*)
    Viruses (enterovirus, adenovirus, and herpes simplex viruses)
    Mycobacterium tuberculosis

  - Ziehl-Neelsen staining and culture for *M. tuberculosis* (ideally a 2–5 mL is needed to improve yield)

- Save (freeze) a sample of blood and CSF for further investigations if needed.

The initial CSF findings may dictate the initial treatment (see Table 14.2).

Consider noninfective causes of abnormal CSF findings, in particular: drugs, autoimmune diseases, e.g., collagen vascular diseases or malignant meningitis, e.g., lymphomatous spread.

14.2.1 Radiology

X-rays, e.g., chest X-ray and isotope scans, may help determine the source of infection. For imaging the CNS, magnetic resonance imaging (MRI) is more sensitive than computerized tomography (CT), but often less available.

14.3 Definitions of the Syndromes of CNS Infections

Meningitis is the inflammation of the brain meninges, characterized by white blood cells in CSF. It can be caused by a wide range of organisms, particularly viruses, bacteria, and fungi. It may be associated with inflammation of the brain parenchyma (encephalitis), presenting as impairment of consciousness (meningoencephalitis).

Encephalitis is the inflammation of the brain parenchyma. This is a pathological diagnosis definitively made with a brain biopsy or at autopsy. However, surrogate markers such as CSF microscopy or the findings of neuroimaging (particularly MRI) are used. The child is febrile and encephalopathic with an altered level of consciousness or a behavioral change. They may also have signs of meningeal irritation and/or have focal neurological symptoms or signs.

Myelitis is the inflammation of the spinal cord, which usually presents as back pain, followed by paralysis, sensory disturbances, and incontinence of urine and/or feces. It may present acutely or in a slow progressive fashion, with asymmetry.

Infective space-occupying lesions (SOL) include brain abscesses and extra-axial collections of pus, e.g., subdural empyema. Lesions may be single or multiple depending on the cause. Typically the child is febrile and will have focal neurological symptoms or signs. They may have signs of meningeal irritation (depending on whether the meninges are involved) or be encephalopathic.

Children who are immunocompromised may present with milder or atypical symptoms and signs for any of these CNS syndromes. Infants may not have a fever. A careful history should be taken to establish whether a child could be immunocompromised, particularly if their illness is unexplained, including asking the mother about risk factors for HIV.

14.4 Acute Bacterial Meningitis (ABM)

14.4.1 Background

The incidence of meningitis is highest during childhood, particularly during the neonatal and infancy periods. The incidence varies considerably throughout the world, with the highest in Africa and Asia, although it has reduced with the introduction of vaccines against *Haemophilus influenzae*, *Streptococcus pneumoniae,* and Meningococcus [2].

The causative organisms are dependent upon age, vaccination status, and immune status of the child. *H. influenza* and *S. pneumoniae* can occur before the child has reached the age for vaccination. *S. pneumoniae* is associated with more severe disease, greater morbidity, and sequelae. It is associated with pneumonia, otitis media, sinusitis, head injury, and sickle cell disease.

14.4.2 Presenting Signs and Symptoms

The typical features of ABM consist of fever, headache, photophobia, and neck stiffness, though most children with ABM do not have all these features. Infants may present with nonspecific signs of infection, including poor temperature control, lethargy, not interested in feeding, and a bulging fontanelle [2].

Signs include:

- Meningism (neck stiffness; Brudzinski and Kernig signs are rare in children).
- Altered level of consciousness in severe cases.
- Petechial or purpuric rash suggests meningococcus.
- Seizures (may be focal or generalized) in 30 %.
- Cranial nerve signs: 15 %.
- Other focal neurology: 10 %.
- Septicemic shock, multiorgan involvement, and abnormal clotting studies—particularly with meningococcus.

Infants or immunocompromised children may not display typical features, and an LP may be the only way to exclude meningitis.

14.4.3 Recommended Assessments

14.4.3.1 Lumbar Puncture

If ABM is suspected, an LP is essential to make the diagnosis, identify the organism, and determine the sensitivity of the organism to antimicrobials. It should be performed unless a specific contraindication exists (Table 14.1). It may be repeated if the initial CSF is normal.

14.4.3.2 Neuroimaging

In a child with suspected meningitis, brain imaging findings may be normal on admission. An MRI or CT scan may help in the differential diagnosis and should be performed acutely, particularly if there are any contraindications to an LP (see Table 14.1). Imaging may also be useful in the management of a child with definite meningitis if their condition deteriorates, and they become encephalopathic, develop focal deficits, or if a complication of the infection is suspected later, e.g., hydrocephalus.

Other investigations to consider include:

- Blood tests:
  - CBC and differential may show low or high white cell count, left shift, atypical white cells, low, or high platelets.
  - Blood culture.
  - CRP, renal, and liver enzyme.

Table 14.3 Organisms and treatment of acute bacterial meningitis

Age	Organisms	Initial empirical therapy	Notes
Neonates	*Group B streptococci, Escherichia coli, Listeria monocytogenes*	Ampicillin (50–100 mg/kg 6 h) plus gentamicin (2.5 mg/kg every 8 h) *or* cefotaxime (50 mg/kg every 6–8 h)	Vancomycin (15 mg/kg every 6 h) may be added in suspected staphylococcal meningitis
1–3 months	As above or *S. pneumoniae, N. meningitidis, H. influenzae*	Ampicillin (50–100 mg/kg every 6 h) plus cefotaxime (75 mg/kg every 6–8 h) *or* ceftriaxone (50 mg/kg every 12 h)	
3–6 months	*S. pneumoniae, N. meningitidis, H. influenzae*	Cefotaxime (75 mg/kg every 6–8 h, up to a maximum of 12 g daily) *or* Ceftriaxone (50 mg/kg every 12 h, up to a maximum of 4 g daily) plus vancomycin (15 mg/kg every 6 h, up to a maximum 1 g per dose)	Rifampicin may be added if dexamethasone is administered to prevent tuberculosis in patients at risk of tuberculosis
>6 months	*S. pneumoniae, N. meningitidis, H. influenzae*		

- Rapid antigen testing for several bacteria (*S. pneumoniae, N. meningitidis, H. influenzae*).
- Clotting/coagulation studies if child appears ill or has a petechial rash.
- Chest X-ray or imaging of the sinuses may be helpful depending on the history or clinical signs.

Store serum for specific antibody tests. A convalescent sample should be taken 3 weeks after the onset of the illness.

14.4.4 Recommended Interventions

Meningitis should be treated promptly. Since it is difficult to distinguish between viral meningoencephalitis and bacterial meningitis in neonates, antibiotics and antivirals, e.g., acyclovir, should be used. The antimicrobials used need to cover a wide range of organisms including the gram-positive and gram-negative organisms. Local information about the causative organisms and resistance patterns should inform the choice of antimicrobials.

Recommended antimicrobial regimens depend upon the age, most likely organisms and local resistance patterns. Initial therapy should be with empirical regimens (Table 14.3), until the organism has been identified. Antimicrobial treatment should last for 14–21 days in neonatal meningitis, and 7–14 days in older children, depending on the organism. Antimicrobials may need to be changed when the culture and sensitivity results are available. Repeating the lumbar puncture after 48–72 h after onset of treatment may help with management, recording the response to treatment.

Supportive care is important:

- Maintaining blood pressure to ensure adequate cerebral perfusion
- Careful fluid management
- Correction of electrolyte disorders
- Respiratory support may be needed
- Control of seizures with benzodiazepines, phenobarbital, phenytoin, or sodium valproate

Corticosteroids improve the outcome in meningitis in children in high-income countries [3], but there is little evidence in poor countries.

14.4.5 Complications

Raised intracranial hypertension and progression to a brainstem herniation syndrome, effusions and empyema, acute symptomatic seizures, cerebritis, abscess formation, hydrocephalus, electrolyte disturbances (particularly a low sodium or a metabolic acidosis), and venous sinus thrombosis leading to cerebral infarction are possible complications.

14.4.6 Outcome

Mortality is about 5 %, with neurological sequelae about 15 % [4]. Cognitive impairment/educational difficulties, behavioral problems, hemiplegia, spastic quadriplegia, dystonia, spasticity, hearing loss or visual loss, and epilepsy are the most common.

14.5 Viral (Aseptic) Meningitis

The epidemiology depends on geography, climate, and vaccination coverage. Epidemics occur and new viruses can emerge. Viral meningitis is common, but is rarely associated with shock.

The most commonly used agents are outlined in Table 14.4.

14.6 Presenting Signs and Symptoms

See section above on ABM. Headache is common in older children and impaired level of consciousness is very uncommon and if present suggests encephalitis.

Table 14.4 Viruses causing most CNS infections

Organisms	Meningitis	Encephalitis	Myelitis	Other clinical features	Comments
Adenovirus	Yes			Conjunctivitis, respiratory infection, or gastroenteritis	
Echovirus	Yes			Conjunctivitis, rash, myositis	
Enteroviruses	Yes	Yes		Rash	
Epstein-Barr virus (EBV)	Yes		Yes	Pharyngitis, lymphadenopathy, splenomegaly, atypical peripheral lymphocytes may have abnormal LFTs	
Coxsackie	Yes	Yes		Rash, hand, foot and mouth disease, myocarditis, pericarditis, pleurisy	
Cytomegalovirus (CMV)	Yes	Yes	Yes	Hepatitis and retinitis (uncommon unless immunocompromised)	
Herpes simplex virus type 1	Yes	Yes	Rare	May be associated with a cold sores or skin lesions, but rarely seen Suggested by focal seizures, personality changes, and aphasia	Transmitted orally
Herpes simplex virus type 2	Yes	Yes		Neonatal	Primarily sexual contact
Human herpes virus (HHV) 6	Yes			Roseola infantum (slapped cheek rash), febrile seizures	
Human herpes virus (HHV) 7	Yes			Similar to HHV-6	
Human immunodeficiency virus		Yes		May present with developmental delay, subacute encephalopathy, or opportunistic CNS infections	
Lymphocytic choriomeningitis virus	Yes			Orchitis, myocarditis, parotitis, alopecia	History of contact with rodents

(continued)

Table 14.4 (continued)

Organisms	Meningitis	Encephalitis	Myelitis	Other clinical features	Comments
Measles	Yes	Yes	Rare	Morbilliform rash, conjunctivitis, lymphadenopathy, pneumonitis	
Mumps	Yes	Yes		Parotitis, pancreatitis (with elevated amylase and lipase), hearing loss	
Poliovirus	Yes	Rarely	Yes	Rash	
Rabies		Yes		Furious rabies with agitation, hydrophobia, or hypersalivation is much more common than the "paralytic" or "dumb" type with flaccid ascending paralysis	Most commonly dog and bat bites Endemic in Africa and Asia
Varicella zoster (VZV)	Yes			May have typical chicken pox rash with fluid-filled blisters	
Arboviruses					
Dengue	Yes	Yes		May occur during primary or secondary infections. High prevalence of sequelae	SE Asia
Equine encephalitis	Yes	Yes	Yes	High mortality	North and South America
Japanese encephalitis		Yes	Yes	Basal ganglia involvement	SE Asia
Lacrosse	Yes	Yes		Increased fever and hyponatremia associated with clinical deterioration	USA
St. Louis encephalitis	Yes	Yes		High prevalence of sequelae	Culex sp. Late summer early autumn in USA
West Nile		Yes	Yes	Guillain-Barre syndrome, multifocal chorioretinitis, hepatitis, myocarditis, nephritis, pancreatitis, and splenomegaly	Ubiquitous Culex sp.

14.6.1 Recommended Assessments

Assess the clinical state as above.

If viral meningitis is suspected, an LP is essential and the CSF may show typical changes (Table 14.2). Mild elevation of the liver enzymes or pancreatic enzymes can occur with some viruses.

Other investigations include swabbing the throat and rectum for viral isolation (viral culture medium needed). A serum sample should be saved to compare with a convalescent sample taken 3 weeks after the onset of the illness. Infants rarely need neuroimaging.

14.6.2 Outcome

Outcomes are generally good, although hearing should be tested.

14.6.3 Recommended Interventions

Ensure cardiovascular status is stable.

No specific treatment is needed. Full recovery usually occurs within 2 weeks, although some patients may have post-viral fatigue syndrome (rare in infancy). Test hearing after recovery.

14.7 Chronic Bacterial Meningitis

The major causes of chronic bacterial meningitis are *Mycobacterium tuberculosis* and fungi, in particular *Cryptococcus species*, *Candida albicans,* and *Coccidioides immitis*. Although tuberculosis meningitis occurs in immunocompetent children, tuberculosis and fungal meningitis should be considered particularly in immunocompromised children. These infections can be transmitted during pregnancy, although congenital meningitis is rare.

14.7.1 Tuberculosis Meningitis (TBM)

14.7.1.1 Presenting Signs and Symptoms

Tuberculosis meningitis may occur as a separate clinical syndrome or in young children as part of miliary tuberculosis. Most infants present with fever, vomiting,

cough, and impaired consciousness. Seizures are common. Bulging fontanelle is noticeable in younger infants. In older children cranial nerve palsies, hemiparesis, or opisthotonus may occur [5].

14.7.1.2 Recommended Assessments

Laboratory investigations:

- Hyponatremia is common.
- CSF: Pleocytosis with lymphocytic predominance (usually <1,000 cells 10^6/L); increased CSF protein and decreased CSF glucose.
- Acid-fast bacillus is rarely seen and culture often negative.
- PCR can be helpful in reliable laboratories.

Diagnosis is often based upon high index of suspicion, history of contacts, positive tuberculin test, and evidence of TB in other organs, particular in the lungs.

CT or MRI scans and cranial ultrasound commonly show hydrocephalus and less often basal enhancement and/or infarction of the basal ganglia. Chest X-ray is helpful in the diagnosis.

14.7.1.3 Recommended Interventions

Isoniazid, rifampicin, streptomycin, and pyrazinamide are the combination of choice. Corticosteroids improve outcome in HIV-negative children [6], but there is no evidence they improve outcome in HIV-positive children with TBM. Streptomycin, pyrazinamide, and dexamethasone are given for 2 months, and the isoniazid and rifampicin for 18 months. Ventriculoperitoneal shunting is often required for hydrocephalus.

Follow-up contacts with the family and neighbors.

14.7.1.4 Outcome

TBM is increasing and is associated with HIV infection. Mortality is high and neurological sequelae are common.

14.7.2 Fungal Meningitis

This commonly occurs in immunocompromised hosts and may be the first sign of an AIDS defining illness. It is reported from immunocompetent children as well.

14.7.2.1 Presenting Signs and Symptoms

The presentation may be more insidious than TBM. Infants present with respiratory distress, not tolerating feeds and/or abdominal distension. Older children have more typical features of meningitis. Fundoscopic examination may reveal disseminated Candida.

14.7.2.2 Recommended Assessments

Similar to TBM, but hyponatremia less common. The organisms may be seen with fungal stains of the CSF, but the organism is usually isolated from other parts of the body, and meningitis is suspected from the pleocytosis.

14.7.2.3 Recommended Interventions

Candida sp.: amphotericin B in combination with flucytosine

Cryptococcus sp.: amphotericin B and flucytosine for 6–10 weeks in HIV-negative patients. For HIV-positive patients, amphotericin B and flucytosine for 2 weeks and then fluconazole for 10 weeks.

14.7.2.4 Outcome

The mortality rate is very high and sequelae are common in those that survive.

14.8 Infective Space-Occupying Lesions

Brain abscesses or extra-axial collections can be caused by bacteria, fungi, or parasites with the most common causal organisms in infancy being Staphylococci, *Streptococcus* (aerobic and anaerobic), and *H. influenzae*. Anaerobic organisms such as *bacteroides*, *Streptococcus milleri,* and *Fusobacterium* are also commonly found. CNS tuberculosis presenting as a tuberculoma should be considered. Fungi (*Aspergillus* species) and parasites have also been reported. Many abscesses will contain mixed flora (approximately 40 %).

These lesions may be caused by hematogenous or local spread and should be considered in children with the risk factors outlined in Table 14.5. They may be single or multiple, with the site related to predisposing factor. Hematogenous spread is found mainly in the supply of the middle cerebral artery, but may also occur via the veins from the sinuses to the frontal lobes. Direct invasion from infections of the sinuses or middle ear cause abscesses in the temporal lobes or cerebellum.

Table 14.5 Risk factors for brain abscesses

Congenital heart disease
Sinus or ear infections
Poor dental hygiene
Immunosuppression
Complication of bacterial meningitis
Child with a ventriculoperitoneal shunt
Skull fracture
Congenital lesions of head and neck which communicate with the CNS, e.g., dermal sinuses
Aspiration of a foreign body

14.8.1 Presenting Signs and Symptoms

This depends on location of the lesion(s) in the CNS. It typically causes irritability, fever, and a focal neurological deficit. Brain abscess are more common in infants than older children [7]. In infancy, the fontanelle can bulge and the head circumference can increase rapidly. There may be lethargy or impaired level of consciousness. RICP and herniation syndromes can develop. If the abscess ruptures into the ventricular system, it causes an acute neurological decompensation with signs of meningitis.

14.8.2 Recommended Assessments

Elevated nonspecific markers of infection may occur. Blood cultures are rarely positive.

Cardiac assessment including echocardiography should be done.

LP is usually contraindicated due to the risk of brain herniation syndromes.

14.8.2.1 Neuroimaging

Cranial ultrasound may be useful in a neonate. CT is useful and will detect most SOL, except those in the posterior fossa. Contrast should be given as extra-axial collections can be missed on an unenhanced CT scan, and a ring enhancement of lesions is characteristic.

MRI is the modality of choice. Contrast should be given since ring enhancement of lesions is more commonly seen than on CT scans. Enhancement may be seen in single demyelinating lesions (v uncommon in infancy). Diffusion-weighted and MR spectroscopy can also be helpful in differentiating a single parenchymal lesion from a tumor.

Brain biopsy may be helpful, but is rarely performed. Differential diagnoses include brain tumors, tuberculomas, lymphoma, single demyelinating lesion, and intraparenchymal hemorrhage.

14.8.3 Recommended Interventions

Antimicrobials may be used for small lesions (<2 cm) or those in whom the causative organism has been identified. Most brain abscesses require surgical drainage, followed by prompt initiation of empirical broad-spectrum antimicrobial therapy, usually for 6 weeks but longer in immunocompromised children. Surgical specimens should be sent for histology and for microbiology. The first choice antibiotics would include a third-generation cephalosporin and metronidazole, but advice should be sought from microbiologists or infectious disease team. If an associated foreign body, e.g., central line or ventriculoperitoneal shunt, is found, it should be removed.

14.8.4 Outcome

Depends of severity and location of parenchymal damage. Up to 40 % of children have neurological sequelae and 25 % have epilepsy.

14.9 Encephalitis

Encephalitis can be caused by a wide range of viruses (Table 14.4), many of which have specific geographical distributions. See Chap. 16 for more details.

14.9.1 Presenting Signs and Symptoms

The clinical manifestations of encephalitis vary according to the site and severity of parenchymal involvement. In neonates, encephalitis generally presents with nonspecific symptoms and signs of systemic sepsis including fever, poor feeding, irritability, lethargy, seizures, or apnea. History of maternal fever in the peripartum may be present in some cases of enterovirus or adenovirus infections. History of maternal genital herpes is seen in only 20–27 % of infants with herpes infection. Hence, an absence of parental history of HSV infection does not exclude neonatal HSV infection. Skin lesions in the neonate are seen in some cases of neonatal herpes encephalitis. Focal neurological signs may be present.

In older children, the usual presentation of encephalitis in older children is with acute onset fever, headache, seizures, behavioral changes, and impairment of consciousness leading to coma. A prodromal illness with myalgias, fever, anorexia, and lethargy, reflecting the systemic viremia, may occur. Seizures are common and may be generalized or focal. Cortical involvement may lead to disorientation and

confusion, basal ganglia involvement to movement disorders, and brainstem involvement to cranial nerve dysfunction. Associated spinal cord involvement (myelitis) may cause flaccid paraplegia with abnormalities of the deep tendon reflexes.

14.9.2 Recommended Assessments

Early in the illness, the CSF is clear and colorless; the opening pressure may be high. CSF cell count may be normal or slightly elevated, with a mixed pleocytosis (neutrophils and mononuclear cells), which later becomes lymphocytic. Lack of cells in the CSF does not exclude the diagnosis, and a repeat lumbar puncture after 1–2 days may subsequently demonstrate pleocytosis. Red blood cells in the CSF may be seen in late stages of HSV encephalitis or from vasculitis or tissue necrosis.

Confirmatory diagnosis is performed by culture, rapid diagnostic tests including antigen detection and PCR, demonstration of rise in specific antibody titer, and/or direct visualization of virus.

EEG helps distinguish generalized (diffuse slowing with high voltage slow waves; occasionally, spikes and spike) from focal encephalitis (focal slow waves or spikes), but can be normal. The EEG is particularly helpful in HSV encephalitis, since characteristic periodic lateralizing epileptiform discharges (PLEDS) may be seen.

MRI is a sensitive method of diagnosing well-established encephalitis, but may be normal early in the illness (particularly neonates). It detects inflammation and edema in the cerebral cortex, gray-white matter junction, basal ganglia, or cerebellum. Specific areas of involvement may suggest an etiology: inferomedial temporal lobe and frontal lobes involvement in HSV; bilateral thalamic and basal ganglia in Japanese encephalitis; hippocampal, cerebellar, and mesencephalic areas in rabies; and disseminated lesions in brainstem and basal ganglia in eastern equine encephalitis. MRI can differentiate acute encephalitis from ADEM.

14.9.3 Recommended Interventions

Children with acute encephalitis need to be monitored closely and thus are often admitted to the intensive care to observe and manage complications and for diagnostic work-up. Some viruses have specific antiviral agents: acyclovir for treatment of HSV encephalitis, ganciclovir or foscarnet for CMV encephalitis, and oseltamivir and zanamivir for either influenza A and B. No specific antiviral therapy is available for enteroviral and arboviral encephalitis.

Seizures are common and need to be treated aggressively. Continuous EEG may detect nonconvulsive seizures. Passive immunity in the form of intravenous immune globulin may be helpful in immunocompromised individuals who cannot mount an effective immune response. The role of corticosteroids has not been established.

14.9.4 Outcomes

The outcome in encephalitis is determined by etiology, host factors (age and immune status, severity of illness), level of consciousness at presentation, early intensive management, and institution of specific therapy [8]. Most arboviral encephalitis except eastern equine encephalitis and Japanese encephalitis have a good prognosis in children. The prognosis of HSV encephalitis has improved significantly with the use of early acyclovir therapy. Children with severe encephalitis and/or delayed therapy may be left with permanent neuro-deficits.

14.10 Lyme Neuroborreliosis

14.10.1 Presentation

There are three clinically defined stages of Lyme disease. Localized early Lyme disease consists of a single primary erythema migrans skin lesion at the site of the tick bite. The second stage, disseminated early Lyme disease, can include multiple erythema migrans lesions, carditis, meningitis, and cranial nerve palsies. Arthritis is a manifestation of the third stage (late Lyme disease). Different tick and Borrelia species exist in North America and Europe.

In general, neurologic manifestations are more common in European cases. However, whereas painful radiculitis (Bannwarth's syndrome) is much more common in adults in Europe compared to the North America, children in both regions typically present with meningitis and facial nerve palsy [9, 10]. Although CNS Lyme disease rarely causes frank acute encephalitis in children and therefore is unlikely to be confused with other CNS infectious and inflammatory disorders discussed here, we included it in this chapter as it still causes significant morbidity in endemic regions. The issue of chronic Lyme encephalopathy and post-Lyme disease syndrome are beyond the scope of this chapter [9].

14.10.2 Assessment

Although a matter of some debate among clinicians, patients with isolated facial palsy without meningeal symptoms or signs in whom Lyme disease is suspected most likely do not require LP. If meningeal symptoms or signs, or, less commonly, findings suggestive of parenchymal involvement, are present in the setting of suspected CNS Lyme disease, LP is mandatory. Culture and PCR of cerebrospinal fluid are insensitive tests for the diagnosis of CNS Lyme disease. Therefore, the diagnosis of CNS Lyme disease is usually made on the basis of typical neurological symptoms in the setting of positive serology. In interpreting the results of serologic

tests, it is important to remember that the high background prevalence of seropositivity in endemic areas requires a careful approach in determining causality. However, in general, CSF pleocytosis in the presence of positive peripheral Lyme serology and suggestive symptoms should be presumed to represent neuro-Lyme and treated as such, unless an alternative etiology is identified.

A two-step approach for serologic testing using a sensitive enzyme immunoassay (EIA) or immunofluorescent assay (IFA) followed by a standardized Western immunoblot is the algorithm of choice. The principal role of the Western blot is to differentiate false- from true-positive serologies, particularly when ELISA values are in the low-positive or borderline/equivocal range.

Brain MRI typically does not show parenchymal lesions, but can show nonspecific leptomeningeal enhancement, cranial or peripheral nerve root enhancement, and less commonly white matter lesions.

14.10.3 Intervention

Isolated facial nerve palsy due to Lyme disease can be treated with amoxicillin 50 mg/kg/day for 21–28 days in children younger than 8 years and doxycycline 100 mg twice a day for older children. Lyme meningitis or encephalitis requires treatment with intravenous ceftriaxone 100 mg/kg daily (up to 2 g) for 14–28 days. Given the controversies surrounding chronic Lyme disease, treatment for 28 days is probably warranted.

14.10.4 Outcome

The above or similar treatment regimens are associated with excellent outcomes in both North America and Europe [10].

14.11 Mycoplasma

Mycoplasma pneumoniae is primarily a respiratory tract pathogen that is an important cause community-acquired pneumonia. CNS complications develop in <0.1 % of children.

M. pneumoniae causes a wide range of CNS complications which can be divided into those that are thought to be a result of the direct invasion of the CNS, i.e., meningitis, encephalitis, Bickerstaff brainstem encephalitis, stroke, and acute bilateral striatal necrosis and those that are postinfectious immunologically mediated disorders, i.e., ADEM, postinfectious hemorrhagic leukoencephalitis, transverse

myelitis, Guillain-Barré syndrome, or acute motor axonal neuropathy. The differentiation is not easy. The meningitis and encephalitis can present with status epilepticus which is difficult to control.

Children usually present with a respiratory prodrome (except in children <5 years of age), with the neurological signs of direct invasion occurring within a week later, while 1–3 weeks in postinfectious immune-mediated complications such as ADEM, transverse myelitis, and Guillain-Barré syndrome.

14.11.1 Recommended Assessments

The diagnosis of *M. pneumoniae* infection is made on serology, culture, and/or PCR. The organism is rarely detected in CSF or brain tissue. The detection of IgM or IgA in acute sera, demonstration of either seroconversion from negative to positive, or a four-fold rise to anti-mycoplasma titer between acute and convalescent sera indicates an acute or recent infection. *M. pneumoniae* is very difficult to culture, so this is rarely used for the diagnosis. PCR assays using primers directed at a variety of genes have been developed and are useful for detection of mycoplasma in respiratory specimens. They are very sensitive and help in diagnosis before the development of specific antibodies.

14.11.2 Recommended Interventions

Antimicrobial therapy of mycoplasma infections of the CNS is unproven. Since some of the CNS manifestations are caused by the direct involvement of the CNS, it seems prudent to treat with antimicrobials. Erythromycin, azithromycin, tetracyclines, fluoroquinolones, ketolides, streptogramins, and chloramphenicol have good activity against mycoplasma. The macrolides have poor CNS penetration and a fluoroquinolone may be better.

Corticosteroids, intravenous immune globulin, and plasma exchange have been used in the postinfectious immunologically mediated disorders, with anecdotal improvement, but no clinical trials have been conducted.

14.11.3 Outcome

The outcome varies by clinical syndrome. Complete recovery occurs in children with aseptic meningitis. Neurological sequelae, such as cognitive impairment, focal neurologic deficits, or epilepsy, occur in up to 60 % following encephalitis or ADEM. Mortality is rare.

14.12 Neurocysticercosis

Taenia solium is endemic in Latin America, India, China, and many parts of sub-Saharan Africa. It occurs in areas with poor conditions where pigs have access to human feces. Cysticerci are ingested from infected pigs or fecal matter, then invade striated muscle and the CNS. Most active cysts are asymptomatic, and they usually die within 2 years without any clinical manifestations. The CNS manifestations usually occur when a cyst is degenerating or as a result of a chronic, calcified lesion.

14.12.1 Presenting Signs and Symptoms

The main clinical features are seizures, symptoms of RICP, alterations of mental status, and focal neurological signs [11]. Seizures may be generalized tonic-clonic seizures, despite the focal lesions. Neurocysticercosis may present with headaches (including migraine) or neurocognitive deficits or myalgia.

The clinical features depend upon the size, number, type, location, and stage of the cysticerci:

- Ventricular cysts may cause seizures or meningeal irritation. Nausea, vomiting, headache, ataxia, and confusion occur, but focal neurological deficits are uncommon. RICP may occur.
- Cysts in the basal cisterns present with meningeal signs, hydrocephalus, vasculitis, and stroke.
- Cysticercal encephalitis caused by multiple parenchymal cysts, associated with diffuse cerebral edema, occurs particularly in young girls, and these patients may develop severe neurological sequelae.
- Spinal cysticercosis presents with radicular pain or paresthesia or progressive cord compression.
- Ophthalmic manifestations include blurred vision, proptosis with restriction of ocular movements, papilledema, atypical optic neuritis, cyst, or nodules in the eye.

14.12.2 Recommended Assessments

Neuroimaging is the diagnostic test of choice (Table 14.6). The cysts may be single or multiple, scattered throughout the brain, and in different stages. Both CT and MRI are useful for the detecting the stages. Sometimes the invaginated scolexes can be seen as an eccentric mural nodule, which, if multiple, give rise to the "starry night effect," which is pathognomonic of neurocysticercosis. Single-enhancing lesions on CT scans have increased signal intensity on MRI and may be caused by resolution or calcification. They need to be differentiated from tuberculomas,

Table 14.6 Neuroimaging findings in neurocysticercosis

	CT scan	MRI scan
	Better for detecting calcified lesions	Better for detecting intraventricular or subarachnoid cysts demonstrating inflammation around cysts
Active	Rounded, hypodense areas	CSF-like signal
Degenerate	Diffuse hypodense lesion with an irregular border, enhances on contrast	Low signal areas on T2-weighted MRI images
Calcified	Inactive calcified nodule	low intensity on proton-weighted nodule

although abscess, fungal infection, vasculitis, and neoplasia may produce similar appearances.

Immunological tests are not reliable for the diagnosis of neurocysticercosis. Standard enzyme-linked immunosorbent assay techniques are insensitive and non-specific. The enzyme-linked immunoelectrotransfer blot assays on blood or CSF have a higher sensitivity and specificity, but its usefulness varies with region.

Electroencephalography is variable, since it may show focal or generalized abnormalities, but is often normal. CSF may have mild abnormalities such as elevated protein or pleocytosis often with eosinophils.

14.12.3 Recommended Interventions

There is no evidence to support the treatment of asymptomatic lesions. In symptomatic neurocysticercosis, the use of cysticidal agents and steroids for epilepsy is controversial. Cysticidal therapy appears to improve the resolution of cysts but may be associated with an exacerbation of neurological symptoms, with case reports of severe cerebral edema and death in patients with multiple cysts. Praziquantel (20 mg/kg/day) and albendazole (10 mg/kg/day) for at least 8 days are the most commonly used cysticidal agents [12]. Randomized clinical trials of cysticidal drugs have failed to show consistent clinical benefit, and an increase in hydrocephalus and seizure are frequency reported. Corticosteroids are thought to reduce the inflammatory response and prevent the neurological deterioration, but randomized controlled trials have been inconclusive. The seizures in neurocysticercosis are usually easily controlled with AEDs; phenobarbitone and phenytoin induce the metabolism of praziquantel.

14.13 Malaria

Plasmodium falciparum is one of the four species that infects humans and is responsible for most of the CNS complications. The erythrocytic stages of the parasite are responsible for the symptoms, particularly the later erythrocytic stages which

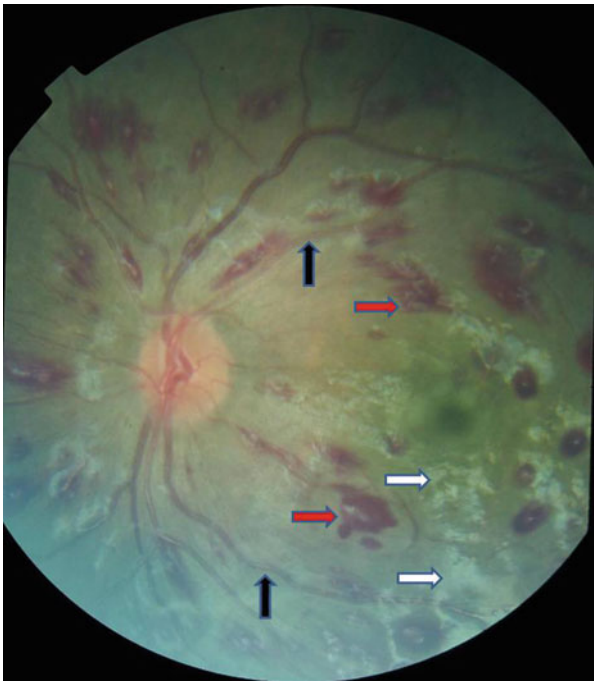

Fig. 14.1 A photograph of the retina of a child with cerebral malaria showing hemorrhages (*red arrows*), exudates (*white arrows*), and discoloration of the retinal vessels (*black arrows*) (Courtesy Nicke Beere)

sequester within postcapillary venules of the deep vascular beds, especially the brain, which is thought to cause the severe manifestations [13]. The direct CNS involvement of *P. falciparum* is difficult to define, since there are no pathognomonic features.

14.13.1 Presenting Signs and Symptoms

Falciparum malaria should be suspected in any child who has visited or even transiently landed at an airport in an endemic area within the last 3 months and develops CNS symptoms. Children usually have a history of fever, headache, irritability, restlessness, or drowsiness. Vomiting and to a lesser extent diarrhea are common. Fever is usually present, although its absence does not exclude the diagnosis. Seizures are common and often precipitate the lapse into coma. Brainstem signs including dysconjugate eye movement and decerebrate posturing occur. Falciparum malaria is associated with a distinctive retinopathy, which includes retinal hemorrhages, retinal whitening, color changes in the vessels, and less frequently papilledema (Fig. 14.1) [14]. These features are associated with sequestration in the brain and may help differentiate cerebral malaria from other causes of encephalopathy.

Seizures are common in falciparum malaria, but the cause is unclear. They are not simply febrile seizures; since many occur when the child is apyrexial, they are

often complicated in that they are repetitive (more than one during the acute illness), focal, or prolonged. They do not appear to be related to electrolyte abnormalities, hypoglycemia, or antimalarial drugs.

14.13.2 Recommended Assessments

The diagnosis of malaria can be made by detecting asexual parasites on a peripheral blood film. The lack of a detectable parasitemia does not exclude the diagnosis of cerebral malaria, since the parasites may be sequestered within the deep vascular beds, or chemoprophylaxis may have suppressed the parasitemia. Thus, blood films need to be examined every 6 h for 48 h to exclude this infection.

Rapid diagnostic tests such as the immunochromatographic test for *P. falciparum* histidine-rich protein 2 and lactate dehydrogenase may be helpful, particularly in the absence of a positive blood smear. Parasite messenger RNA or DNA PCR testing is more sensitive than microscopy, but is expensive, more laborious, and does not estimate parasite load.

The following blood investigations should be done:

- CBC
  - Anemia, usually with evidence of hemolysis (raised unconjugated bilirubinemia, low haptoglobin concentration), is a consequence of the infection.
  - Thrombocytopenia is common, but rarely severe enough to cause bleeding.
- Coagulation screen
  - Fibrin degradation products are raised, but laboratory features of frank disseminated intravascular coagulation are uncommon.
- Glucose
  - Hypoglycemia is common and needs to be treated.
- Blood gas status
  - Hypoxemia is associated with pulmonary edema in nonimmune individuals and chest infections.
  - Metabolic acidosis is common, particularly associated with a high lactate and low PCO_2, in children with tachypnoea to compensate for the acidosis.
- Renal function since impairment is common
- Electrolytes
  - Hyponatremia is mainly caused by salt depletion, but some cases may be caused by inappropriate ADH secretion or cerebral salt wasting syndrome.
  - Hypophosphatemia is a feature of severe malaria and may be exacerbated by glucose therapy.

The CSF is usually acellular, and other diagnoses such as encephalitis should be considered if a pleocytosis is found, but cerebral malaria cannot be excluded. CSF lactate concentrations are raised, but total protein and glucose concentrations are usually normal.

Blood cultures may detect bacteremia, particularly caused by gram-negative organisms. Concurrent urinary tract infections can occur.

14.13.3 Recommended Interventions

Treatment of severe falciparum malaria is complicated by the emergence of parasites that are resistant to antimalarial drugs and the difficulty of obtaining specific antimalarial drugs locally. A combination of antimalarials with different actions should be used, in order to prevent the emergence of resistant parasites. This should include a first-line parenteral drug, either the cinchinoid alkaloids (quinine and its diastereomer quinidine) or the artemisinin compounds (http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html). The artemisinin compounds are more parasiticidal, but less available in North America.

The cinchinoid alkaloids are effective against the latter erythrocytic stages. Most authorities recommend a loading dose to rapidly achieve high therapeutic levels. Side effects are common, particularly cinchonism (tinnitus, hearing loss, nausea, restlessness, and blurred vision) and cardiovascular side effects (hypotension).

The artemisinin compounds (artesunate, artemether, and arteether) are fast acting and act against all blood stages, reducing the time to parasite clearance and fever resolution in comparison to the cinchinoid alkaloids. Artesunate is the favored drug, since it can be administered intravenously or intramuscularly, is associated with less neurotoxicity in animal models, and has reduced mortality in adults with severe malaria.

14.13.3.1 Other Antimalarial Drugs

Currently, other antimalarial drugs should be combined with parenteral antimalarials to prevent the emergence of resistant parasites. Atovaquone-proguanil (Malarone™) and mefloquine are the most commonly used.

14.13.3.2 Supportive Treatment

Supportive treatment is important in children with severe malaria, since most children die within 24 h, before the antimalarials have had time to work. Children with severe falciparum malaria should be monitored closely. Blood glucose and fluid balance should be measured every 6 h, parasitemia and hematocrit every 12 h.

Electrolytes, tests of renal function, albumin, calcium, phosphate, and blood gasses should be performed at least daily during the acute stages.

14.13.4 Outcome

The mortality of cerebral malaria in nonimmune individuals ranges from 15 to 26 %, with patients usually dying within the first 4 days of the illness, often from renal failure or pulmonary edema, acidosis, or brainstem herniation.

Neurological sequelae occur in about 5 % of nonimmune individuals and include cranial nerve lesions, extrapyramidal tremor, polyneuropathy, epilepsy, or psychiatric manifestations. In African children living in endemic areas, hemiparesis, ataxia, and cortical blindness are the most common sequelae, but some children are left in a vegetative state. Impairment of a wide range of cognitive functions has been documented, particularly in memory, executive functions, and language.

14.14 Tetanus

Tetanus is caused by toxins produced by *Clostridium tetani* and is characterized by increased muscular tone and spasms. It occurs in two different clinical situations, neonates (neonatal tetanus) and older children and adults (non-neonatal tetanus). The route of entry in neonatal tetanus is the umbilical cord while, in non-neonatal tetanus, wounds on the lower limbs, compound fractures, and non-sterile intramuscular injections, dental procedures, or infections, e.g., otitis media. Often the route of entry is not identified. Tetanus toxoid vaccination has eliminated tetanus from many countries, although it is still seen in many parts of the developing world.

14.14.1 Presenting Signs and Symptoms

Tetanus is a clinical diagnosis that is made easily in areas where it is seen frequently [15]. It is characterized by increased tone and spasms, which occur spontaneously or are provoked by touching the body, sound, or light.

14.14.1.1 Neonatal Tetanus

Neonates with tetanus present a median 6 (range 3–10) days after birth with refusal to feed, mainly due to difficulty in opening the mouth. Thereafter, sucking stops and "risus sardonicus" may develop. Increased tone, progressing to rigidity, and opisthotonus occur. Spasms of the limbs develop early, but become generalized.

14.14.1.2 Non-neonatal Tetanus

The incubation period is usually 4 days to 3 weeks after the insult. The first symptom is often inability to open the mouth fully owing to rigidity of the masseters (trismus or lockjaw). Pain, headache, stiffness, rigidity, opisthotonus, laryngeal obstruction, and spasms may follow. The spasms are most prominent in the first 2 weeks and are very painful. Dysphagia can occur. Autonomic dysfunction (labile blood pressure especially hypertension, tachyarrhythmias, hyperpyrexia, and hypersalivation) usually starts some days after the spasms. The condition tends to improve thereafter, but the rigidity may last beyond the duration of both spasms and autonomic disturbance, for up to 6 weeks. Tetanus can be localized at the site of injury causing local rigidity and pain.

14.14.2 Recommended Assessments

Tetanus is a clinical diagnosis; since *C. tetani* is difficult to culture, a positive result does not indicate if the organism contains the toxin-producing plasmids, and *C. tetani* may be present without disease in patients with protective immunity.

14.14.3 Recommended Interventions

The main aims of management are to support the patient during the time it takes for new vesicles to replace those that the toxin is bound. This includes good-quality nursing to reduce stimuli that may precipitate spasms, neutralizing the toxin with tetanus immunoglobulin, treating the infection (preferably with metronidazole), reducing spasms and respiratory complications with paralysis and ventilation, treating the cardiovascular complications (autonomic dysfunction), and providing sufficient fluids and calories.

14.14.4 Outcome

In neonates mortality is high, with 65 % neonates dying in hospitals that lack facilities for ventilation, but if ventilation and intensive care are available, the mortality decreases to 22 %. In neonates who survive, microcephaly, mild neurological, developmental, and behavioral problems have been reported.

In older children, mortality varies from 20 to 50 %, with the lowest mortalities in hospitals that can perform tracheostomies and/or provide ventilation. The commonest cause of death is respiratory failure (secondary to uncontrolled spasms), autonomic dysfunction, and septicemia.

14.15 Neurobrucellosis

Brucellosis is still endemic in many parts of the world and is often acquired by contact with infected animals (mainly cattle, sheep, goats, dogs, or pigs) or ingestion of unpasteurized milk.

14.15.1 Presenting Signs and Symptoms

It usually causes a nonspecific febrile illness, which waxes and wanes (undulant fever), often with arthralgia. It affects many organs of the body, but CNS involvement is rare in children [10]. *Brucella* sp. can cause meningoencephalitis, brain abscess, cranial nerve palsies (particularly VIII nerve), myelitis, radiculitis, and a polyneuropathy. It is associated with poor concentration, depression, and chronic fatigue.

14.15.2 Recommended Assessments

The CSF often has a pleocytosis with raised protein, but normal glucose. *Brucella* sp. are difficult to culture, but cultures of blood or bone marrow may isolate the organism. The diagnosis is usually made on a rising titer in serological tests, particular the brucella microagglutination test or brucella-specific ELISA. Brucella antibodies may also be found in the CSF.

14.15.3 Recommended Interventions

The treatment of brucellosis varies with age and country. In general, children younger than 10 years should be treated with trimethoprim/sulfamethoxazole (10 mg/day of trimethoprim iv or po) and rifampicin (20 mg/kg per day divided in two doses) for at least 4 weeks. Tetracyclines may be used in older children instead of the trimethoprim/sulfamethoxazole and streptomycin or gentamicin can be used instead of rifampicin.

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Chapter 15
Management of Acute Neuromuscular Disorders

Ching H. Wang and Thomas Sejersen

Abstract Acute disturbance of motor function can be caused by spinal cord lesions, peripheral neuropathies, disorders of the neuromuscular junctions, and diseases of the muscles. These represent the main stations within the neuromuscular axis. The clinical presentation and diagnostic procedures of these disorders were discussed in Chap. 4. In this chapter we discuss the therapeutic interventions for these disorders. We list the most common acute disorders within each station of the neuromuscular axis and discuss the treatment strategies for each of these disorders. Autoimmune disorders affect all of these stations and the treatment strategies are fairly similar. However, there are subtle differences between different disorders. Medication treatments are available in many of these disorders and timely administration of these medications can be life saving. Some of these disorders require supportive care and close monitoring in the intensive care unit. Most of them require continuing physical therapy and rehabilitation to ensure complete recovery.

Keywords Spinal cord • Neuropathy • Neuromuscular junctions • Myopathy • Channelopathies • Acute management

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15.1 Introduction

Acute motor disturbance in children is easily detected and often raises intensive concerns in parents. This prompts them to seek medical attention urgently. Identifying the cause of motor disturbance is the first step toward an effective therapy. We have, in Chap. 4, listed several possible causes of acute motor disturbances and the approaches to identifying anatomical location of the lesion. We also listed the laboratory testing to establish accurate diagnoses. In this chapter, we will focus on the management and therapeutic interventions for these acute motor disturbances. We will discuss clinical management strategies according to the locations of the lesion in the neuromuscular axis—spinal cord, peripheral nerves, neuromuscular junctions, and muscles. We will concentrate on the established practices and only include those experimental protocols that are based on strong scientific rationale and seem promising in their efficacy.

15.2 Management of Acute Spinal Cord Dysfunctions

Acute sensory-motor dysfunction caused by spinal cord pathology includes inflammatory/postinfectious autoimmune disorder, vascular thrombotic event to spinal arteries, traumatic injury, neoplasm of the spinal cord, and exacerbation of degenerative motor neuron diseases. We will discuss the management strategies for each of these etiologies in the following sections.

15.2.1 Acute Transverse Myelitis (TM) and Neuromyelitis Optica (NMO)

Transverse myelitis and NMO are the two most common inflammatory disorders of the spinal cord. Both TM and NMO are considered postinfectious/autoimmune diseases [1]. The clinical presentations and diagnostic workups are discussed in details in Chap. 17.

Treatment for established TM and NMO includes high-dose IV methylprednisolone at the dose of 30 mg/kg/day with a maximal dose of 1,000 mg per day for 3–5 days [2]. This is usually followed by a tapering course of oral prednisone over the next 4–6 weeks, starting at 1 mg/kg/day. If the symptoms do not improve within 7–10 days of initiation of the steroid treatment, then a course of IVIG may be given. The dose and protocol of IVIG treatment can be varied according to institutions [3]. A total dose of 2 g/kg body weight is usually given and administered in five divided doses (400 mg/kg/day). Alternative protocols include a single infusion of the entire dose of 2,000 mg/kg or in two divided doses (1,000 mg/kg/day). Due to the risk of anaphylactic reaction to IVIG, a test dose (10 mg/kg) of IVIG is usually given first over 30 min with ready access to epinephrine as an antidote. Pretreatment of antipyretics (such as acetaminophen) and antihistamine (such as Benadryl) is usually

included in the protocol. Careful monitoring of vital signs should be followed throughout the infusion. To prevent masking a preexisting immunoglobulinopathy such as IgA deficiency, a set of blood immunoglobulin profile should be obtained prior to the administration of IVIG. In severe and refractory cases, a second course of methylprednisolone may then be given. Plasmapheresis has been proven effective in treating TM and NMO. While plasmapheresis is commonly done in adult patients, it is not as easily done in pediatric patients due to difficulty in vascular access. However, in older children and adolescent patients, plasmapheresis should be considered prior to repeated IVIG treatment. In chronic relapsing cases, periodic IVIG or plasmapheresis may be needed. Alternatively, chronic immunosuppression such as cyclophosphamide (Cytoxan) or mycophenolate (Cellcept) or rituximab (Rituxan) may be given [4]. Treatment of these chronic immunosuppressive medications requires careful monitoring of peripheral lymphocyte counts. Aggressive treatment of any infection is indicated in these immunosuppressed patients.

15.2.2 Vascular Events of Spinal Cord

The vascular supplies to spinal cord are susceptible to thrombotic events and can result in acute flaccid paralysis. The anterior spinal artery supplies the anterior two third of the spinal cord, including the anterior and lateral columns in the white matter and the anterior horn cells in the gray matter which give rise to the motor nerves. Thrombotic occlusion of the anterior spinal artery and its terminal sulcal branches is the most common vascular event of the spinal cord in children, resulting in "anterior spinal artery syndrome" [5]. This includes acute flaccid paralysis associated with disturbances in pain and temperature sensations. Occlusion of the posterior spinal arteries produces symptoms of dorsal columns and resulting in deficits in proprioceptive and vibratory senses and milder weakness. The cause of spinal arteries occlusion in children is often unknown. However, association with acute trauma to spinal cord has been reported. Intraspinal vascular malformation or infections are rare causes of spinal cord infarction. MRI study of the spinal cord may be used to establish the level(s) of infarction. Spinal angiogram is used to establish the intraspinal vascular malformation.

Treatments of acute spinal cord infarction are mostly supportive. Systemic use of high-dose steroid has not been studied and was not recommended [6]. Short term IV anticoagulation treatment is sometimes used in children but has not been systematically studied in terms of its clinical benefit. Intravenous thrombolytic treatments have not been established in acute vascular events in pediatric population.

15.2.3 Traumatic Injury to Spinal Cord

Management of traumatic injury to spinal cord is an extremely broad topic and warrants further reading in literatures devoted to this topic [7]. We will outline the most crucial steps in managing this acute condition:

1. Maintaining airway patency and monitoring vital signs: This is no different from managing other traumatic injury to the central nervous system. If the injury involves upper spinal cord and brainstem, the respiratory drive may be compromised and endotracheal intubation may be needed. Patients with spinal cord injury tend to become hypotensive and fluid resuscitation is often needed. Urine output needs to be monitored, and in the case of accompanied bladder dysfunction, an indwelling urine catheter may be needed to maintain the urine output. In patients with compromised mental status, an oral-gastric tube may be needed to empty the stomach content and to prevent aspiration.
2. Immobilization of the cervical spines: A hard cervical collar is first placed with the reinforcement of sandbags on each side of the neck to provide good support to the spine. Tilting or turning of the neck should be avoided and the patient should be transported on a hardboard on the gurney.
3. Imaging studies: Plain spine films to the region of injury are indicated once the patient is stabilized. Further studies such as CT scan or MRI may be needed to locate and assess the extent of bony and soft tissue injury.
4. Treatment with high dose steroid: A dose of methylprednisolone (30 mg/kg) followed by IV infusion of 5.4 mg/kg/h for the next 23 h is currently adopted in emergency treatment of spinal cord injury.
5. Surgical intervention: The trauma team will assess if there is an indication for surgical intervention. Indications for surgical intervention include bony fragments impinging on spinal cord, epidural hematoma compressing the cord, fractures of the vertebral bodies, or herniated discs requiring surgical repair.

15.2.4 Management of the Spinal Cord Compression Syndromes

Acute spinal cord compression is a true neurological emergency that warrants rapid diagnosis and intervention. Spinal cord compression can occur from several causes. Metastatic tumors, epidural abscess, focal expansion of bony structures, and hematoma are the most common causes. The salient features of spinal cord compression include a demarcation of acute sensory-motor disturbances distal to the compression and the bowel/bladder dysfunctions. Urinary incontinence and retention both occur in spinal cord compressions. In children with a history of posterior fossa tumor, the “drop metastasis” is often the primary cause of spinal cord compression. In spinal epidural abscess fever may accompany focal tenderness. Epidural hematoma occurs in trauma or bleeding disorders. Focal tenderness is often elicited by palpation or percussion.

Management of acute spinal cord compression starts with identifying the cause. In patients with previous history of posterior fossa neoplasms, MRI of the brain and spinal cord is needed to visualize the entire neural axis. Studies of CSF and blood can help to identify infectious etiology or metastatic neoplasms. Treatments are dependent on the cause of compression. An emergency radiation therapy may be

needed for drop metastasis that is diffuse and widespread. Focal surgical decompression may be needed if the lesion is surgically accessible. A 3–4-week course of antibiotic treatment is often needed for epidural abscess. In immunocompromised hosts, empirical coverage of fungal and tuberculosis infections may be needed. Correcting bleeding disorders is indicated for epidural hematoma.

15.2.5 Hereditary Motor Neuron Diseases

Motor neuron diseases in children such as spinal muscular atrophy (SMA) or juvenile amyotrophic lateral sclerosis (ALS) result in chronic progressive weakness that can become life threatening. Progressive weakness of respiratory muscles may cause respiratory insufficiency. Acute respiratory infections may result in increased secretion and obstruction of the airways. In acute respiratory infection appropriate antibiotic treatment and aggressive clearance of the airway is indicated. During this time, positive pressure airway support in the form of bilevel positive airway pressure (BiPAP) is noninvasive and usually well tolerated. Airway clearances using manual chest physiotherapy in combination with mechanical cough assistance are most effective. Sometimes endotracheal intubation is temporally needed. Patients in milder disease (types II and III SMA) or in early course of the disease are usually able to return to their baseline state of health after the infection is treated and the ventilator support discontinued. However, if the progressive weakness results in respiratory insufficiency requiring chronic ventilator support, then the patient may not be able to wean off the support. In this case, there need to be careful discussions between the health professionals and the family members regarding the balance between prolonging life and quality of life issues and provide the family with options for different levels of care. Ideally, these discussions should have taken place prior to the acute exacerbation. A consensus statement for standard of care for spinal muscular atrophy is recently published that discusses in more details regarding acute and chronic care for this group of patients [8].

15.3 Management of Acute Neuropathies

While most hereditary sensory-motor neuropathies are chronically progressive, there are several acquired motor neuropathies that could present in acute settings and result in acute motor disturbance. This group of disorders usually presents as acute or subacute weakness with or without sensory symptoms. In young children acute gait disturbance with frequent falls is the most common complaint. Occasionally there are complaints of “pins and needles” or “bugs crawling” sensory disturbances. Diagnosis of peripheral neuropathy often relies on abnormality in nerve conduction studies. Acute or chronic demyelinating neuropathies show characteristic slowing in conduction velocity, whereas toxic and metabolic neuropathies

usually involve the neuronal axons and result in decreased conduction amplitudes. In this section we will discuss treatments for four types of acute motor neuropathies: acute inflammatory demyelinating polyneuropathy (AIDP, also called Guillain–Barré syndrome), chronic inflammatory demyelinating polyneuropathy, toxic/metabolic neuropathies, and traumatic neuropathies.

15.3.1 Acute Inflammatory Demyelinating Polyneuropathy: Guillain–Barré Syndrome

Clinical presentation and diagnosis of AIDP are well discussed in Chap. 4. Management of AIDP mostly depends on the speed of progression and severity of weakness. Supportive care is the most important measure to reduce morbidity and mortality. In patients with rapidly progressing weakness, an admission to pediatric intensive care unit is often needed. Careful monitoring of respiratory status is crucial in patients with ascending weakness. A bedside pulmonary function test (PFT) should be used in these patients. Ventilatory support may be needed in patient with respiratory insufficiency. Maintaining adequate nutrition with enteral feeding may be needed in patients with difficulty swallowing, and monitoring their fluid status should be part of the ICU care routine. For those with dysautonomia blood pressure may become fluctuating. Cardiac arrhythmia and painful radiculopathy should be adequately treated. An indwelling urine catheter may be needed for those with bladder dysfunctions. Bedside physical therapy should be started as soon as possible to prevent consequences of prolonged immobilization and to assist functional recovery.

The main therapeutic treatments for AIDP include intravenous immunoglobulin (IVIG) and plasmapheresis. Protocol of IVIG treatment is similar to other autoimmune disorders of the nervous system as mentioned previously in transverse myelitis and NMO. A total dose of 2,000 mg/kg body weight given in five divided doses (400 mg/kg/day) is commonly adopted. Plasmapheresis is considered equally effective as IVIG in treating AIDP. However, in young pediatric patients the vascular access is often difficult and plasmapheresis usually reserved for those patients refractory to IVIG therapy. Treatment with high-dose steroid is considered ineffective in a Cochrane review [9].

15.3.2 Chronic Inflammatory Demyelinating Peripheral Neuropathy (CIDP)

CIDP is considered the chronic counterpart of AIDP. The main difference is that it has a subacute or chronic (weeks to months) course of sensory and motor symptoms. Some CIDP cases present as one chronic progressive episode but most cases

have a chronic relapsing course. Sensory disturbance such as numbness or paresthesia ("pins and needles" or "bugs crawling") is more common in CIDP than AIDP. These can sometimes present without motor weakness. The subacute onset of symptoms during the first episode may sometime escape parental attention until they become obvious which then prompted them to seek medical attention. These cases are often treated initially as AIDP. In the relapsing form the recurrent episodes are easily noticed and it is only after these relapses that the diagnosis becomes clear. Diagnosis of CIDP is discussed in Chap. 4.

Management of CIDP is similar to AIDP except that IV methylprednisolone is also used to treat CIDP. IVIG is still the mainstay of treatment for initial episode or subsequent relapses [10]. Some cases only respond to high-dose steroid treatment but not IVIG. Plasmapheresis is indicated in patients refractory to IVIG and IV methylprednisolone. In patients with frequent relapses, a set schedule of IVIG or chronic treatment of oral prednisone may be needed. Chronic immunomodulation such as mycophenolate (Cellcept), cyclophosphamide, or rituximab may be used in patients with frequent relapses and refractory to chronic IVIG or oral steroid treatment. However, careful monitoring of blood counts and aggressive treatment of any opportunistic infection is needed when using these agents.

15.3.3 Bell's Palsy

Bell's palsy is caused by dysfunction of the ipsilateral facial nerve. It is considered an autoimmune complication of a preceding infection. The inflammation of the facial nerve results in compression across the stylomastoid foramen. The compression on the posterior auricular branch results in pain behind the ear on presentation. The disease involves all five branches of the facial nerve and causes weakness on both upper and lower face. This is different from facial weakness caused by central lesions (prior to facial nucleus) which often spare the upper face (frontalis and orbicularis oculi muscles) due to dual innervations of these muscles by both sides of supranuclear neurons. Involvement of chorda tympani nerve could result in loss of taste in the anterior two third of the tongue.

The facial weakness due to Bell's palsy usually affects one side of the face and progresses rapidly and reaches nadir within 3 days. In severe cases, complete paralysis results in difficulty in eye closure and speech and eating. Treatment with oral prednisone (1 mg/kg/day up to 60 mg/day) for 7 days is effective in shortening the course [11]. However, little or no benefit if the treatment is given 7 days after the onset of symptoms. If herpes infection is identified, then acyclovir (Zovirax) or valacyclovir (Valtrex) should be given. In patients with difficulty in eye closure, an eye patch should be used during sleep to prevent corneal damage. Physical therapy has been shown to shorten the course. Surgical decompression has been considered in patients with complete paralysis after 2 weeks of onset. However, this is not currently recommended by the American Academy of Neurology [12].

15.3.4 Neuropathies Due to Toxic Agents or Metabolic Disorders

In this group of peripheral neuropathy, axonal injury is the most common pathogenesis and the sensory disturbances are often more prominent than motor weakness. Medications commonly associated with a side effect of peripheral neuropathy are antibiotics and chemotherapy agents. Vitamin deficiencies and heavy metal poisoning are the most common metabolic causes. Almost all antituberculosis drugs (isoniazid, ethambutol, and linezolid) can cause axonal neuropathy presented as numbness and paresthesia. Other antibiotics such as chloramphenicol and nitrofurantoin may cause painful dysesthesia. Aminoglycosides and platinum-based chemotherapy agents are known to have ototoxicity and cause hearing loss to high-frequency sounds. Chemotherapy agents such as vincristine, cisplatin, cytosine arabinoside, and adenine arabinoside are known to cause sensory-motor axonal neuropathies. Vincristine is most commonly associated with loss of proprioceptive and vibration senses [13]. Deficiencies of vitamin B1 (thiamine), B6 (pyridoxine), and B12 (cobalamin) are all associated with peripheral neuropathies. These could be due to nutritional deprivation, congenital defects in intestinal absorptions, or intake of toxic agents (isoniazid in pyridoxine deficiency, alcoholism in thiamine deficiency). Heavy metals such as lead and mercury are the most common causes of neuropathy from environmental toxins. Lead poisoning from old house paint or toys is common in pediatric population that can cause sensory-motor neuropathies and encephalopathy. Mercury poisoning from industrial exposure or ingestion of contaminated seafood or well water is the common cause of sensory-motor neuropathy [14]. Accidental ingestion of arsenic or rat poison is the other source of heavy metal poisoning.

The most effective management of neuropathies caused by toxic agents is withdrawing the offending agents. Most patients show gradual recovery from their weakness but sensory disturbances could be more long lasting. In the case of isoniazid treatment for TB, pyridoxine supplement should be given. Vincristine should be avoided in patients with hereditary motor-sensory neuropathy (HMSN) type I and type II. Chelating treatment such as EDTA may be needed for heavy metal poisoning. Nutritional supplement of vitamin B group is needed in children with vitamin deficiency caused by malabsorption or deprivation. Megaloblastic anemia should prompt rapid investigation of B12 deficiency and supplement [15].

15.3.5 Neuropathies Due to Traumatic Injury

Traumatic injury to peripheral nerves is uncommon in pediatric population. Serious nerve injuries caused by direct blow or cut to the peripheral nerves such as those occur in motor vehicle accidents require immediate surgical attention. We will consider only the more common brachial plexus injuries during traumatic birth and common sports injuries in older children.

Brachial plexus injury mostly presented at birth due to shoulder dystocia. Erb's palsy is the most common type that resulted from upper nerve roots (C5, C6) injury. The weakness in wrist extensors and elbow flexors causes the forearm to be held in pronation with the wrist flexed and shoulder adducted. Injury to the lower nerve roots (C8, T1) results in the arm held flexed at the elbow and wrist extended (Klumpke's palsy). This is much rarer than Erb's palsy. Management of brachial plexus injury includes supportive arm sling to protect further injury to the nerves. Passive range of motion should be started in 2 weeks to prevent joint contractures.

Sports injuries to peripheral nerves can occur in almost every peripheral nerve originating from brachial or lumbar sacral plexus. The detailed discussion of each of these injuries is beyond the scope of this book. We will only discuss the injuries in the elbows and knees that are the most common traumatic neuropathy in school age children. Elbow injuries occur in playing baseball, softball, and tennis and are the most common. The injury could be secondary to entrapment caused by inflammation of the surrounding soft tissues or direct stretching injury to the ulnar nerve. Knee injuries are often observed in soccer, football, hockey, and weight lifting. Entrapment or direct blow to the common peroneal nerve is the most common occurrence. Most of these injuries respond to conservative treatment of rest and physical therapy. However, in severe injuries surgical intervention may be needed. The severity of injury is often guided by nerve conduction study and electromyography.

15.4 Management of Dysfunction at the Neuromuscular Junctions

Disorders at the neuromuscular junctions such as myasthenia gravis usually present as chronic weakness, but rarely, acute exacerbation by interval infection or other factors could cause life-threatening weakness that requires urgent management. Infection of Clostridium botulinum results in blockade of presynaptic release of acetylcholine and acute weakness in infant that requires urgent treatments. The clinical presentation and diagnosis were discussed in Chap. 4. We will discuss the managements of these conditions here.

15.4.1 Acute Myasthenic Crisis

Neonatal myasthenia from transplacental maternal anti-AchR antibody is an acute but rather benign condition. The infant is hypotonic and has weak cry and poor sucking effort. Ventilator support is sometimes needed. Attention to nutritional support is important and gavage feeding is often needed. The infant gradually recovers and can be weaned off these supports in 4–6 weeks. Anticholinesterase therapy may

shorten the course and can be stopped after the infant becomes asymptomatic. Since the anti-AchR titer does not correlate well with clinical strength, there is no need to check the titer repeatedly [16].

Children with generalized myasthenia are more susceptible to myasthenic crisis than those with isolated ocular myasthenia. The cause of acute exacerbation of generalized weakness is often unknown but acute febrile illness, pregnancy, and some antibiotics use (such as aminoglycosides) were known to precipitate myasthenic crisis. During this acute exacerbation the patient has problem with dysarthria, hypophonia with nasal speech, ptosis, difficulty with swallowing, weak cough, and respiratory distress. Although the percentage of seropositive myasthenia gravis (MG) is lower in children than adult, many of them do respond to anticholinesterase such as pyridostigmine (Mestinon). Regular dose of treatment in infant and young children is 0.5–1 mg/kg/dose giving every 4–6 h. In older children, a total dose of 7 mg/kg per day of Mestinon is given in 3–5 doses [17]. The management of acute exacerbation is often dependent on the severity of weakness. Mild exacerbation may be managed as outpatient with adjusted dose of Mestinon. In young children, the acute weakness associated with respiratory infection should be hospitalized for observation. In patients with respiratory distress, supportive care including endotracheal intubation should be provided in an intensive care unit. Additional therapies such as high-dose corticosteroids, IVIG, and plasmapheresis are used to treat myasthenic crisis. In patients hospitalized for surgical procedures (such as thymectomy), the pyridostigmine can be given in IV form using 1/30 conversion rate from oral dose (i.e., every 60 mg of oral dose can be given in 2 mg IV) given in the same intervals. Bedside physical therapy should be started as soon as possible to facilitate functional recovery.

15.4.2 Infant Botulism

Infant botulism is caused by ingestion of contaminated food with colonized Clostridium botulinum. The bacteria then propagate in the intestinal tract and secrete botulinum toxin. Botulinum toxin inhibits the acetylcholine release from the motor nerve terminals in the neuromuscular junctions and also at the parasympathetic ganglia. This results in generalized weakness and autonomic dysfunction. The infant presents with decrease movement, hypotonia, feeding difficulty, constipation, dilated and sluggishly reactive pupils, cardiac arrhythmia, and respiratory distress. Electromyography using repetitive stimulation at 30–50 Hz shows facilitation phenomena and an increment of compound muscle action potential (CMAP) greater than 100 %. The spectrum of clinical symptoms ranges from asymptomatic carrier to life-threatening acute quadriparesis.

Treatment of infant botulism includes supportive care and botulinum immunoglobulin (BIG). The severely affected infant requires supportive care in the intensive care unit. Ventilator support including endotracheal intubation or BiPAP may be needed. Infants requiring prolonged intubation and severe constipation due to ileus may need total parental nutrition (TPN). Treatment of cardiac arrhythmia and hypertension may be needed. In the acute phase, treatment of IV botulinum immunoglobulin (BIG) shortens the recovery course and hospital stay [18].

15.5 Management of Acute Muscular Dysfunctions

Skeletal muscle is the end organ of the neuromuscular system and is the largest organ system of the human body. Acute dysfunction of the skeletal muscles results in motor weakness and hypotonia. This can be seen in degenerative diseases such as congenital myopathies and muscular dystrophies, autoimmune diseases such as polymyositis, energy production disorders such as metabolic myopathies, electrolyte imbalance such as periodic paralysis, and acute reaction to neuromuscular blockades in malignant hyperthermia. The clinical presentation and diagnosis were discussed in Chap. 4. We will address the acute managements of these muscle disorders except the acute symptoms and treatments of metabolic myopathies which were discussed in Chap. 10.

15.5.1 Acute Exacerbation of Congenital Myopathies and Muscular Dystrophies

Congenital myopathies and muscular dystrophies are two main categories of hereditary muscle diseases. They usually present as chronic and progressive diseases. However, acute exacerbation of these disorders from interval illness could result in multisystem organ failure and requires urgent care. The multidisciplinary approach to the care for congenital muscular dystrophies, Duchenne muscular dystrophy, and congenital myopathies has been published recently [19–22]. They address both chronic and acute care for these disorders and should be consulted for further details. Maintenance of respiratory function includes support for hypoventilation due to weakness of respiratory muscles and clearance of the airway from increased secretions. Maintenance of cardiac functions using medications or intracardiac devices may be needed. Many patients with end-stage cardiac diseases may require cardiac transplants. Indications and contraindications for cardiac transplants in patients with systemic muscle diseases should be evaluated on a case-by-case basis. Nutritional support should be started early to promote early recovery. Correction of chest wall deformity and scoliosis may be needed to improve the cardiopulmonary functions. Maintenance of bone health can prevent disuse osteopenia and fractures that will require urgent orthopedic care.

15.5.2 Management of Acute Inflammatory Myopathies

Inflammatory myopathies in children are caused by autoimmune processes such as dermatomyositis and, rarely, polymyositis and infection of the muscles by various microbes (infectious myositis). Clinical signs of dermatomyositis include butterfly rash across the nasal bridge, purple-pink discoloration of the eyelids (heliotrope), erythematous thickening of the extensor surface of the joints such as knuckles, elbows, and knees (Gottron's sign), dilated capillaries of nail bases, and subcutaneous

calcium deposits. They are present initially as subacute onset of muscle weakness and can later be associated with acute exacerbation. Polymyositis are usually associated with autoimmune diseases such as juvenile systemic lupus erythematosus (SLE). Infectious myositis can be caused by viral, bacterial, fungal, and parasitic infections.

Treatment for new onset or acute exacerbation of dermatomyositis usually starts with a course of high-dose IV methylprednisolone at a total dose of 2,000 mg/kg divided into 4–5 daily doses followed by tapering course of oral prednisone starting with 2 mg/kg dose. While the goal is to bring the patients into remission and off steroid treatment, some patients may need a chronic low dose prednisone given in every other day schedule to maintain in remission. Other therapeutic modalities include IVIG, plasmapheresis, and other immunomodulations such as methotrexate, cyclophosphamides, and rituximab. Muscle strength improves with these treatments, but some skin signs may remain even if the patients are in remission.

Treatments for polymyositis usually aim at treating the associated systemic autoimmune diseases. Treatment for infectious myositis includes using appropriate antibiotics for bacterial and parasitic infection and supportive and physical therapy.

15.5.3 Management of Malignant Hyperthermia

Malignant hyperthermia (MH) is a true medical emergency that has a high mortality rate if left untreated. Therefore, recognition of the condition is the most important first step in management. Familial malignant hyperthermia is an autosomal dominant condition most often associated with congenital myopathies. Mutations in ryanodine receptor (*RYR1*) gene are known to cause central core, multi-minicore, and centronuclear myopathies and can be inherited in dominant or recessive transmissions [23]. It is the dominantly inherited mutations that render the patients most susceptible to MH. The condition is often caused by persistent muscle contraction due to abnormal influx of calcium from sarcoplasmic reticulum (due to *RYR1* gene mutations) upon exposure to triggering anesthetic agents. The most common triggering anesthetics include the volatile gases such as halothane, sevoflurane, and desflurane as well as depolarizing muscle relaxants like succinylcholine. The clinical symptoms include muscle rigidity, hyperthermia, myoglobinuria, hypermetabolism, electrolytes abnormalities, and cardiac arrhythmia.

Treatments of MH include supportive care and pharmacological therapy. Upon recognition of MH the anesthesia should be stopped immediately and the patient be admitted to an intensive care unit for further management. Hyperthermia should be treated with cooling blanket or cooled IV fluid. Serum electrolytes, muscle enzyme creatinine kinase, and urine output should be monitored closely. In the case of myoglobinuria, the renal function should be closely monitored. Volume loading and diuretics may be needed. Electrolyte abnormalities should be corrected as soon as safely possible to prevent cardiac arrhythmia.

Dantrolene is the specific pharmacological agent that is used to treat MH [24]. Dantrolene relaxes muscle contraction by blocking calcium influx from sarcoplasmic reticulum. A dose of 1 mg/kg IV push is used with an increment dose up to a

maximum of 10 mg/kg. In refractory cases continued IV infusion at 2.5 mg/kg/h may be needed until the symptoms subside. In some cases maintenance oral or IV dose of 4–8 mg/kg/day in 3–4 divided doses may be needed for the following 2–3 days to maintain muscle relaxation.

The most effective management of MH is preventive measures. Patients with family history of MH, previous anesthesia problems, or suspected or confirmed diagnosis of muscle diseases should avoid the triggering anesthetics listed above.

15.5.4 Management of Periodic Paralysis

Several hereditary periodic paralyses can cause acute onset of weakness in children, with durations ranging from hours to days. These disorders are observed in children of all ages but most commonly occur in those older than 10 years old. Exposure to cold temperature followed by exercise triggers the muscle rigidity and weakness in paramyotonia congenita [25]. High carbohydrate intake after prolonged exercise and resting are associated with hypokalemic periodic paralysis. The weakness affects both legs but can also cause generalized paralysis requiring supportive care in the hospital. Most of them recover to the full extent after a period of resting. Mutations of genes encoding sodium, potassium, calcium, and chloride channels have all been associated with periodic paralysis. Some of them are associated with myotonia and some of them are associated with progressive muscle weakness. We will discuss the treatments for the most common causes of periodic paralysis associated with hyperkalemia and hypokalemia.

15.5.4.1 Treatment for Hyperkalemic Periodic Paralysis

Familial hyperkalemic periodic paralysis and paramyotonia congenita are both caused by mutations in the sodium channel gene (*SCN4A*) of the skeletal muscles and can occur with or without myotonia. Treatment for this condition is to avoid exposure to cold temperature after exercise. Avoiding prolonged and vigorous exercises and high potassium intake is effective for preventing hyperkalemic periodic paralysis. For acute treatment, oral glucose loading accompanied by small dose of subcutaneous insulin effectively lower the serum potassium level. Treatment with mexiletine on a chronic basis can prevent the attacks [26]. Diuretics including thiazides and acetazolamide also help to lower the serum potassium level. Secondary hyperkalemia caused by adrenal insufficiency requires steroid supplements.

15.5.4.2 Treatment for Hypokalemic Periodic Paralysis

Hypokalemic periodic paralysis occurs more commonly than hyperkalemic periodic paralysis and affects men more than women. It is associated with mutations in the calcium channel gene (*CACNA1S*) and sodium channel gene (S*CN4A*) of the

skeletal muscles [27, 28]. In the cases of Andersen-Tawil syndrome associated with hypokalemic periodic paralysis, the symptoms are associated with a mutation in the potassium channel gene (*KCNJ2*) [29].

Acute treatment for hypokalemic periodic paralysis includes oral potassium chloride at 0.5–1 mEq/kg body weight and may repeat in 30 min with additional 0.3 mEq/kg. In patients who are too weak to swallow, IV potassium supplement at 0.05–0.1 mEq/kg given in bolus over 10 min is preferred to IV infusion. Careful monitoring of EKG and serum potassium level is needed. Preventive treatments include daily oral supplement of potassium chloride, carbonic anhydrate inhibitors such as acetazolamide or dichlorphenamide, and potassium-sparing diuretics such as spironolactone are all effective [30]. Avoid prolonged vigorous exercise followed by large carbohydrate intake. In the acquired hypokalemia periodic paralysis associated with thyrotoxicosis, antithyroid therapy should be given to achieve euthyroid.

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Chapter 16
Stroke and Cerebrovascular Diseases

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Abstract Cerebrovascular disorders in children include arterial ischemic stroke (AIS), hemorrhagic stroke (HS), and cerebral venous sinus thrombosis (CVST), each of which has distinct clinical features, etiology, and course, further distinguished according to age at onset. Stroke is as common as brain tumor in children and is one of the ten commonest causes of childhood death; two thirds of affected children are left with long-term impairments, resulting in significant functional disability. The diagnosis of a vascular stroke syndrome in childhood requires astute and targeted clinical assessment in addition to appropriate neuroimaging, as up to a third of children with such presentations will ultimately have a nonvascular diagnosis ("stroke mimics"). Cerebrovascular imaging is usually required to define the underlying vascular basis for AIS and HS and to make the diagnosis of CVST. Early assessment of children with acute stroke should focus on making an accurate diagnosis and recognition of potentially treatable secondary complications (e.g., raised intracranial pressure, hydrocephalus). International clinical guidelines are available to inform acute and secondary management. This chapter focuses on the differential diagnosis of acute stroke in children, the clinical and demographic features of vascular stroke syndromes, and the diagnostic and management approach to these disorders.

Keywords Stroke • Children • Cerebrovascular • Management • Arterial ischemic stroke • Hemorrhagic stroke • Cerebral venous sinus thrombosis • Perinatal stroke

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16.1 Introduction

Cerebrovascular diseases in children include disorders affecting arteries, veins, and/or the capillaries in the brain and include both congenital and acquired ischemic and hemorrhagic disorders. Stroke is defined by the World Health Organization (WHO) as "a clinical syndrome characterised by rapidly developing signs of focal or global disturbance of cerebral function, lasting more than 24 h or death, with no apparent causes other than of vascular origin" [1].

However, the diagnosis of a vascular stroke syndrome in childhood requires neuroimaging as up to a third of children with such presentations have a misleading nonvascular "stroke mimic" diagnosis. The childhood vascular stroke syndromes include arterial ischemic stroke (AIS), hemorrhagic stroke (HS) usually defined as primary nontraumatic cerebral subarachnoid or intraventricular hemorrhage and frequently secondary to an underlying vascular malformation, and cerebral venous sinus thrombosis (CVST). Ischemic stroke has an incidence of 2.4 per 100,000 person years, while HS has an incidence of 1–4/100,000 children [2]. The incidence of cerebral venous sinus thrombosis (CSVT) is at least 0.67/100,000 children per year [3]. Perinatal stroke is a distinct clinical entity and is discussed separately.

16.2 Arterial Ischemic Stroke (AIS) in Children

16.2.1 Presenting Symptoms of AIS

The clinical presentation of AIS beyond the neonatal period varies according to the cause, age, and the vascular territory involved. The mode of onset of neurological symptoms strongly predicts etiological diagnosis of childhood AIS [4]. In a study of 56 children, Braun et al. reported that a non-abrupt onset of symptoms is strongly associated with arteriopathic stroke, particularly with presumed inflammatory arteriopathies. In contrast the majority of children with non-arteriopathic stroke (cardioembolic and cryptogenic) had an abrupt onset.

Younger children often present with irritability, seizures, lethargy, or alteration in sensorium. Acute focal neurological deficit including hemiparesis may be absent and when present, can be subtle and easily missed. Focal neurological deficits such as hemiplegia are the most common presentation of AIS in older children. Language and speech difficulties, headache, and altered mental status may also be seen. Seizures can be the presenting symptom of AIS in 22–52 % of cases [5] particularly in younger children. Posterior circulation AIS (affects around 15 % of cases) presents as ataxia, vertigo, and vomiting [6]. The presence of Horner's syndrome may be a sign of internal carotid artery dissection [7].

16.2.2 Recommended Assessments and Diagnosis of AIS

16.2.2.1 AIS Mimics and Delays in Diagnosis

Clinical stroke in children can often be difficult to recognize resulting in delays in diagnosis. Rafay et al. studied 209 children with AIS and reported a median interval from symptom onset to AIS diagnosis of 22.7 h with a prehospital delay of 1.7 h and an in-hospital delay of 12.7 h [8]. The diagnosis of stroke was suspected on initial assessment only in 38 % of the children. Obstacles to early diagnosis included lack of experience with stroke in the emergency departments, milder deficits, frequent non-focal presentations of stroke in children (37 %), wider differential diagnosis for focal deficits in childhood, and delay to imaging combined with the poor sensitivity of acute CT scanning for the diagnosis of pediatric stroke (53 %). Even when hemiparesis is recognized, it is often attributed to "stroke mimics" such as migraine, seizures, or Todd's paralysis [2]. Frequent final diagnosis in these children included migraine, seizures, psychogenic disorders, tumors, drugs, posterior reversible leukoencephalopathy syndrome, musculoskeletal abnormalities, and metabolic disorders. History and clinical presentation often do not aid the differential diagnostic process and timely comprehensive investigations, especially brain magnetic resonance imaging (MRI), are essential to make an accurate diagnosis.

16.2.3 Clinical Assessments

Figure 16.1 outlines recommended assessments for AIS.

16.2.3.1 History

In addition to the history of presenting symptoms, a comprehensive history of underlying risk factors is recommended [9] (Table 16.1). The etiology of childhood AIS is often multifactorial and more than one risk factor may be present. Disorders like cardiac disease and sickle cell disease (SCD) may be known before the occurrence of AIS. Other relevant history includes head or neck trauma (associated with dissection), unexplained fever or recent infection (particularly varicella), migraine history, vasculitis, drugs, metabolic disorders, and blood disorders. Any previous history of thrombosis or vascular events in the child or family members may be a clue to prothrombotic disorders or a genetic vasculopathy. Most children with AIS have non-atheromatous arterial abnormalities of the intracranial or cervical circulation on magnetic resonance angiography (MRA) [10], the morphology and evolution of which predict a high risk of recurrence and determine treatment. This emphasizes the importance of cerebrovascular imaging at the earliest opportunity.

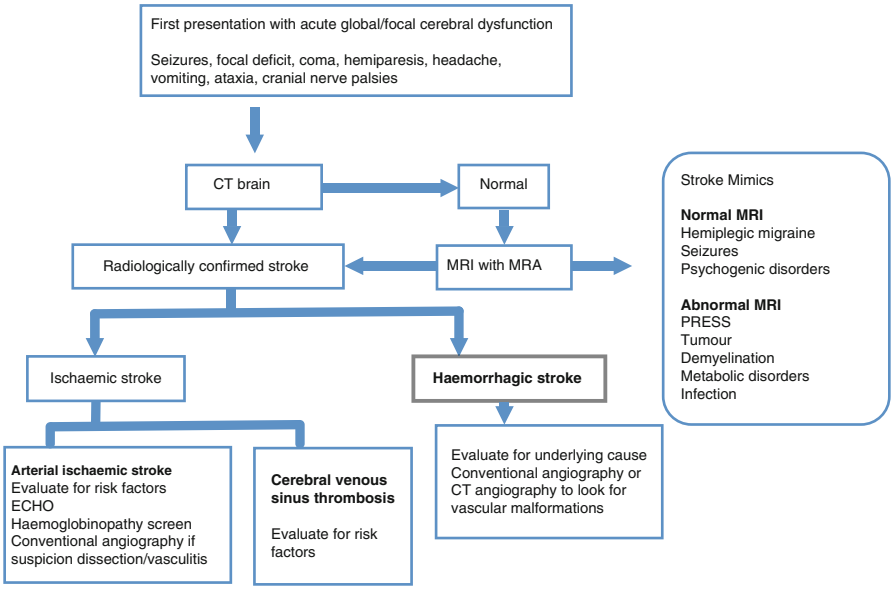

Fig. 16.1 Flow diagram for diagnostic assessment for acute stroke in childhood. *CT* computed tomography, *ECHO* echocardiogram, *MRI* magnetic resonance imaging, *MRA* magnetic resonance angiography, *PRES* posterior reversible encephalopathy syndrome

16.2.3.2 Clinical Examination

In addition to a comprehensive neurological examination, particular attention should be paid to any alteration in sensorium. The most common cause of death in children with AIS is untreated raised intracranial pressure (ICP), and hence recognition and regular monitoring for signs of raised ICP are essential for timely intervention. Signs such as papilledema, cranial nerve palsies, pupillary size, and reactivity should be recorded at the earliest opportunity and frequently monitored. The recently validated pediatric NIH stroke scale [11] provides a useful tool for acute assessment. A systematic evaluation of cardiovascular system (including blood pressure) is essential. Evaluation of other vascular beds such as skin (for neurofibromatosis) and eyes is recommended [12].

16.2.3.3 Neuroimaging

This is a mandatory part of the assessment of any child presenting with clinical stroke particularly because a third of the patients have nonvascular pathology. Initial CT scanning misses the diagnosis in 50–85 % of confirmed pediatric AIS cases [6, 8]. Magnetic resonance imaging (MRI), in particular diffusion-weighted sequences, is frequently required. MRI enables early identification of cerebral ischemia and differentiation of vascular stroke syndromes [13] from each other and

Table 16.1 Causes and risk factors for arterial ischemic stroke (AIS) in children

Cardiac	*Hematologic disorders*
Congenital heart disease	Hemoglobinopathies (SCD, beta thalassemia)
Rheumatic heart disease	Iron deficiency anemia
Cardiomyopathy	Thrombocytosis
Endocarditis	Polycythemia
Myocarditis	Leukemia
Cardiac arrhythmias	MTHFR mutation
	Prothrombin gene mutation *G20210A*
	Protein C/S deficiency
	Antithrombin III deficiency
	Anticardiolipin antibody
	Factor V Leiden mutation
	Lupus anticoagulant syndrome
Metabolic disorders	*Infection*
Fabry disease	Meningitis
Mitochondrial disorders: MELAS	Varicella
Homocystinuria	HIV
Hyperhomocysteinemia	Tuberculosis
Hyperlipidemias	Lyme's disease
Vasculitis	*Cerebral arteriopathies*
SLE	Arteriopathy with sickle cell disease
Dermatomyositis-polymyositis	Transient cerebral arteriopathy
Behcet disease	Post-varicella angiopathy
Wegener granulomatosis	Moyamoya syndrome (secondary to Down's syndrome, prior cranial irradiation, neurofibromatosis, or other known cause)
Sarcoidosis	Fibromuscular dysplasia
Henoch-Schonlein purpura	Metabolic arteriopathy
Polyarteritis nodosa	Cryptogenic arteriopathy
Kawasaki disease	Radiation-induced arteriopathy
Takayasu's disease	
Primary CNS vasculitis	
Genetic arteriopathies	*Arterial dissection*
COL4A1 associated arteriopathy	Intracranial
ACTA2 mutation	Extracranial
Neurofibromatosis 1	*Drugs*
PHACE	Cocaine
CADASIL cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (*NOTCH3*)	Oral contraceptives
Alagille syndrome (*JAG1*)	*Trauma*
William-Beuren syndrome	Head or neck trauma
Aicardi-Goutieres syndrome (*SAMHD1*)	

from stroke mimics. It also allows vascular imaging of the circle of Willis. A normal CT brain is sufficient to exclude a hemorrhagic stroke but not AIS or CVST. Despite this, it could be very helpful in acutely sick children with clinical stroke particularly

when facilities for MRI are not available. In children with AIS, MRA should be performed with brain MRI and should include imaging of the aortic arch to the circle of Willis. Intraluminal vascular imaging techniques such as computed tomography (CT) angiography and catheter cerebral angiography have a role in evaluation for dissection and vasculitis [13]. In children with posterior circulation strokes, dissection should be specifically sought and if necessary catheter angiography may need to be done to definitively exclude this.

16.2.3.4 Cardiac Assessment

All children with AIS should have a transthoracic echocardiogram and electrocardiogram to look for undiagnosed congenital or acquired cardiac disease.

16.2.3.5 Laboratory Investigations

This should include a full blood count with a blood film to look for anemia, one of the frequent risk factors associated with AIS reported in up to 40 % of children in some series [9]. Hemoglobin electrophoresis should be done for sickle cell disease (SCD) and other hemoglobinopathies. The role of inherited or acquired hypercoagulable states as risk factors for AIS is increasingly recognized [14]. A comprehensive thrombophilia screen should include testing for genetic polymorphisms in methylenetetrahydrofolate reductase (MTHFR), mutations in prothrombin, and factor V Leiden genes in addition to protein C, protein S, antiphospholipid antibodies, antithrombin III, fibrinogen levels, and plasminogen activation studies. Plasma homocysteine should be measured in all children with ischemic stroke, and both lipoprotein-a and serum lipids should be measured to look for hyperlipidemias. In adolescent boys with posterior circulation strokes, enzyme (alpha galactosidase A) levels for Fabry's disease should be measured. A comprehensive vasculitis screen should also be undertaken to look for disorders associated with cerebral or systemic vasculitis as discussed in Table 16.1. Cerebrospinal fluid examination may be done if infection or meningitis is clinically suspected or to provide supporting evidence of vasculitis.

16.2.4 Recommended Interventions for AIS

Interventions in childhood stroke are largely extrapolated from evidence in adult studies (despite different risk factors and pathogenesis in adults) due to the lack of pediatric data. Treatment of AIS not only includes acute treatment aimed at limiting the area of acute infarction and preserving neurological function, but also includes secondary prevention of stroke recurrence in these children.

16.2.4.1 Acute Treatment

Acute Supportive Care

Acute supportive care principles apply for all of the stroke syndromes. The principles of managing an acutely ill child with appropriate assessment and management of airway, breathing, circulation, and disability are vital.

Maintenance of normothermia, normoglycemia, and normal oxygen saturations aimed at limiting the area of ischemic penumbra is recommended. In children with stroke with a depressed or deteriorating level of consciousness, early neurosurgical referral is recommended for assessment (consider continuous ICP monitoring) and treatment of raised intracranial pressure. If required a decompressive hemicraniectomy may need to be considered. Smith et al. have shown that decompressive craniectomy is associated with reduced mortality and moderately good outcome in children with malignant middle cerebral infarction [15]. Treatment of hypertension and hypotension in childhood AIS has not been studied. The principles of management of blood pressure in childhood AIS are to maintain adequate cerebral perfusion aiming to avoid sudden acute changes in blood pressure. Any clinical or electrographic seizures should be promptly treated with antiepileptic medication; however, routine use of prophylactic antiepileptic therapy in the absence of clinical seizures is not advocated. An assessment of safety of swallowing and nutrition should be undertaken as soon as possible in order to minimize the risk of aspiration.

Acute Specific Therapy for AIS in Children

There are three sets of published guidelines on the treatment of childhood AIS [16–18] which are based on consensus and opinion of experts in the field. The recommendations are summarized in Table 16.2.

Acute Systemic Thrombolytic Therapy

Acute treatment of stroke in adults with thrombolysis between 3 and 6 h of symptom onset is associated with better outcomes. Since the pathophysiology of AIS in children is distinct from adults, thrombolysis treatment cannot be directly applied to childhood AIS. Although there have been a few reports of the use of tissue plasminogen activator (tPA) in children with AIS, the safety and efficacy of either intravenous or intra-arterial thrombolysis in children is not known. Also, no guidance regarding indications/contraindications, dosing, or outcome is currently available. Grunewald et al. have recently summarized the available experience on thrombolytic therapy in childhood AIS [19]. Most of these data suggests high incidences of hemorrhage and complications with the use

Table 16.2 Summary of recommendations for acute medical management and secondary prevention of AIS in children

Therapy	AHA for management of stroke in infants and children	RCP	ACCP pediatric guidelines
Acute medical treatment for AIS			
Acute systemic thrombolytic therapy	Until there are additional published safety and efficacy data, thrombolysis with tPA is not recommended for children with AIS outside a clinical trial. There was no consensus in older adolescents	No guideline Comment: currently no evidence to support use of thrombolytic agents (tPA) in the acute treatment of AIS in children	No guideline Comment: the use of thrombolytic agents in children with AIS is rare, and the risk/benefit ratio is unknown at this time
Acute anticoagulation therapy	Unfractionated heparin or LMWH may be considered for up to 1 week after AIS pending further evaluation to determine the cause	Anticoagulation should be considered in children with confirmed arterial dissection and in children with cardio embolism (should be discussed with a consultant pediatric cardiologist and neurologist)	Unfractionated heparin or LMWH is recommended for 5–7 days and until cardioembolism or vascular dissection has been excluded
Sickle cell disease (SCD)	Acute management should include optimal hydration, correction of hypoxemia and hypotension For acute cerebral infarction, exchange transfusion to reduce hbS to <30 % is reasonable	Consider urgent exchange transfusion to reduce hbS to <30 % and increase hb to 10–12.5 g/dL; if the patient has had a neurological event in the context of severe anemia or if exchange transfusion is going to be delayed for >4 h, urgent top-up transfusion should be undertaken	IV hydration and exchange transfusion to reduce hb S levels to 30 %
Secondary prevention			
Anticoagulation therapy for secondary prevention	Anticoagulation with LMWH is useful for long-term anticoagulation of children with: (a) Substantial risk of recurrent cardiac embolism (b) Selected hypercoagulable states	Anticoagulation should be considered: (a) Until there is evidence of vessel healing, or for a maximum of 6 months, in patients with dissection (b) If there is recurrence of AIS despite treatment with aspirin (c) In children with cardioembolism, following discussion with the cardiologist	Anticoagulation is reasonable for: (a) Extracranial arterial dissection (b) Recurrent AIS (c) Cardioembolism (d) Antiphospholipid antibody syndrome (e) Inherited prothrombotic state with no other cause of AIS

Antiplatelet therapy for secondary prevention	Aspirin (3–5 mg/kg/day) is a reasonable option for the secondary prevention of AIS in children (*except* children with SCD or with high risk of recurrent embolism or a severe hypercoagulable disorder)	Aspirin (5 mg/kg/day) should be given once there is radiological confirmation of AIS, except in patients with evidence of hemorrhage on imaging and those with SCD Patients with cerebral arteriopathy other than dissection or moyamoya syndrome should be treated with aspirin	Aspirin (initial dose, 325 mg) within 24–48 h after onset is recommended for most patients

of thrombolysis in children. Thrombolysis in Pediatric Stroke (TIPS), a 5-year, prospective cohort, open-label dose-finding trial of the safety and feasibility of intravenous tPA to treat acute childhood AIS, is currently ongoing. Hence, until there are additional published safety and efficacy data, thrombolysis with tPA is currently not recommended for children with AIS. Mechanical thrombectomy is also not advocated as there is no safety data in children and theoretically increased risks.

Acute Treatment in AIS with Sickle Cell Disease

Optimal hydration and an exchange transfusion are recommended with the aim to reduce the hbS% to less than 30 %.

Acute Treatment for AIS Secondary to Arterial Dissection

Anticoagulation with unfractionated or low molecular weight heparin (LMWH) is recommended for treatment of extracranial arterial dissection. The AHA and ACCP guidelines recommend starting treatment with LMWH for 5–7 days in children with acute AIS of unclear origin until dissection is excluded. However, RCP guidelines recommend anticoagulation only if dissection is confirmed. Treatment with subcutaneous low molecular weight heparin should be continued for duration of 3–6 months or longer if symptoms persist. This should be monitored using anti-Xa levels. Oral warfarin may be used as an alternative for long-term anticoagulation.

Acute Treatment for AIS with Cardiac Disease

For children with a cardiac disorder at high risk of recurrent embolism, anticoagulation therapy with UFH or LMWH is recommended in the acute setting. Longer term, either anticoagulation or aspirin should be used to prevent recurrent stroke.

16.2.4.2 Secondary Prevention of AIS

AIS recurs in between 6 and 20 % of all children and in over 60 % of children with SCD. The risk of recurrence is increased in children with multiple risk factors and in those with non-atherosclerotic cerebral arteriopathies [20]. Hence, children with first episode of AIS should be monitored for evolution and morphology of cerebral arteriopathies with elective annual cerebrovascular imaging. In the event of ongoing ischemic symptoms, this may need to be repeated sooner. The form of secondary

preventive therapy should be directed by the underlying cause and associated risk factors in the individual patient.

Antiplatelet Therapy

Initiation of aspirin is recommended after all radiologically confirmed AIS for secondary prevention [21] (except children with SCD, cardioembolic disease, or a severe hypercoagulable disorder who should receive anticoagulation).

Secondary Prevention in Sickle Cell Disease (SCD)

Children with SCD with a confirmed cerebral infarction should be placed on a regular program of red cell transfusion therapy in conjunction with measures to prevent iron overload children. Data from the STOP 2 study [22] suggests that transcranial Doppler middle cerebral artery velocities returned to pretreatment levels if regular transfusion therapy is discontinued after 3 years, and hence the current recommendations are to continue lifelong transfusion therapy.

If children with SCD evolve in to moyamoya morphology of arteriopathy and continue to have neurological symptoms, revascularization surgery may need to be considered. Hydroxyurea may be considered in children and young adults with SCD and stroke who cannot continue on long-term transfusion therapy. Bone marrow transplantation may be another option for children with SCD with AIS, though lack of donors is a major practical consideration.

Secondary Prevention in Moyamoya

Moyamoya is characterized by stenosis or occlusion of the terminal internal carotid arteries with basal collateral vessels, which is associated with a high rate of recurrent AIS. Both AHA and RCP guidelines recommend that children with moyamoya and progressive ischemic symptoms should be referred to revascularization surgery based on evidence of better clinical outcome after surgery. Despite these recommendations, there is still a lack of consensus about the timing of surgery [23]. Some groups require more than one clinical or radiological event (suggesting a tendency to recurrence), while others rely on a variety of imaging parameters, including studies of cerebral perfusion and cerebrovascular reserve. If these patients undergo surgery, special care should be taken to avoid systemic hypotension, hypovolemia, hyperthermia, and hypocarbia during the intraoperative and perioperative periods to minimize the risk of perioperative stroke. Children with moyamoya are also frequently treated with aspirin to decrease the influence of a thrombotic component for recurrent stroke unless they have had hemorrhagic events.

Secondary Prevention of AIS Due to Vasculitis

CNS vasculitis can occur in isolation as a primary condition or secondary to systemic vascular diseases. The diagnosis and management in these children often involves evaluation of multiple vascular beds such as kidney, eyes, lungs, skin, and gut to determine the extent of the disease, and tissue diagnosis should be achieved if possible. These children should be managed in conjunction with a rheumatologist. The diagnosis of primary CNS angiitis is often challenging and brain biopsy has some role in these patients. Treatment of CNS vasculitis often involves long-term immunosuppression with steroids or other immunosuppressive drugs such as methotrexate or cyclophosphamide [24].

16.2.5 Rehabilitation

Early rehabilitation of children with stroke should be undertaken soon after the diagnosis in the acute setting. Physiotherapy, occupational therapy, and speech therapy assessments should be undertaken soon after the stroke. Early liaison with community services is recommended for a smooth transition to community.

16.2.6 Outcomes

Mortality from childhood AIS is around 5 %, significantly less than that associated with hemorrhagic stroke [25]. However, at least two thirds of survivors have neurological impairments. AIS can affect a wide range of neurocognitive domains, and a high proportion of children have a reduced health-related quality of life [26].

16.3 Cerebral Venous Sinus Thrombosis (CVST) in Children

16.3.1 Presenting Symptoms of CVST

Headache, seizures, and encephalopathy are the most common presenting features in children with CSVT [3]. These are usually secondary to global cerebral dysfunction and raised intracranial pressure due to impaired venous drainage. In addition, these children may also present with focal neurological signs (motor/sensory deficit, cranial nerve palsies) and seizures secondary to focal venous ischemia or hemorrhage [3].

16.3.2 Recommended Assessments for CVST

16.3.2.1 Clinical: History and Examination

Risk factors associated with CVST include dehydration, malignancy, drugs (L-asparaginase), cardiac disease, inflammatory bowel disease, and ENT infections [3]. Patients should be assessed for signs of intracranial hypertension such as papilledema, cranial nerve palsies, pupillary size, and reactivity.

16.3.2.2 Neuroimaging

CT with contrast, ideally performed as a CT venogram study, is a very sensitive test for identification of CVST. However, plain CT can be negative in up to 40 % of the cases. If clinical suspicion for CSVT is high, and CT venogram is not performed, an MR venogram (MRV) is the investigation of choice.

16.3.3 Follow-Up and Reimaging in CVST

Children with CSVT should be monitored for symptoms and signs of raised intracranial pressure. If clinical findings are persistent or progressive, repeat imaging to exclude hydrocephalus or clot propagation is recommended. In children not receiving anticoagulation, a repeat venogram study should be done in 5–7 days to assess for thrombus propagation off treatment [27]. However, other routine follow-up neuroimaging in the absence of clinical symptoms or signs is not generally productive.

16.3.4 Recommended Interventions for CVST

Acute supportive measures include treatment of seizures, dehydration, and underlying infection if present. Early identification and treatment of raised intracranial pressure can be life saving. Decompressive surgery may need to be considered in those with malignant intracranial hypertension [28].

16.3.4.1 Acute Specific Treatment of CVST

Recently published AHA guidelines on CVST recommend anticoagulation with LMWH in children and neonates with CSVT [27] based on better clinical

outcomes associated with treatment [3]. The presence of intracranial hemorrhage or hemorrhagic transformation seen in a third of cases with CVST is not a contraindication for anticoagulant therapy. Anticoagulant therapy with low molecular weight heparin should be continued for 3–6 months or longer if symptoms persist. Oral warfarin may be used as an alternative. In children with CVST who are not treated with anticoagulation, thrombus propagation is documented in approximately 25 % and is associated with increasing brain infarction and worse clinical outcome [29].

16.3.4.2 Role of Endovascular Thrombolysis in CVST

Although there are some anecdotal reports on the use of endovascular thrombolysis in CVST with rapid recanalization and good neurological outcome in adults and children [30], the exact role of thrombolysis in the management of CVST is currently unclear, especially with regard to patient selection, optimal timing, and contraindications to this therapy. Hence, there is insufficient evidence to recommend this in the pediatric age group at this stage, although it could be considered in older children whose thrombosis is progressive despite adequate anticoagulation.

16.4 Hemorrhagic Stroke

Acute nontraumatic hemorrhagic stroke in children is associated with high mortality and morbidity. The hemorrhage is often secondary to underlying vascular malformations. In a recently published population-based study of 116 children with nontraumatic hemorrhagic stroke, 15 (13 %) were found to have underlying cerebral aneurysms, 35 (31 %) brain arteriovenous malformations, 17 (15 %) cavernous malformations, 16 (14 %) medical etiologies, 3 (2.5 %) brain tumors, and 29 (25 %) undetermined etiology [31].

16.4.1 Hemorrhagic Stroke: Description of Presenting Symptoms

Affected children often present with diffuse acute onset symptoms such as headache, vomiting, coma, and seizures; focal deficit may be detected on examination. Family history of sudden deaths due to spontaneous intracranial or pulmonary bleeding may be suggestive of hereditary hemorrhagic telangiectasia or familial aneurysmal disease.

16.4.2 Recommended Assessments of Hemorrhagic Stroke

16.4.2.1 Clinical Evaluation

In addition to a complete neurological examination, a thorough cutaneous examination should be done to look for any evidence of telangiectasia, which may suggest hereditary hemorrhagic telangiectasia as an underlying cause. Clinical evaluation should include assessment of conscious level, measurement of blood pressure, and raised intracranial pressure, which is the most common cause of death in this group.

16.4.2.2 Neuroimaging

Children with nontraumatic hemorrhagic stroke should be initially evaluated with an urgent CT brain and CT angiography. These patients may have a subarachnoid, intracerebral, intraventricular hemorrhage, or a combination of these. Adolescents with a pure subarachnoid hemorrhage are more likely to have an underlying aneurysm [31]. All patients with nontraumatic hemorrhagic stroke should subsequently be evaluated for underlying vascular malformations like arteriovenous malformation or aneurysms using a cerebral angiography [17]. If initial cerebrovascular imaging is negative, it is important to recognize that a vascular malformation cannot be excluded without undertaking a delayed catheter angiogram. MRI is the best technique to explore cavernomas where angiography is generally not contributive due to the occult nature of the malformation [32].

16.4.3 Recommended Interventions for Hemorrhagic Stroke

16.4.3.1 Acute Supportive Care

The principles for acute management are similar to those outlined in acute supportive management of AIS. A significant proportion of these children may need to be cared on intensive care units for neuroprotection and monitoring of intracranial pressure. Raised intracranial pressure may need to be treated neurosurgically; the STICH trial [33] does not demonstrate better outcomes in patients who routinely had urgent hematoma evacuation, but this may need to be undertaken in some cases.

16.4.3.2 Acute Specific Treatment for Nontraumatic Hemorrhagic Stroke

These children may need urgent specific treatment for the underlying malformation if there is ongoing risk of acute bleeding in the form endovascular glue/coil

embolization for AVMs or aneurysms. If an underlying coagulation disorder is detected, replacement with appropriate factors should be initiated.

16.5 Perinatal Stroke

Perinatal stroke has an estimated incidence of 1 in 1,500 to 1 in 5,000 live births and includes both ischemic and hemorrhagic infarcts from early gestation through the first month of life that eventually lead to hemiplegic cerebral palsy [34]. Perinatal stroke includes acute neonatal stroke (cerebral infarction occurring within 28 days of birth) and presumed perinatal ischemic stroke (PPIS) which defines children presenting outside a normal perinatal period with chronic, focal infarction on neuroimaging. The etiology of perinatal stroke is diverse and includes AIS, CVST, and hemorrhagic strokes [34]. The frequency of each of these may vary in term infants compared to preterm infants.

16.5.1 Description of Presenting Symptoms for Perinatal Stroke

Most of the perinatal strokes are recognized in the neonatal period due to early onset seizures, although symptoms can be more subtle leading to a significant delay in the diagnosis. Seizures are more frequently late (12–24 h) and focal compared to seizures due to neonatal hypoxic ischemic encephalopathy. Children with PPIS are not recognized until later infancy when they present with early hand preference or developmental delay.

16.5.2 Recommended Assessments for Perinatal Stroke

16.5.2.1 Clinical Evaluation

A clear history for risk factors associated with perinatal stroke should be obtained. These include maternal risk factors such as chorioamnionitis, placental abnormalities, premature rupture of membranes, and preeclampsia.

Infant-related risk factors include birth trauma, intrauterine growth retardation, twin gestation, infection, cardiac disorders, and coagulation/prothrombotic disorders. Presence of multiple risk factors is common and increases the risk of perinatal stroke [34]. Thrombophilic disorders have been reported as a risk factor in several studies of perinatal stroke and a comprehensive thrombophilia screen is recommended [35].

16.5.2.2 Neuroimaging

This is an essential part of assessment in children with suspected perinatal stroke. The modality of imaging used is dependent on the clinical condition of the neonate. Cranial ultrasound (CUS) is often readily available and is sensitive for detection for hemorrhagic strokes and may also detect some ischemic lesions. However, CUS is frequently normal in neonates with CVST or AIS. CT brain is a useful alternative in an acutely sick neonate and will detect intracranial hemorrhage and AIS, but may also be normal in early AIS. MRI with MRA is the definitive investigation of choice and should be undertaken if the suspicion of perinatal stroke is high. MRI with diffusion-weighted imaging helps with improved visualization and precise characterization of the extent and location of the infarct, which may be useful in predicting outcome.

16.5.3 Recommended Interventions for Perinatal Stroke

The principles of acute supportive care are similar to those in older children with AIS and CVST as discussed above. Neurosurgical intervention for hematoma evacuation or ventricular drainage may be required in neonates with severe raised ICP. The optimal therapy for neonates with AIS or CVST has not been determined. Severe thrombocytopenia, clotting factor deficiency, or vitamin K deficiency, if present, should be treated. The role of anticoagulant therapy remains unclear, but may be useful in neonates with severe prothrombotic disorders or cardiac disorders.

Anticoagulation therapy in neonates with CVST is controversial due to concerns regarding increased risk of hemorrhage. However, recent data indicate that anticoagulation with LMWH is safe in neonates and that neonates who do not receive anticoagulation frequently (33 %) demonstrate propagation of their thrombus [29]. Treatment with LMWH or UFH may be required even in the setting of intracranial hemorrhage in the event of propagation of the thrombus or if there is confirmation of a hypercoagulable state. Recently published AHA guidance on CVST recommends consideration of treatment with LMWH for 6 weeks to 3 months in neonates with acute CVST based on several case series and large observational studies [27].

16.5.4 Outcome of Perinatal Stroke

Children with perinatal stroke often develop long-term disabilities including motor deficits, cognitive and behavioral disorders, and epilepsy. More than half will develop long-term motor or cognitive problems, and the recurrence rate after perinatal stroke is very low [34].

16.6 Conclusions and Directions for Future Research

Despite the several published clinical guidelines on childhood AIS and venous sinus thrombosis, the majority of the literature on treatment of childhood stroke is extrapolated from adult literature reflecting the lack of evidence in children. Good multicenter pediatric studies with an international collaborative effort (e.g., International Pediatric Stroke Study) are needed with precise categorization of underlying stroke syndrome to systematically study these disorders and acquire useful data on diagnosis and efficacy of treatments used. At the same time, investigation of underlying pathogenesis and disease mechanisms causing childhood arteriopathies and stroke in children will provide a useful insight and help to provide new therapeutic options.

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Chapter 17
Viral Infections and Autoimmune and Demyelinating Conditions of the Central Nervous System

Marc Tardieu, Ariane G. Soldatos, and Mark P. Gorman

Abstract Although individually uncommon, infectious, inflammatory, and autoimmune conditions collectively comprise an important subset of acute pediatric neurology. In this chapter, we discuss encephalitis, transverse myelitis, and optic neuritis. We discuss both a general initial approach to diagnosis and management prior to a specific diagnosis being made, as well as characteristic features of some of the most important entities, including herpes simplex virus encephalitis, enterovirus encephalitis, Lyme disease, acute disseminated encephalomyelitis, transverse myelitis, and optic neuritis.

Keywords Encephalitis • Herpes simplex virus • Enterovirus • Lyme disease • Mycoplasma • Acute disseminated encephalomyelitis • Transverse myelitis • Optic neuritis

17.1 Terminology and Classifications

Encephalitis, myelitis, and optic neuritis refer to pathological inflammation of the brain, spinal cord, and optic nerve parenchyma, respectively. In the clinical setting, pathological specimens are rarely obtained and, therefore, the diagnosis of "acute

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encephalitis" is used when a child, typically previously healthy, rapidly develops neurological symptoms over hours to days, frequently in association with signs suggesting an inflammatory origin such as fever and meningism. Myelitis, and much less frequently optic neuritis, can accompany encephalitis or occur as an isolated process. Data supporting an inflammatory cause often, but not always, includes abnormal cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) results.

Although a consensus definition for acute encephalitis has not been formally developed, the case definition of the California Encephalitis Project (CEP) is useful. In the CEP, patients are diagnosed with encephalitis in the setting of encephalopathy (depressed or altered level of consciousness lasting 24 h or more, lethargy, or change in personality) or ataxia, if they also have one or more of the following: temperature of 38 °C or higher, seizure(s), focal neurological findings, CSF pleocytosis, and abnormal electroencephalogram (EEG) or neuroimaging study [1].

From the list of greater than 100 infectious pathogens which can cause encephalitis, clinicians must select the most likely ones based on the clinical context, laboratory results, and neuroimaging findings. This list also varies greatly depending on the geographic region where the patient resides or has traveled. In this chapter, we focus on the most common causes of infectious encephalitis, namely, herpes simplex virus (HSV) and enterovirus, which occur worldwide. In Chap. 13 mycoplasma encephalitis is discussed, as well as Lyme disease, which varies greatly depending on geography but is of major importance in endemic regions in North America and Europe. A more comprehensive list can be found in Chap. 13 (Table 13.4) and the Infectious Disease Society of America guidelines [2]. Of the many infectious agents which we will not discuss, Japanese encephalitis virus and dengue virus are particularly important in endemic regions and have been recently reviewed by authors with direct experience with these conditions [3, 4]. West Nile virus encephalitis has also taken on global importance, but will not be discussed in detail [5].

In addition to direct infections of the central nervous system, inflammatory and autoimmune causes have emerged as an important subtype of encephalitis. Some patients with autoimmune encephalitis have a diagnostic biomarker, such as a specific autoantibody. In other patients, an inflammatory or autoimmune cause may be suspected based on the presenting phenotype, neuroimaging findings, the absence of an identified CNS infection, and nonspecific markers of autoimmunity, such as CSF oligoclonal bands. In this setting, consensus definitions for recognizable disorders, such as acute disseminated encephalomyelitis (ADEM), transverse myelitis, and optic neuritis, are useful [6].

Although the final diagnosis of encephalitis is typically reserved for patients with an infectious, inflammatory, or autoimmune cause, some initially diagnosed patients may ultimately prove to have a different cause. Finally, there is large group of patients, as many as 63 % in the largest published cohort, of children and adults, with "presumed encephalitis" who do not have a definitive cause identified [1]. Further research is required to determine whether the encephalitis in this group is due to an as yet unknown microbe, autoimmune mechanism, or other causes. Thus, acute encephalitis is a broad and provisional diagnosis that covers many different clinical entities.

In this chapter, we will focus on infectious, inflammatory, and autoimmune causes of acute encephalitis in immunocompetent children. Acute meningitis,

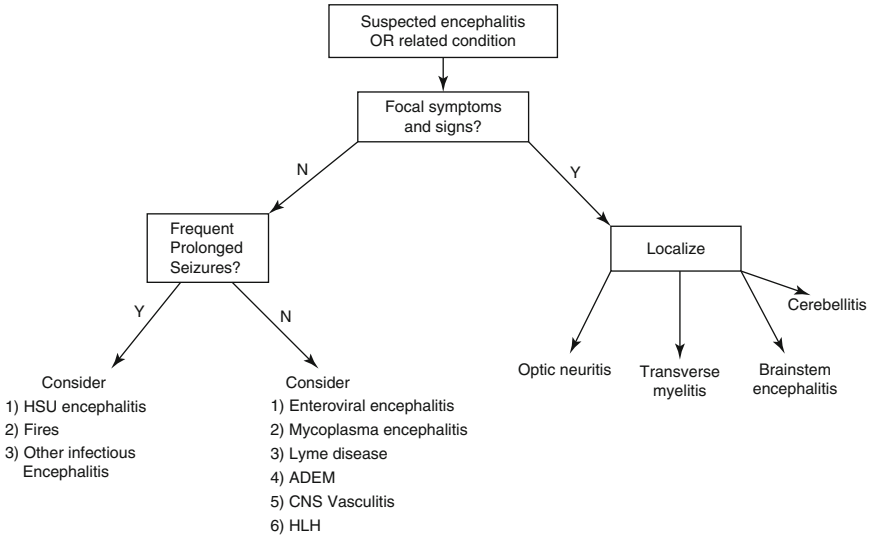

Fig. 17.1 Algorithm for differential diagnosis of suspected encephalitis and related conditions

in which the pathological process is confined to the leptomeninges, may cause altered consciousness and is covered in Chap. 13. Some patients may have overlapping conditions, termed "meningoencephalitis."

When acutely faced with patients with suspected encephalitis and related conditions, we propose a clinical approach based on an initial determination of whether monofocal symptoms and signs are present or absent based on history and exam (Fig. 17.1). We here combine "nonspecific disorders" and "multifocal disorders" as those with symptoms and signs which do not readily lead the clinician to a monofocal localization in the central nervous system. Common symptoms of many of the disorders in this group include fever, altered consciousness, and headache. We will divide this group based on the presence of prolonged or frequent seizures in typical cases, with an arbitrary cutoff set at 50 % based on the largest reported series, although all of these conditions can have associated seizures. In addition, some of the "nonspecific disorders" may have focal or multifocal symptoms, signs, and EEG and MRI abnormalities, but these are often obscured, especially in the acute setting, due to accompanying global alteration of consciousness.

We will also consider "monofocal disorders," which are more easily recognized based on symptoms and signs referable to a single location in the CNS, and may or may not include altered consciousness, depending on the affected region. Although some of the monofocal disorders, such as optic neuritis, do not typically fall within the category of encephalitis, we included these disorders in this chapter due to overlapping presentations and pathophysiological processes. Although critically important in making a final diagnosis, we chose not to include MRI results in the initial approach to suspected encephalitis because it is frequently not available in the acute setting.

17.2 General Acute Approach to Assessment and Interventions

When evaluating a patient with suspected encephalitis, myelitis, and/or optic neuritis, a rapid but comprehensive history should be obtained, and a determination of whether the major symptoms are monofocal is made (Fig. 17.2). The immune status of the patient (immunizations, immunocompromised state), geography (including travel), and exposures (such as animals, insects, and sick contacts) should also be sought. In conjunction with the season of year, these features can significantly shorten the list of likely pathogens. A personal or family history of autoimmunity should also be directly questioned.

A complete neurological exam should be performed to further the nonspecific versus monofocal distinction. Signs of increased intracranial pressure, such as papilledema, should be specifically sought. Although the general physical exam is typically normal, it may provide clues to the underlying diagnosis.

If symptoms or signs of increased intracranial pressure are present, emergent computed tomography (CT) of the head is recommended to rule out contraindications to lumbar puncture (LP), which should then be rapidly obtained. CSF should be sent for gram stain and bacterial culture, cell counts, glucose, and protein. Basic

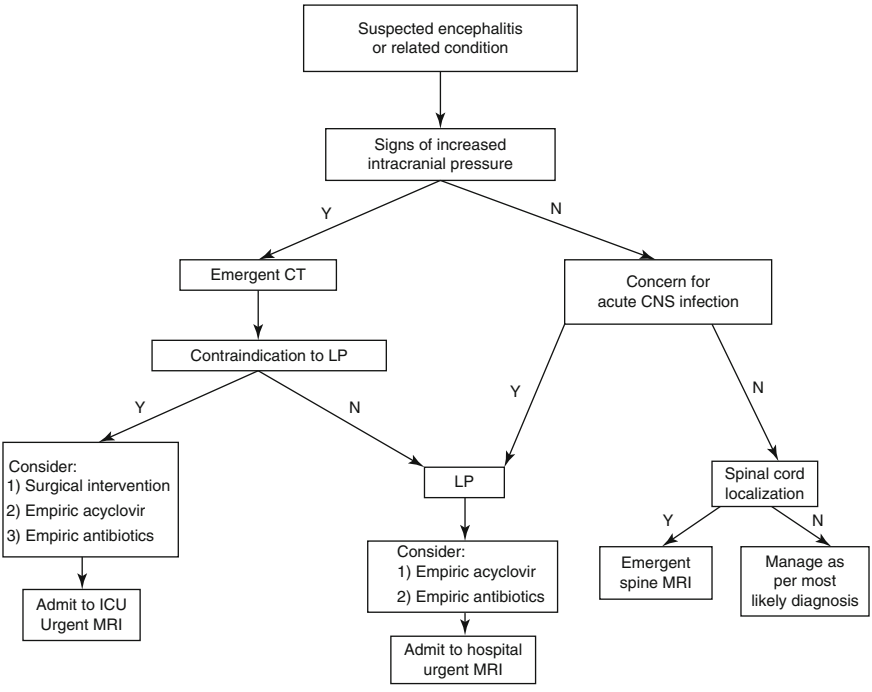

Fig. 17.2 Algorithm for initial management of suspected encephalitis and related conditions

blood tests should include complete blood counts, blood cultures, comprehensive metabolic panel, coagulation studies, and toxic screens when appropriate. Additional testing on CSF and blood should be guided by the clinical presentation and epidemiologic clues, especially geographic region, with an emphasis on the most common and potentially treatable conditions. Collecting and freezing additional CSF to be available for later use can be valuable, if initial testing is unrevealing or more clues subsequently emerge pointing to a specific cause.

If herpes simplex encephalitis is being considered based on the clinical presentation detailed below, empiric acyclovir should be rapidly started and continued until CSF HSV PCR results are available or additional data, particularly MRI results, make this condition unlikely. If bacterial meningitis is possible based on the initial presentation, empiric antibiotics should also be strongly considered. Use of corticosteroids in the acute phase is generally not recommended but may be started later if specific inflammatory or autoimmune causes are identified.

Seizures should be managed in the usual manner (see Chaps. 2 and 11). If there is abnormal mental status and nonconvulsive status epilepticus is being considered, emergent electroencephalogram (EEG) may be needed. All patients with encephalitis should be admitted to the hospital with a low threshold for intensive care unit admission. Finally, oxygenation, temperature, blood glucose, and sodium and fluid balance should be carefully assessed and managed appropriately to avoid superimposed brain injury. Once all of the above emergent issues have been addressed, brain MRI with and without gadolinium should be performed as soon as feasible as the findings can have significant diagnostic value, even if a CT scan was obtained, as MRI has greater sensitivity. If spinal cord or optic nerve pathology is also suspected, dedicated MRI of those regions should also be performed, preferably at the same time, especially in children who require sedation.

17.3 Disorders with Nonspecific or Multifocal Presentations

17.3.1 With Seizures as a Major Finding

17.3.1.1 Herpes Simplex Virus Encephalitis

Presentation

Herpes Simplex Viruses (HSV) are ubiquitous enveloped, double-stranded, DNA viruses. In childhood, HSV type 1 primary infection most commonly causes gingivostomatitis or no obvious symptoms. HSV-1 seropositivity increases from approximately 20 % in 1- to 3-year-old to 60 % in 13- to 15-year-old children [7]. After primary infection, HSV-1 remains latent lifelong in the trigeminal ganglion. HSV-2 infection is generally rare in children.

Neonatal HSV encephalitis is a distinct entity and will not be covered in detail here. Outside of the neonatal period, HSV encephalitis is almost universally caused by HSV-1, typically during a primary infection in children, rather than from reactivation of latent virus as occurs in adults. Within the pediatric age range, most cases occur between 6 months and 3 years, with a median age of 1.5 years in a French series of 85 patients [7]. Initial symptoms in the same study included fever >38.5 °C and seizures in more than 90 % of patients. Of note, most patients with HSV encephalitis do not have associated herpetic skin lesions.

Indeed, these symptoms are nonspecific and overlap with febrile seizures, as do other etiologies of encephalitis discussed below. Therefore, although they are covered in detail in Chaps. 2 and 11, we will briefly discuss febrile seizures. Most importantly, the diagnosis of idiopathic febrile seizures should be restricted to the age range of 6 months to 5 years. CNS infection or inflammation should be strongly considered as the cause for seizures in the setting of fever outside of this age range. Within this age range, the presence of altered consciousness outside of the expected postictal state should also significantly increase the concern for a cause other than idiopathic febrile seizures.

Assessment

In HSV encephalitis, CSF profile typically will show a lymphocytic pleocytosis and elevated protein, but as many as 21 % of pediatric patients can have normal findings, particularly when LP is performed very early in the disease [7]. Thus, CSF HSV PCR is the mandatory diagnostic test of choice. It can be negative within 72 h of illness onset and therefore should be repeated if clinical suspicion remains.

If febrile seizure is the leading diagnosis and none of the above concerns are present, neurological investigations are not necessary. However, if concerns about the age of onset or presentation exist in a child who has not previously experienced idiopathic febrile seizures, LP to exclude meningoencephalitis as the etiology is mandatory. In particular, we recommend that all children less than 6 months of age with fever and seizures undergo LP. One study of 390 episodes of complex febrile seizures in children aged 6–72 months found overall rates of 1.5 % for bacterial meningitis and 0.3 % of herpes simplex encephalitis [8]. All of the children with CNS infection had an abnormal mental status exam, confirming the value of this finding when deciding whether a LP is necessary.

In HSV encephalitis, neuroimaging classically shows unilateral involvement of the temporal lobe (Fig. 17.3a), but the parietal lobe can also be affected and bilateral lesions can be present (Fig. 17.3b). MRI was abnormal in all 13 patients in whom it was obtained in the French series, compared to 71 % of CT scans [7]. Similarly, EEG often shows abnormal activity in the temporal lobes, with periodic lateralized epileptiform discharges being considered a classic finding.

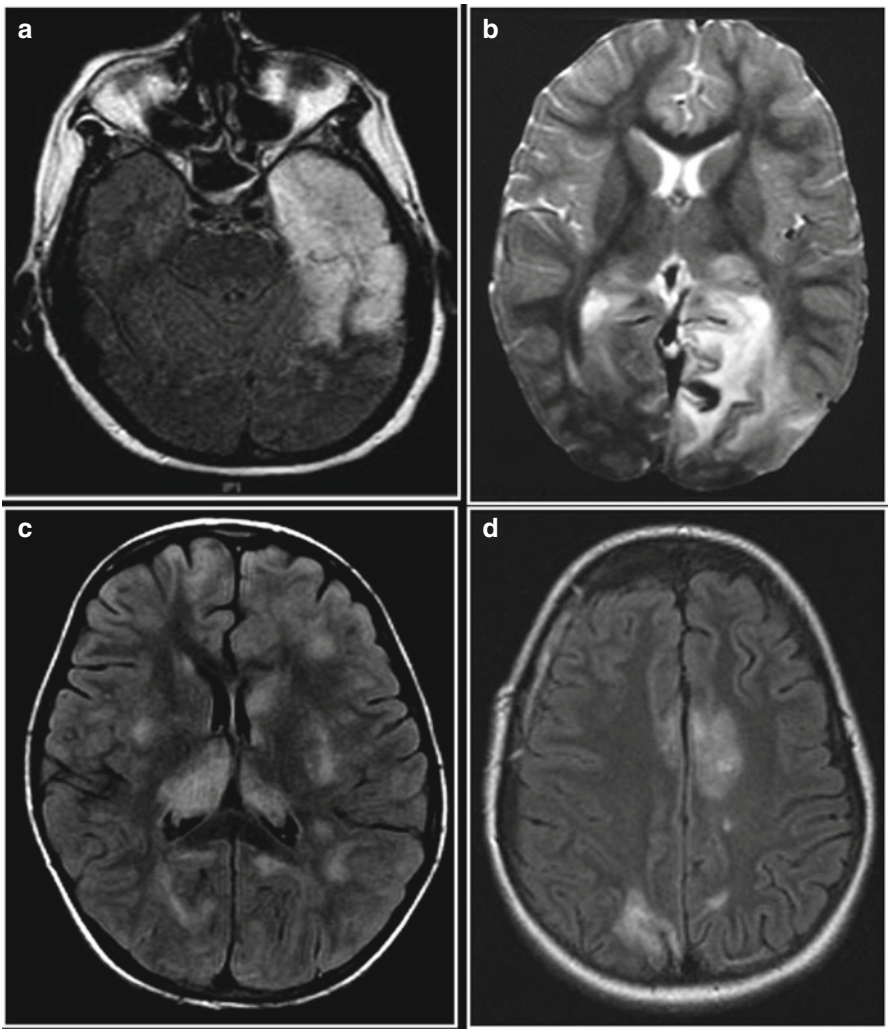

Fig. 17.3 (**a**) Herpes simplex encephalitis: Axial FLAIR MRI showing severe hyperintensity affecting the left temporal cortex and subcortical white matter in a patient who presented with fever, seizures, and altered consciousness. (**b**) Herpes simplex encephalitis: T2-weighted MRI showing hyperintensity in the left parietal and occipital lobe, showing extra-temporal involvement can occur outside of the neonatal period. (**c**) Acute disseminated encephalomyelitis (ADEM): Axial FLAIR MRI showing multifocal, asymmetric hyperintense lesions affecting the subcortical and deep white matter, basal ganglia, and cortex in a patient who presented with altered consciousness, weakness, and ataxia whose course was consistent with ADEM. (**d**) Small vessel CNS vasculitis: Axial FLAIR MRI showing multifocal, asymmetric hyperintense lesions with prominent cortical and subcortical white matter hyperintense lesions in a patient who presented with headaches, weakness, and cognitive changes whose brain biopsy was consistent with small vessel CNS vasculitis

Intervention

If HSV encephalitis is suspected, empiric acyclovir should be started until CSF HSV PCR is resulted negative. If the initial CSF PCR is negative and high clinical suspicion persists, the patient should be maintained on acyclovir until a repeat CSF PCR result to exclude the possibility of an initial false negative.

The recommended treatment for HSV encephalitis is intravenous acyclovir for 21 days. For neonates up until 12 years of age, we recommend using 60 mg/kg per day, in three divided doses. For patients older than 12 years of age, 30 mg/kg/day in three divided doses should be used. For cases of severe cerebral edema, steroids or decompressive craniotomy have been considered.

For patients in whom febrile seizures are considered, who undergo LP and who are found to have CSF pleocytosis, we recommend empiric antibiotics and acyclovir as described above until CSF culture and HSV PCR results are available.

Outcome

Acyclovir has reduced mortality from >70 % to as low as 2.5 % in children [7]. However, despite a median delay of only 2 days between the onset of fever and initiation of acyclovir treatment in the French series, 56 % of 51 patients with long-term follow-up had epilepsy and 73 % had cognitive impairment [7].

17.3.1.2 Human Immunodeficiency Virus (HIV) Encephalopathy

It is estimated that 2.5 million children worldwide were diagnosed with HIV-1/AIDS in 2009, of whom 90 % lived in sub-Saharan Africa. Before the advent of antiretroviral (ARV) therapy, neurological involvement was reported in 50–60 % of children, with it being the initial manifestation in up to 18 % of children. Although the frequency of neurological manifestations in settings where ARV are widely available has declined, neurological involvement continues to have significant clinical and educational consequences for many children, particularly those in resource-limited settings.

Presenting Signs and Symptoms

HIV encephalopathy (HIVE) occurs in up to a quarter of infected children, lower with the introduction of ARVs [9]. It is characterized by neurodevelopmental delay, poor brain growth (manifesting as microcephaly and/or cerebral atrophy), motor impairment with spasticity, pseudobulbar palsy, ataxia, and other cerebellar signs, movement disorders, seizures, myoclonus, and behavioral problems. Early infection of the CNS (in utero or at birth) and greater viral load during early infancy are associated with more severe encephalopathy. The CNS manifestations may precede the

development of the features of AIDS and can occur in a relatively immunocompetent child. Expressive language appears to be more impaired than receptive language.

HIVE can be progressive or static. Subacute progressive encephalopathy manifests as progressive global regression, with loss of skills over a period of months. A plateau may occur in which the acquisition of new skills slows or stops, but previously acquired milestones remain. Children with static encephalopathy acquire skills more slowly than normal children.

Behavioral problems such as attention-deficit/hyperactivity disorders (ADHD), anxiety disorders and depression, conduct disorders, and oppositional defiant disorders are reported.

Opportunistic infections (OI) that are most commonly seen are acute bacterial meningitis (ABM), tuberculous meningitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), toxoplasma encephalitis, and cytomegalovirus (CMV) encephalitis. ABM is most commonly caused by *S. pneumoniae* and *H. influenzae*. Tuberculosis is common in many resource-poor countries, where it frequently coinfects HIV-infected individuals. There is an interaction between antituberculosis drugs and ARV, with recommendations available from the CDC: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm. ART may also result in reconstitution of antimycobacterial immune responses, which lower the subsequent risk of developing TB in HIV-infected patients. The typical neuroimaging findings of TBM (hydrocephalus and basal enhancement) are less evident in HIV.

Cytomegalovirus encephalitis manifests as a subacute or chronic encephalitis, ventriculitis, acute ascending radiculomyelitis, or acute or subacute neuropathy. Herpes simplex and varicella-zoster viruses cause encephalitis in children. Progressive multifocal leukoencephalopathy, caused by a human Polyomavirus, is rarely reported. Toxoplasma encephalitis is rare. Fungal meningitis is less common in children than in adults.

Lymphoma is the most common (space-occupying lesion) SOL in children and needs to be differentiated from tuberculoma. The primary lymphomas are often high-grade, multifocal B-cell tumors. Children present with subacute onset of change in mental status or behavior, headaches, seizures, and new focal neurology. Outcome is poor.

Cerebrovascular disease, presenting as either hemorrhage or ischemic strokes, is the most common cause of focal neurological deficits in children with HIV-1. Ischemic strokes may arise from embolism or acquired protein C or protein S deficiencies or secondary to vasculitis (e.g., VZV). A characteristic vasculopathy involves aneurysmal dilatation of vessels of the circle of Willis, with or without ischemic infarction or hemorrhage. Some patients with such a dilatation evolve a Moyamoya-like syndrome. Lipodystrophy is associated with cerebrovascular disease.

Peripheral neuropathies are characterized by a distal sensory or axonal neuropathy, which is directly related to HIV-1 infection, and can be aggravated by ARV. Acetyl-L-carnitine or gabapentin may be helpful. Acute and subacute demyelinating neuropathy due to HIV-1 infection is relatively unusual in children with HIV, occurring either at the time of seroconversion or as part of an immune reconstitution syndrome.

Myopathies can be caused by the HIV itself, ARV (ZDV and d4T), OIs, or lymphoma.

Mitochondrial toxicity is related to ARV (d4T and ddI), presenting with neuropathy, myopathy, lactic acidosis, cardiomyopathy, lipoatrophy, pancreatitis, and bone marrow suppression.

Immune reconstitution inflammatory syndrome (IRIS) is a frequent, occurring within the first few weeks of starting ARVs. It may be precipitate by *Mycobacteria* sp., HSV, VZV, JC virus, and *C. neoformans*. It may manifest as progressive multifocal leukoencephalopathy, opisthotonus-myoclonus, and acute inflammatory demyelinating polyradiculoneuropathy. Corticosteroids may be useful.

Seizures may be related directly to viral damage or may be secondary to OI, tumors, cerebrovascular disease, drug toxicity, and metabolic derangements. There are considerable interactions between ARV and antiepileptic drugs (AEDs). Some AEDs (phenytoin, phenobarbital, and carbamazepine) induce cytochrome p450 complex, resulting in subtherapeutic ARV levels with treatment failure. Other ARVs (e.g., protease inhibitors) may cause toxic levels of AEDs. Gabapentin, topiramate, tiagabine, and pregabalin have no effects on the cytochrome p450 system. Lamotrigine and levetiracetam are recommended in North America. Sodium valproate is used in resource-poor countries.

Recommended Assessments

HIV infection is diagnosed on serology. Other assessments include searching for other infections, particularly tuberculosis.

Recommended Interventions

Antiretroviral (ARV) drugs have made a significant impact on the CNS manifestations of HIV. Regimens usually include drugs with different mechanisms to prevent the development of resistance, and new regimens are being developed (http://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0/). However, many ARVs do not penetrate into the CNS. Nucleoside reverse transcriptase inhibitors (NRTIs) such nevirapine, azidothymidine, and abacavir enter the CNS, but the protease inhibitors (except indinavir/ritonavir, lopinavir) have poor penetration.

Prevention of OI is important (http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf).

Nutritional support is important and may prevent and improve neurological features of HIV.

Outcome

With the advent of ARVs, the prognosis of HIV infection of the CNS is good, provided that complications such as OI and lymphoma can be avoided.

17.3.1.3 FIRES (Fever-Induced Refractory Epileptic Encephalopathy in School-Aged Children)

Presentation

There are various acronyms in the literature worldwide describing a common phenotype of previously healthy and developmentally normal children who present with a mild febrile respiratory or gastroenteric illness and then develop severe refractory seizures, usually including status epilepticus, often leading to treatment with medically induced coma, with absence of extra-neurological major organ dysfunction. This has been described as FIRES (febrile infection-related epilepsy syndrome), DESC (devastating epileptic encephalopathy in school-aged children), NORSE (new-onset refractory status epilepticus), and AERRPS (acute encephalitis with refractory, repetitive partial seizures). In a recent retrospective multicenter study of 77 patients, the median age of presentation was 8 years [9]. Ninety-six percent of patients had a prodromal febrile illness, with fever preceding the onset of seizures by an average of 4 days. The seizures are usually partial onset in the temporal and/or frontal regions, with or without secondary generalization, are extremely difficult to control, and usually lead into status epilepticus and/or occur up to hundreds of times per day [9]. Most patients have a very protracted intensive care stay and hospitalization, with a median duration of mechanical ventilation of 41 days [9]. In most cases, the etiology of FIRES remains elusive, although immunologic mechanisms have been most often proposed in the literature.

Assessment

In the above study, CSF pleocytosis was present in 57 % of patients, but CSF WBC count was <10 cells/mm^3 in 65 % of such cases [9]. Oligoclonal bands were present in 4 of 12 patients tested. Initial brain MRI was normal in 55 % and showed hyperintense signal in the hippocampi and/or peri-insular regions in the remainder [9]. Extensive infectious, immunologic, and neurometabolic work-ups are generally unrevealing. However, anti-glutamic acid decarboxylase (GAD) and anti-voltage-gated potassium channel (VGKC) complex antibodies have been detected in a few patients [9]. Thus, in addition to basic CSF testing and brain MRI, we recommend sending serum and CSF autoantibody panels in all patients with FIRES.

In children, other acute encephalopathies with anti-neuronal antibodies include anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, which can include refractory seizures. However, more than 80 % of 32 patients less than 19 years old in one series had prominent psychiatric symptoms and a movement disorder, which distinguish this condition [10]. In the same series, 31 % of girls had an ovarian teratoma as part of a paraneoplastic process. Thus, appropriate imaging should be performed to look for an associated tumor in patients with NMDA receptor encephalitis.

Because of the severity of FIRES and the usually elusive etiology, brain biopsy is often considered. In a recent case series of pediatric small vessel CNS vasculitis (discussed below), two patients with a presentation similar to FIRES were diagnosed on the basis of a non-lesional brain biopsy despite normal brain MRI [11].

However, brain biopsy was normal or showed nonspecific gliosis in 12 of 13 patients in the large case series of FIRES patients; one patient had leptomeningeal inflammation [9]. Thus, the role of brain biopsy in FIRES and the relative contribution of small vessel CNS vasculitis to the etiology are unclear and require further study. The authors strongly consider brain biopsy in patients without detectable autoantibodies, particularly in the rare patients with a single epileptic focus, in order to assess for inflammatory changes as well as an occult brain malformation.

Intervention

Although efforts to control seizures are appropriate, no conventional antiepileptic drugs are helpful. Many patients are treated with medically induced coma, usually titrated to burst suppression on EEG. The effectiveness of this approach remains unclear as many patients relapse on tapering the agents. Some providers have moved away from this approach due to concern for adverse effects [9]. Empiric immunomodulatory treatment is often ineffective, but a few reported patients have responded to steroids or intravenous immunoglobulin [9]. One of the authors (MT) utilizes early plasmapheresis. In general, despite lack of clear evidence, we advocate very early immunomodulation as some patients likely have an autoimmune cause and rare patients may have an identifiable autoantibody. The ideal choice of treatment and timing of initiation is unclear.

Outcome

The prognosis of FIRES is poor with death in the acute phase in 12 %, refractory epilepsy in 93 % of survivors, and normal cognition in very few [9].

17.3.2 May or May Not Have Seizures

17.3.2.1 Enteroviral Encephalitis

Presentation

Enteroviruses include poliovirus serotypes 1–3 (see below), non-polio enteroviruses (Enterovirus, echovirus, Coxsackie virus A, Coxsackie virus B, and hepatitis A to D viruses), and the newly reclassified human parechoviruses. The central nervous system manifestations include meningoencephalitis and anterior motor horn-tropic (polio-like) myelitis. In a combined adult and pediatric case series of 73 patients with enteroviral encephalitis from the California Encephalitis Project, the presentation was generally milder than other viral or nonviral causes of encephalitis, with less frequent occurrence of alteration of consciousness [12]. In the CEP,

patients with EV encephalitis were younger than those with other causes of viral encephalitis, with a median age of 12–15 years. Cases peaked in the summer and fall seasons. Common symptoms included lethargy (62 %), altered consciousness (49 %), and seizures (30 %) [12]. EV71 is a particularly virulent serotype which can be fatal and has been implicated in outbreaks [5].

Assessment

CSF should be sent for PCR for enteroviruses. However, the enterovirus may be only transiently present in the CSF even by PCR leading to negative results. Therefore, it is important to look for systemic evidence of enteroviral infection using PCR of pharyngeal and rectal specimens.

Intervention

Treatment is supportive. The anti-picornaviral pleconaril has not been shown to improve outcome, but has been used on a compassionate basis for severe cases.

Outcome

As above, enteroviral encephalitis is generally milder than other viral causes of encephalitis. However, the mortality in the CEP cases was 9 % [12], indicating that it can be a very serious illness. The long-term outcome of enteroviral encephalitis in children is not well studied.

17.3.2.2 Poliomyelitis

Poliomyelitis is caused by polioviruses type 1, 2, and 3 which are ingested and multiply in the tonsils and the Peyer's patches of the gut. In most cases the infection is asymptomatic. In a minority of children a viremia will cause nonspecific symptoms (nausea, vomiting, abdominal pain, and sore throat).

Presenting Signs and Symptoms

CNS complications occur in some children after an incubation period of 10–14 days and manifest in two syndromes:

- Non-paralytic poliomyelitis: the child develops fever, headache, and then 2–5 days later signs of meningeal irritation and severe pain and stiffness of the neck, back, and limbs occur.

- Paralytic poliomyelitis: the paralysis occurs within the first 2 days of the onset of the febrile illness and can affect any muscles but particularly those of the lower limbs. The paralysis is characteristically asymmetrical with the flaccid muscles and absent tendon reflexes. Sensation is intact. The paralysis is maximal within 3–5 days of onset and rarely extends once the temperature is settled. In the bulbar form, involvement of the cranial nerve nuclei and vital centers in the brainstem result in paralysis of the facial, pharyngeal, laryngeal, and tongue muscles, causing swallowing difficulties and aspiration. Hypertension and respiratory failure may also occur and prove fatal.

Recommended Assessments

The CSF initially shows a neutrophilic predominance but after 5–7 days is mainly lymphocytic. Virus can be isolated from throat and stool for up to 3 months after the onset.

Recommended Interventions

There is no specific treatment.

Supportive Care

Bed rest, with the avoidance of injections and exercise during the acute phase. Analgesic is given for the severe pain. Respiratory paralysis will require ventilatory support, bulbar paralysis, nasogastric tube feeding, and possibly tracheostomy. During the convalescent phase, the aim is to improve motor function and prevent deformities.

Outcome

The prognosis depends on the extent of involvement and quality of care during the acute phase. Early identification of and intervention for respiratory and bulbar paralysis reduces mortality to 5–10 %.

17.3.2.3 Subacute Sclerosing Panencephalitis (SSPE)

Subacute sclerosing pan encephalitis (SSPE) is caused by the persistence of measles virus in the CNS. Although SSPE most commonly occurs after a measles infection, it can occur following measles vaccination. It still occurs in many high-income countries [13].

Presenting Signs and Symptoms

The clinical symptoms usually develop insidiously 4–8 years following the infection. The initial symptoms are subtle and include declining school performance, intellectual deterioration with loss of memory and language impairment, changes in behavior (particularly withdrawal and irritability), and an altered sleep pattern. Thereafter myoclonic jerks develop, sometimes in association with seizures. There is a marked deterioration of motor function. Extrapyramidal features and visual loss can occur. In the later stages of SSPE, the myoclonic jerks may disappear as the child loses cognitive functioning, sphincter control, and lapses into coma. The rate of progression may vary, and the symptoms may fluctuate, but most die within 1–3 years of the onset of symptoms. Some children have a more fulminant course, dying within months.

Recommended Assessments

The diagnosis is based upon finding raised measles antibody titer in the CSF. The EEG during the myoclonic phases is characterized by episodes of burst suppression in which high-amplitude slow and sharp waves occur at intervals of 3–5 Hz on a slow background.

MRI scans show focal T-2 intensity white matter signals, followed by atrophic changes. In the later stages, there is significant loss of white matter with involvement of the basal ganglia. The MRI changes do not appear to reflect the clinical stage.

Recommended Interventions

The management of SSPE includes treatment of the myoclonic jerks and seizures and medication that interferes with the degenerative process. The myoclonic jerks may be treated with trihexyphenidyl. Isoprinosine and interferon alpha are thought to prevent progression, but the results of a multicenter trial did not show any benefit in terms of survival or neurological impairment.

17.3.2.4 Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a recognizable form of acute encephalitis which includes neurological symptoms suggesting multifocal lesions, encephalopathy, a presumed inflammatory cause (based on the presence of fever and/or signs of meningitis in CSF), and an abnormal MRI showing several lesions of the cerebral white matter. Although there is no specific biological marker, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) proposed a consensus definition in 2007 [6]. The most important, and somewhat controversial,

recommendation was that the presence of encephalopathy (defined as behavioral change or altered consciousness) is mandatory for the diagnosis of ADEM.

Presentation

Several series have described the clinical symptoms at onset of ADEM [14–16]. However, only the two most recent studies, including a French series of 132 patients, used the IPMSSG definition. The mean age at onset is 6 ± 3 years with 64–80 % of patients having onset before 10 years of age. However, ADEM can occur at any age, including in adults. There is no gender predominance. In 45–67 % of patients, fever precedes neurological symptoms with a mean interval of 4.5 days. The clinical course is usually rapidly progressive over several days. Mental status involvement ranges from lethargy to coma. Additional findings include long-tract dysfunction (hemiparesis, paraparesis) in 59–85 %, brainstem dysfunction (cerebellar ataxia and cranial nerve palsy) in 50 %, and myelitis in 19 to 24 % of patients. Published series differ more widely on the expected frequencies of seizures (11–35 %; 28 % in the largest series) and optic neuritis (6–23 %).

Assessment

Lumbar puncture and MRI are mandatory tests.

The number of white blood cells and the protein content in CSF are frequently, but not systematically, abnormal. The percentage of patients with abnormal CSF findings differed between series (in relation with the adopted definition) but is approximately 60 %. In the French series, cell count >10 cells/uL and protein >0.4 g/L was observed in 53 % and 37 % of patients, respectively [15].

Brain MRI demonstrates supratentorial and infratentorial white matter abnormalities (by definition), most readily identified on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 17.3c). The white matter lesions are typically hyperintense, large, and poorly demarcated. They involve several lobes and are not strictly symmetrical. In the majority of patients, white matter lesions are not isolated. Basal ganglia and brainstem lesions are detected in 40–60 % of patients and cortical lesions in 11–19 %. A few older series reported higher percentages, likely due to differences in definition. Interestingly, gadolinium enhancement is observed in 14–30 % of children, but meningeal enhancement is infrequent. Hypointensity in the white matter (at a level similar to the gray matter) is observed in a small percentage of cases. Spinal cord MRI should be performed in all patients and demonstrates swelling and hyperintensity in 9–25 % of cases, supporting the diagnosis of associated myelitis.

Some providers consider EEG a mandatory test, while others perform EEG only in the setting of suspected seizures. When performed, EEG is usually abnormal although the frequencies of different pathological findings have not been evaluated

carefully. Interictal EEG records often demonstrate continuous, diffuse slow background activity, with less frequent focal slow activity or spikes.

Other assessments are related to the evaluation of the general condition of the patient or directed at differential diagnosis which includes CNS vasculitis, Lyme meningitis, hemophagocytic lymphohistiocytosis, and, in rare cases, autoimmune encephalitis and CNS lymphoma. Certain clinical features should lead to caution before accepting the diagnosis of ADEM, none of them being absolute: an onset before the age of 1 year (especially in a consanguineous family), a gradual course of clinical symptoms, any non-neurological symptoms or signs especially liver or spleen enlargement, lymphadenopathy, cutaneous vasculitic symptoms (including livedo), and uveitis. On MRI, very symmetrical white matter lesions, absence of lesions in basal ganglia or brainstem, signs of arachnoiditis, or lesions restricted to the brainstem and basal ganglia are unusual in ADEM and should lead to a wider differential diagnosis. Because of the long list of conditions which can mimic ADEM, a consensus panel of testing has not been established. However, several biological markers should be considered, mainly to rule out systemic inflammation (ESR, C-reactive protein, complement), HLH (ferritin, triglycerides), and, less frequently, an autoimmune encephalitis (antithyroid and anti-neuronal antibodies). Lactate/pyruvate ratio in blood and CSF is useful to recognize respiratory chain dysfunction, especially for patients with MRI lesions restricted to the brainstem and basal ganglia.

Intervention

The efficacy of high-dose methylprednisolone has been supported by case series evaluating ADEM patients and extrapolated from clinical trials of other inflammatory white matter disorders, but no formal trials of steroids in ADEM have been conducted. The general consensus is that the use of intravenous high-dose methylprednisolone is effective to reduce the length of the episode but does not decrease the risk of subsequent relapse.

The optimal dose of methylprednisolone has not been established. Most physicians use 10–30 mg/kg/day (to a maximum of 1,000 mg/day) of methylprednisolone by intravenous infusion for 3–5 days. For young children (15–35 kg), the different modes of calculation (30 mg/kg, 500 mg/m^2, or 1 g/1.73 m^2) lead to very different doses. The authors use 30 mg/kg/dose daily for 3–5 days. Although intravenous methylprednisolone is accepted as the first-line therapy, the administration, dose, and duration of an oral taper of corticosteroids are debated. A commonly used approach consists of prednisolone at a starting dose of 1 mg/kg/day and tapered over 14–28 days. Corticosteroids are generally well tolerated. Potential side effects include hyperglycemia, hypokalemia, insomnia, hypertension, and psychosis. Although rare, gastrointestinal bleeding due to gastric ulcer is a possibility leading to a recommendation for a prophylaxis during steroid treatment.

Several other therapeutic options have been proposed either in association with methylprednisolone or as a second-line treatment for severe attacks or attacks

lasting more than 10 days. Children that do not respond to the first course of methylprednisolone might improve with a repeat course. Some physicians advocate for an additional 3–5 days of intravenous therapy at the same dose given 10–14 days after the initial treatment. This is a pragmatic clinical approach, but no formal investigation of its efficacy has been published. Intravenous immunoglobulin (IVIG) has been used successfully as an alternative therapy for autoimmune diseases including ADEM in small case series. Plasma exchange, commonly referred to as plasmapheresis, has been used to treat many neurological diseases including Guillain-Barré syndrome. From limited published series and from the authors' clinical experience, plasma exchange is probably beneficial for life-threatening acute demyelination and for prolonged acute phase not responding to corticosteroids. A randomized controlled trial of plasmapheresis in adult patients with a variety of steroid-refractory acute demyelinating attacks supports its use [17]. Five to eight exchanges performed every two days is the usual choice.

Outcome

It remains difficult to predict the outcome of an ADEM episode, although the prognosis is generally favorable. Full recovery after the acute episode is observed in roughly 80 % of patients. The average length of the acute episode is not reported in most series, but clinical experience suggests a week as a median with large variation. Some patients have confusion and seizures for up to 3 months. For such patients, the differential diagnosis should be carefully reassessed. Among the 20 % of patients that do not fully recover, most have normal motor abilities but display behavior or cognitive deficits that can be severe and affect subsequent school performance. There has been little study of prognostic factors for subsequent behavior or cognitive deficits; however, younger age (less than 6 years in one study), longer acute phase, more intense seizures, and presence of cortical lesions on initial brain MRI may increase the likelihood of such deficits. Death is rare but can occur in patients with fulminant disease or acute hemorrhagic leukoencephalitis. Finally, no formal prospective study provides a clear view on the prognostic value of brain MRI performed at 6 months of the acute episode, but is nonetheless frequently obtained in clinical practice. The available published data and clinical experience suggests that there is full or substantial recovery on MRI in most but not all patients.

The other important prognostic issue after an episode of ADEM is the risk of relapse that leads to a subsequent diagnosis of multiple sclerosis. According to several series, the rate of relapse after ADEM is between 8 and 33 %. When these individual series are summed, 75 of 468 (16 %) patients had a relapse. In the French series of 132 patients with ADEM, after a follow-up of 5.4 ± 3.3 years, 24 (18 %) of included patients went on to have a second attack. It occurred within 6 months for 15 children and after 1 year in 5. The first relapse was a second ADEM episode in 5 children (diagnosed as multiphasic ADEM). At the end of follow-up, 11 children (8 %) had a third attack, including 3 of the 5 patients with multiphasic ADEM.

Thus, most patients who went on to have a relapse after a first episode of ADEM were ultimately diagnosed with multiple sclerosis. An increased risk of relapse was associated with the occurrence of optic neuritis at onset, a familial history of multiple sclerosis, and the detection of MS Barkhof criteria on brain MRI.

17.3.2.5 Multiple Sclerosis: Acute Exacerbation

Multiple sclerosis (MS) is an inflammatory CNS disorder characterized by recurrent episodes of CNS demyelination. Approximately 2–5 % of all individuals with multiple sclerosis (MS) have onset of symptoms before 16 years of age [18]. MS in childhood typically follows a relapsing-remitting course [18]. The diagnosis of MS has previously required recurrent episodes (two or more) of demyelination with supportive data from MRI and CSF findings, in the absence of other plausible diagnosis. However, it is now possible to make the diagnosis of MS at the first attack provided the patient meets MRI criteria for dissemination in time and space.

Seventy-five percent of children with MS will have their second attack within 1 year from the first one [18]. It is a diagnostic challenge to differentiate MS from other inflammatory or infectious disorders discussed in this chapter, such as ADEM and neuromyelitis optica.

17.3.2.6 Presenting symptoms

A first attack of MS, commonly termed acquired demyelinating syndrome, most commonly in childhood presents as optic neuritis (14–35 %), monofocal brain stem symptoms, or polyfocal neurological symptoms [18].

Assessment

MRI brain and (cervical) spine, with and without contrast

CSF studies: cell count, IgG index, oligoclonal bands (compared with paired serum samples), total protein

Blood count (with differential), erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA)

Interventions

Acute exacerbations of MS are approximately three times more common in children than in adults. Although there are no randomized controlled trials published for acute relapses, commonly used treatment regimes include use of intravenous methylprednisolone 20–30 mg/kg/day (up to 1 g/day) for 3–5 days, with or without tapering with oral corticosteroids [19]. Other treatment options to consider for acute

relapses are intravenous immunoglobulin (IVIG, 2 g/kg given over 2–5 days) or plasmaferesis [19].

Drugs to prevent further relapses of MS, including beta-interferon, glatiramer acetate, fingolimod, and natalizumab and mitoxantrone, are not covered here.

17.3.2.7 CNS Vasculitis

Inflammation of the blood vessels of the central nervous system can be primary or secondary to infections or systemic autoimmune disorders such as lupus erythematosus. Primary CNS vasculitis can predominantly affect the medium-large or small blood vessels. Within the vasculitic disorders, primary small vessel CNS vasculitis is the one most likely to be confused with infectious or autoimmune encephalitis and is the focus of this section.

Presenting Symptoms

In a cohort of 19 children with primary small vessel CNS vasculitis, 15 (79 %) were girls, and the median age of presentation was 9.8 years [11]. The most common symptoms were cognitive and behavioral changes (100 %), headache (89 %), and seizures (79 %). A variety of systemic and focal neurological symptoms can occur.

Assessment

Patients with suspected CNS vasculitis should undergo gadolinium-enhanced MRI of the brain and spinal cord and MR angiography of the head. The most common finding on MRI consists of bilateral, asymmetric, multifocal T2/FLAIR hyperintense lesions affecting the cortical grey and subcortical white matter, although any region can be affected (Fig. 17.3d). The role of conventional angiography is controversial. One study of 25 patients showed no significant difference between MRA and CA performed within 1 month of each other [20]. In addition, by definition, CA is normal in patients with small vessel CNS vasculitis. Although many providers still perform CA for suspected small vessel CNS vasculitis, over time, it has become the practice of the authors to not perform CA in this setting.

All patients should also undergo lumbar puncture for measurement of opening pressure, cell counts, glucose, protein, oligoclonal bands, immunoglobulin G production, and infectious disease testing. CSF testing revealed at least one abnormality in 15/16 (94 %) patients in one study [11].

Blood testing should include measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and von Willebrand factor antigen, which were elevated in 65 %, 47 %, and 42 %, respectively, of those patients tested in one study [11]. All patients should also undergo thorough screening for systemic disorders associated with CNS vasculitis.

Although the above testing may yield a high suspicion for small vessel CNS vasculitis, brain biopsy is mandatory to confirm the diagnosis. The ideal biopsy should be at least 1 cm^3 and include meninges, and grey and subcortical white matter in an enhancing lesion. If an accessible lesion in a non-eloquent brain region is not present, non-lesional biopsy of the nondominant frontal lobe should be performed and was diagnostic in five of five patients reported in one pediatric study [21].

Interventions

Because of the severity of neurological symptoms, many patients are initially treated with high-dose intravenous corticosteroids once an active infection has been reasonably excluded. However, prolonged use of corticosteroids may decrease the yield of brain biopsy in the setting of suspected CNS vasculitis, prompting the need for a high index of suspicion and rapidly moving to biopsy in appropriate patients. Once the diagnosis is confirmed, an intensive 2-year protocol consisting of a 6-month induction phase (cyclophosphamide 750 mg/m2/month intravenously for seven doses and prednisone 2 mg/kg/day with gradual taper) followed by an 18-month maintenance phase (mycophenolate mofetil and continued prednisone taper) has yielded good results in approximately 70 % of patients at 24 months of follow-up [11].

Outcome

In the above study, 9 of the 13 patients (70 %) with 24-month follow-up had a good neurological outcome as measured by the pediatric stroke outcome measure [11].

17.3.2.8 Hemophagocytic Lymphohistiocytosis (HLH)

Presenting Symptoms

HLH occurs in both a primary autosomal recessive and a secondary form. Both forms can be triggered by systemic infections. Diagnostic criteria for HLH require five of the following eight features: fever, splenomegaly, cytopenia affecting $\geq$2 of 3 cell lines, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow, spleen or lymph nodes, low or absent natural killer cell activity, elevated ferritin, and elevated soluble CD25. In a study of 193 patients with HLH, 72 (37 %) had neurological symptoms which most commonly included irritability, seizures, and meningismus [22]. Some patients may only have CNS manifestations at onset.

Assessment

All parameters in the diagnostic criteria should be measured. Assessment of CNS involvement should include gadolinium-enhanced brain MRI and lumbar puncture.

In the above study, 52 % of patients had elevated CSF cell count and/or protein, some of whom did not have obvious neurological symptoms. Brain MRI was abnormal in 33 % of the patients in whom it was performed and most commonly showed atrophy or white matter lesions [22].

Interventions

The HLH-2004 protocol (http://www.drks.de/DRKS00003791) calls for treatment with dexamethasone, VP-16, and cyclosporine. For patients with progressive neurological symptoms after 2 weeks of therapy or lack of improvement in abnormal CSF, weekly intrathecal methotrexate and dexamethasone for 4 weeks are added. Hematopoietic stem cell transplantation is recommended for patients with familial and persistent nonfamilial disease.

Outcome

In the above study, the overall mortality rate was 44 % and was significantly increased in those patients in whom neurological symptoms and abnormal CSF were both present. In this subgroup, the mortality rate was 57 %. Neurological sequelae, typically developmental delay and epilepsy, occurred in 15 % of long-term survivors [22].

17.4 Acute Focal Disorders

Acute focal disorders include different entities which have in common their acute onset of restricted symptoms in a fully awake child with typically previously normal development. MRI lesions are present at the site of the clinical localization; additional asymptomatic lesions may or may not be present to suggest spatial dissemination of inflammatory demyelination. All of the focal disorders might relapse in the future in the same or different locations and therefore can herald the onset of multiple sclerosis. The risk of subsequent relapse is sharply different according to the initial anatomic location and brain MRI findings.

17.4.1 Optic Neuritis and Papillitis

Clinical symptoms of optic neuritis (an inflammation of one or both optic nerves) or papillitis (inflammation of one or both papilla) can be isolated or be part of a polysymptomatic attack or ADEM. Isolated optic neuritis or papillitis are only considered here (see also Chap. 5).

17.4.1.1 Presenting Symptoms

The main clinical symptom of optic neuritis and papillitis is an acute and isolated modification of vision, sometimes associated with pain in the ocular area in a previously healthy child. It occurs at a mean age of 10–12 years in the main recent series with the youngest patient being 2.2 years old [23, 24]. The female/male ratio is slightly skewed toward female especially after puberty. The modification of vision is unilateral in 40 % of cases and bilateral (either simultaneously or sequentially) in 60 %. It consists of a severe visual decrease in 60–77 % of patients with visual field defect (most commonly central scotoma) and modification of color perception. Headache or pain with extraocular movements is observed in half of the cases. By definition in this clinically isolated syndrome, there are no other neurological symptoms and no alteration of consciousness. External eye examination demonstrates a normal appearance without redness, and ophthalmoscopic examination of the affected eye reveals either disk edema (papillitis) or pallor. Hemorrhages are very unusual. Afferent papillary defect may be present.

Importantly, the funduscopic exam can be entirely normal; in some patients, this has led to an erroneous diagnosis of conversion disorder. If conversion disorder is being considered, we strongly recommend ophthalmology consultation and consideration of further objective testing such as MRI and visual-evoked potentials to avoid misdiagnosis.

17.4.1.2 Recommended Assessment

The need for CSF evaluation in a straightforward case of isolated optic neuritis is somewhat controversial. When performed, an elevated white blood cell count sometimes associated with elevated CSF protein level is present in roughly half the patients. MRI assessment of brain, orbits, and spinal cord should be obtained. It demonstrates optic nerve lesions in most of the cases. Dedicated orbital sequences including FLAIR or T2-weighted coronal sections and post-contrast T1 sequences with fat saturation should be performed (Fig. 17.4b). However, the main use of MRI in this setting is to demonstrate the absence or presence of associated supra- or infratentorial white matter lesions, which are observed in 38–54 % of reported patients.

Other testing for mimics of inflammatory optic neuritis should be guided by the clinical presentation. Optic neuritis can be part of a more general inflammatory disease including Lyme disease, Behcet's disease or vasculitis. It can also be the initial symptom of multiple sclerosis (see outcome). However, after an acute onset in a previously normal child, four differential diagnoses should be carefully evaluated:

- Neuromyelitis optica (NMO) or Devic's disease. This is a rare but severe disease that may be recognized from onset. Its diagnosis requires optic neuritis, myelitis, and at least two of the three supportive criteria: MRI evidence of a contiguous spinal cord lesion extending three or more vertebral segments in length, onset

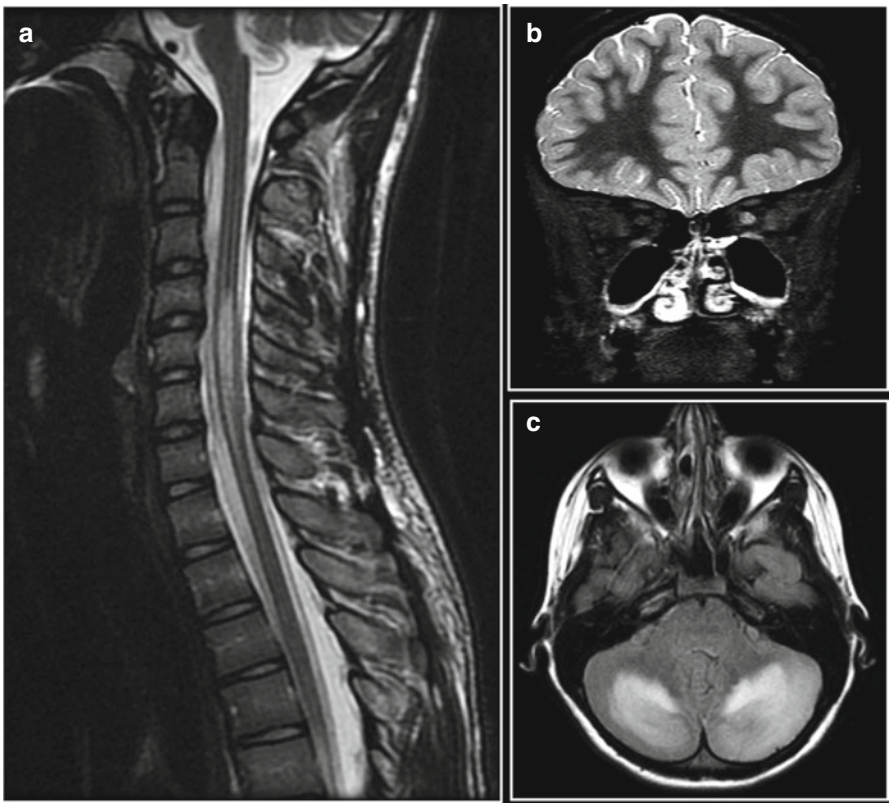

Fig. 17.4 (**a**) Transverse myelitis: Sagittal T2-weighted MRI showing hyperintense signal in the cervical spinal cord of a patient who presented with bilateral leg weakness, sensory loss, and urinary retention. (**b**) Optic neuritis: Coronal T2-weighted MRI showing hyperintense signal and swelling of the left optic nerve in a patient who presented with unilateral vision loss. (**c**) Cerebellitis: Axial FLAIR MRI showing severe bilateral cerebellar hyperintensity and swelling with compression of the fourth ventricle in a patient who presented with headache, vomiting, and lethargy

brain MRI nondiagnostic for multiple sclerosis or NMO-IgG (anti-aquaporin 4 antibodies) seropositivity [25]. Brain MRI may show lesions in characteristic areas such as the hypothalamus and periaqueductal grey area. CSF is usually abnormal with elevated WBC in 55 % and elevated protein content in 74 %. NMO can have either a monophasic or relapsing course. In the latter form, frequent, severe relapses are the usual evolution without treatment. In the acute setting, plasma exchange should be strongly considered for severe attacks which do not respond to corticosteroids. Chronic preventive treatment is difficult and typically requires prolonged oral corticosteroids with a probable beneficial effect of azathioprine, mycophenolate mofetil, and Mabthera (Rituximab) as steroid-sparing agents.

- Leber hereditary optic neuropathy. This genetic disease is related to a mitochondrial respiratory chain dysfunction and specific mutations (usually one of three

mitochondrial DNA point mutations (11778G to A, 34606G to A, 14484T to C)) and should be considered in cases of frequently relapsing ON or if vision remains highly deficient.
- Conversion disorder. A complaint of modified vision with normal fundus examination, normal visual fields (or of concentric reduction) with normal MRI, and normal electrophysiological studies should lead to a consideration of conversion disorder.
- Papilledema cannot be distinguished from papillitis on the basis of fundus examination alone. However, visual acuity is not affected early in the course of moderate papilledema, and headaches are usually present. In cases which cannot be distinguished on clinical exam, neuroimaging followed by lumbar puncture with measurement of opening pressure is diagnostic. Fluorescein angiogram can be used in difficult cases, demonstrating fluorescein leakage at the level of the optic nerve head in case of inflammation. Drusen of the optic nerve head can also give the appearance of pseudopapilledema but are usually recognized by experienced ophthalmologists.

17.4.1.3 Recommended Intervention

Treatment of optic neuritis or papillitis is identical to that of ADEM with use of repeated injections of high doses of methylprednisolone.

17.4.1.4 Outcome and Initial Information

Visual recovery is excellent in 70–96 % of patients. However, relapses either as isolated optic neuritis, multiple sclerosis, or Devic's disease occur in 17–36 % of patients. Pediatric published series support the idea that the risk of relapse is very low in children with normal initial brain MRI, while the risk of MS is high if brain MRI demonstrates several white matter lesions at onset. The prognostic role of MRI lesions should be discussed with families.

17.4.2 Transverse Myelitis

Inflammation of the spinal cord occurs in two general forms. In partial transverse myelitis, the symptoms are asymmetric and milder compared to complete transverse myelitis. The consensus definition of complete transverse myelitis is a focal inflammatory disorder of the spinal cord resulting in bilateral motor, sensory, and autonomic dysfunction, requiring evidence of inflammation within spinal cord by MRI or CSF studies. Although this distinction is often not made explicitly in the existing pediatric literature, the authors have found it useful, and this approach is supported by adult literature.

17.4.2.1 Presenting Symptoms

Major case series have shown similar results [26, 27]. The age distribution is bimodal with a first peak in toddlers under age 3 (10–15 % being less than 1 year old in the two main series) and another peak in the teens. The clinical features depend on the location of lesion(s). The most common site is the thoracic cord between T5 and T10, followed by cervical lesions and lumbar lesions. The usual time from the onset of acute symptoms to functional nadir is 2–7 days, with a wide range from an acute onset over a period of hours or less (22 % in the British series) to a slow onset up to a month to maximum severity. The main symptoms are weakness of the lower or all limbs (up to flaccid paralysis), sensory symptoms, pain, bladder symptoms (either urinary retention or incontinence), and bowel problems (constipation and sphincter hypotony). At examination, the cardinal features are weakness, sensory loss, loss of deep tendon and abdominal reflexes, and sphincter deficit. Symptoms may be stable from onset or progressively involve higher levels of the spinal cord. The presence of dysphagia, respiratory deficit, or autonomic dysfunction is worrisome and should be carefully evaluated.

17.4.2.2 Recommended Assessment

The recommended assessment is similar to that for ADEM and optic neuritis. Lumbar puncture should be obtained in all patients; CSF is abnormal in 50–70 % of children. Both spinal cord and brain MRI should be obtained. Spinal cord should be studied in both longitudinal and transverse plans. A signal modification in T1-, FLAIR-, and T2-weighted images is observed in most patients (respectively 69 and 91 % in the two main series). It demonstrates the lesion as an edematous hypointense T1 signal imaging that is enhanced after gadolinium infusion in 74 % and as a hyperintense lesion in T2 signal (Fig. 17.4a). Most lesions extend over several vertebral segments in length. As for optic neuritis, brain MRI can demonstrate infra- or supratentorial lesions of the white matter. Brain MRI was abnormal in 65 % of patients from the UK series, but it included patients with transverse myelitis associated with brain-related symptoms.

The differential diagnosis of myelitis includes acute polyradiculoneuritis (Guillain-Barré syndrome). However, the presence of bladder and bowel symptoms, absence of abdominal reflexes, presence of a sensory level (as opposed to a stocking and glove distribution), and CSF pleocytosis (as opposed to elevated protein with normal cell counts) should point to transverse myelitis. A vascular etiology should be considered in very acute cases, including infarction, arteriovenous malformation, and hemorrhage. Primary spinal cord tumors should be considered especially in cases with a slow onset. Isolated spinal cord vasculitis appears to be very rare but can mimic idiopathic transverse myelitis. Neuromyelitis optica (Devic's disease) has been discussed in the optic neuritis section.

17.4.2.3 Recommended Intervention

Treatment of transverse myelitis is identical to that of ADEM and use repeated injection of high doses of steroids.

17.4.2.4 Outcome and Initial Information

Several nonrandomized studies, including three from France using historical controls, suggest a beneficial effect of high doses of steroids. In case of persisting symptoms after 10 days, methylprednisolone pulses can be repeated and plasmapheresis might be useful. However, transverse myelitis remains a severe disease. Despite the use of high-dose steroids, 25 and 44 % of children in the British and French series, respectively, were left with significant sequelae, and only 50 and 56 % had a complete recovery. The series reported by Pidcock et al. had more severe outcome, but the recruitment, in this reference center, might have been different. A favorable outcome has been linked in the different reports to a shorter time to diagnosis, a lower level of the lesion, and a start of recovery within 7–8 days of onset. Significant negative predictors include flaccid legs at presentation and sphincter involvement, with conflicting results on rapid progression from onset to nadir within 24 h and on age at onset. Finally, if recovery has not begun within 4 weeks of reaching the nadir of the illness, it is unlikely to occur. Conversely, for all other children, recovery can continue for up to 2 years.

The risk of relapse exists after transverse myelitis either as a new myelitis or as multiple sclerosis. Based on adult reports and our experience, the risk of multiple sclerosis is very rare after severe, complete transverse myelitis but can occur following partial transverse myelitis. As for optic neuritis, the risk of multiple sclerosis is higher in children with abnormal initial MRI, but very few reports state the percentage of multiple sclerosis after transverse myelitis in childhood.

17.4.3 Brainstem Encephalitis

17.4.3.1 Presenting Symptoms

Brainstem encephalitis, also termed rhombencephalitis or occasionally Bickerstaff brainstem encephalitis, is a loosely defined group of diseases having in common an acute onset with symmetrical ophthalmoplegia, ataxia, drowsiness, and pyramidal signs. Isolated, idiopathic brainstem inflammation can be a monophasic condition or can herald the future development of multiple sclerosis. Infections with prominent brainstem involvement include Listeria monocytogenes, tuberculosis, and HSV. Additional symptoms and signs outside of the brainstem can suggest ADEM. Flaccid limb weakness and areflexia suggest accompanying polyradiculoneuritis as

part of Miller Fisher syndrome, which has significant overlap with Bickerstaff brainstem encephalitis. Neuro-Behcet disease frequently involves the brainstem.

17.4.3.2 Recommended Assessment

LP should be performed in all cases. MRI can be normal or demonstrates hyperintense T2 signal in the brainstem. Electrophysiological examination of peripheral nerves is required in cases in which polyradiculoneuritis is suspected. Additional testing is guided by clinical suspicion of the above associated disorders.

17.4.3.3 Recommended Intervention

Appropriate treatment is dependent on the specific diagnosis. Before the exact etiology is defined, antibiotics with coverage for Listeria and acyclovir should be considered. Once infections are reasonably ruled out, corticosteroid treatment similar to that used for ADEM may speed symptom resolution.

17.4.3.4 Outcome

The outcome of brainstem encephalitis is highly dependent on the underlying etiology.

17.4.4 Acute Cerebellitis

Acute cerebellar ataxia is sometimes differentiated, in reviews and chapters, from acute cerebellitis, the latter being more severe. In our opinion, acute cerebellar ataxia is a clinical description of presenting symptoms, signs, and localization, while acute cerebellitis refers to a pathophysiological mechanism. Both disorders as described in the literature are likely due to inflammatory processes but have differing presentations and could potentially be placed on a spectrum from mild (acute cerebellar ataxia) to severe (cerebellitis).

17.4.4.1 Presenting Symptoms

Most of the reported series are hospital-based and probably skewed toward more severe cases. Acute cerebellar ataxia can be observed in children of all ages. However, in a combined series of 112 cases, half of the cases occurred before 4 years of age [28]. The onset of ataxia is usually acute, with marked gait ataxia and

dysmetria. The child may avoid standing altogether. Hypotonia and tremor of the extremities, head, and trunk are usually obvious, and, in older children, speech is often affected. Three associated symptoms should be explored: (1) eye movements with nystagmus can be observed but are surprisingly uncommon, whereas sudden random movements of eyes should raise other possible diagnoses; (2) signs of meningitis or raised intracranial pressure; and (3) myoclonic movements of the arms and any brainstem-related symptoms.

Acute cerebellitis can induce very severe symptoms usually related to posterior fossa swelling. Altered mental status is very frequently present. Other associated neurological symptoms, such as nausea and vomiting, cranial nerve six palsies, and papilledema, suggest raised posterior fossa pressure. Symptoms that are more directly related to brainstem involvement are altered respiratory pattern, blood pressure changes, or other cranial nerve palsies. These symptoms may reflect a life-threatening situation, associated with herniation either upward through the tentorium or downwards through the foramen magnum. The severe acute symptoms often completely mask more cerebellum-specific symptoms such as dysmetria and ataxia, which may only become evident as the patient's overall condition improves.

17.4.4.2 Recommended Assessment

The CSF is abnormal in about half of patients with mild lymphocytic pleocytosis and moderately elevated protein content. In case of symptoms suggesting raised posterior fossa pressure, lumbar puncture is contraindicated. If it is not an immediate life-threatening situation, brain and spinal cord MRI should be performed. In severe cases (typically termed cerebellitis in the literature), global swelling of the cerebellum with a compressed fourth ventricle and occasionally signs of herniation either upward transtentorially or of the cerebellar tonsils into the foramen magnum can be demonstrated (Fig. 17.4c). In typical cases of acute cerebellar ataxia, brain MRI is usually normal.

Acute inflammatory cerebellar ataxia can be a symptom of a more diffuse inflammatory disease of the nervous system that may relapse in the future, including ADEM and brainstem or cerebellar clinically isolated syndromes. Miller Fisher syndrome causes acute ataxia, as well as external ophthalmoplegia and areflexia without peripheral weakness but is rare in children. Opsoclonus-myoclonus syndrome is defined by the association of three of four features: opsoclonus or ocular flutter (but not nystagmus), ataxia and/or myoclonus, behavioral change and/or sleep disturbances, and neuroblastoma. Misdiagnosis with acute inflammatory cerebellar ataxia is frequent at onset, especially if the pathological eye movements are absent or missed. The diagnosis should be carefully considered if ataxia persists [29]. Noninflammatory mimics of acute cerebellar ataxia include intoxications, stroke, channelopathies, neurometabolic disorders and tumors.

17.4.4.3 Recommended Intervention

The disease is self-limited in most mild cases and does not require any treatment. In more affected or very uncomfortable children, steroid treatment should be considered, although no formal study has been conducted. In severe cases, acute swelling of the cerebellum is an emergency. High-dose pulses of methylprednisolone, as performed in ADEM, are probably the best medical treatment, but surgical decompression of the posterior fossa may be necessary and can be lifesaving.

17.4.4.4 Outcome and Initial Information

The ataxia in mild cases resolves completely over 2–8 weeks. However, the outcome of severe cases with acute swelling of the cerebellum is highly variable and includes rapid deterioration and death without intervention. Survivors can have permanent cerebellar motor and cognitive deficits. Relapsing acute cerebellar ataxia is very unusual in children and should lead to careful consideration of the above differential diagnoses.

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Chapter 18
Spasticity, Dystonia, and Other Movement Disorders: A Comprehensive Treatment Guide

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Abstract Spasticity and movement disorders are rarely in focus of acute management in pediatric neurology. However, certain conditions do require more acute medical interventions, including acute dystonic reactions, intensified preexisting spasticity and/or dystonia, and rapid development of spasticity in the post-acute phase following focal (e.g. stroke) or global (e.g. anoxia) CNS pathology. In the present chapter we present typical symtoms, underlying pathophysiology, recommended assessments, and recommended interventions for spasticity and movements disorders, with an emphasis on acute management.

18.1 Introduction

Movement disorders and spasticity rarely are in the focus of acute management in pediatric neurology. The following conditions typically lead to aggravation of movement disorders requiring acute medical intervention:

- Acute dystonic reactions (e.g., after "masked" intake of dopamine antagonists)
- Intensified preexisting spasticity and/or dystonia (with or without oral medication, intrathecal baclofen pump (ITB), or deep brain stimulation (DBS))

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Table 18.1 Triggers that aggravate preexisting movement disorders

Technical triggers	Biological triggers	Psychosocial triggers
Ventricular shunt systems (VPS)	Infections, such as (aspiration) pneumonia, urinary tract infections, upper airway infections, gastrointestinal infections (all with or without fever)	Psychological stress such as change in daily routines, in care takers, and in school or institutions; victimization; Munchhausen syndrome by proxy
Intrathecal baclofen pump systems (ITB)	Fluid-intake imbalance	Change in adherence to medications
Deep brain stimulators (DBS)	Constipation	(Unreported) complementary medications with new behavioral rules
Any other foreign material inside the body like cochlear implants (CI)	Gastro-esophageal reflux Pain, such as musculoskeletal (e.g., hip luxation) fractures, scoliosis, pain during/after physical therapy, posture problems, and phantom pain Change in tolerance of medications Aggravated comorbidity (e.g., epilepsy in cerebral palsy)	

- Rapid development of spasticity in the post-acute phase after acute focal (stroke) or global (anoxia) CNS pathology

Acute treatment goals have (1) to escape from sometimes life-threatening intensity and (2) to identify technical triggers, (3) biological triggers, and (4) psychosocial triggers (see Table 18.1).

When treating acute aggravation of spasticity, dystonia, or other movement disorders, keep in mind that the individual need can be significantly and unexpectedly "less or more" compared to the "established" dose regimens. Assure adequate monitoring and safety for your intervention. In any case of doubt, this is the intensive care unit. If technical systems (e.g., shunts, ITB, DBS) are involved, establish the direct contact to surgery as soon as possible (orthopedic or neurosurgery) and plan every next step in an interdisciplinary team approach including the expert physician that treats the involved patient continuously.

After overcoming the acute needs, reevaluation of daily care is mandatory such as postural management (sleeping, lying, sitting, standing, walking, braces, orthotics, etc.) and transfers, feeding, digesting, dental care, hygienic care, and medications.

18.2 Spasticity

18.2.1 Description of Presenting Symptoms

Damage to the motor areas of the central nervous system (brain or spinal cord) may give rise to a specific type of movement disorders subsumed under the term (pyramidal tract syndrome or) upper motor neuron syndrome (UMNS). In the context of this

syndrome, a more easily triggered muscle stretch reflex and *a velocity-dependent increase of muscle tone* upon passive stretching of affected motor segments are considered the most important clinical criteria for the presence of spasticity [1]. Classic descriptions of UMNS differentiate between clinically negative and clinically positive symptoms. Negative symptoms include paresis, impaired control and coordination of movement, and easy fatigability of the motor system. Positive symptoms are spasticity [1], more easily triggered tendon reflexes, mass reflexes, abnormal posture (spastic dystonia), and changes in the mechanical properties of muscles with a tendency to develop contractures (after months/years/decades) [2–4]. Spasticity may lead to considerable restrictions in joint motility (= active and passive joint range of movement; ROM) and as a consequence to impaired active and passive mobility. About 50 % of those affected suffer from chronic pain (daily or some time every day).

Important areas of life including participation in work-related and social activities are affected.

Depending on the specific pattern of injuries involved, each patient shows a unique combination of spastic posture and motor elements. It typically changes in the course of time as additional secondary and tertiary dysfunctions of the musculoskeletal system appear. Therefore, every time before the patient undergoes a new treatment path, it is necessary to update assessment and documentation of neurological symptoms.

In addition to the clinico-neurologic examination, a video documentation of the patient's initial state is very helpful; the therapist should evaluate function, activity, and participation based on appropriate, validated, and reliable clinical scales and tests as mentioned below.

18.2.2 Recommended Assessments

18.2.2.1 Clinical Assessments

There is a great variety of assessments to measure different components of patients presenting with spasticity. Patients have to be assessed during activity (sitting, walking, running, jumping) as well as passively. Cooperation of the patient influences the degree of measurable spasticity significantly and has to be considered when interpreting the findings during clinical assessment.

The *(Modified) Ashworth Scale (MAS)* and the *Modified Tardieu Scale (MTS)* are the most frequently used measurement to evaluate the degree of spasticity on the WHO-ICF domain of body structure and function. Both can be used at all ages and MAS is especially useful for large joint movements (knee, elbow) [5, 6]. Where the MAS scales the resistance of a passive joint movement to externally imposed movement with a approximate velocity of 1 cm/s, the MTS assesses "fast" passive joint mobility, thereby provoking the typical "catch" phenomenon. Due to the fast joint movement, it can easily be assessed with smaller joint movements (e.g., upper extremity, ankle joint).

Range of motion (ROM) allows assessment of passive joint mobility using a goniometer (neutral-0-method). It helps to differentiate between dynamic shortening of a movement versus fibrotic contracture of a muscle and therefore always has to be measured together with MAS and MTS. The active ROM helps to detect

impairment of selective motor control, thereby representing WHO-ICF domain of function and activity. Due to active performance active ROM cannot be assessed in uncooperative patients [7, 8].

Video documentation is required to assess the patients' activity level, and in contrast to the aforementioned methods, which are assessed with the patient is lying or sitting, inspection of the patients' active mobility adds significant value about the patients' spasticity pattern during locomotion [9, 10].

Besides these clinical assessments, which are necessary in all patients, there is a wide range of additional tools to measure motor function affected by spasticity: motor function test, e.g., the Gross Motor Function Measure (*GMFM* 88, or 66) [11] or the Assisting Hand Assessment (*AHA*) [12] to evaluate bimanual skills of children with unilateral spasticity. Both tests are helpful to detect changes over time and are valid from the later 2nd year of live.

Structured interviews (e.g., Canadian Occupational Performance Measure—COPM) or questionnaires (e.g., Pediatric Evaluation of Disability Inventory—PEDI or CPCHILD) help to assess activity and participation or quality of life of patients presenting with spasticity, but these usually do not play a significant role in the management of acute spasticity [13, 14].

18.2.2.2 Diagnostic Workup

Neuroimaging (cranial MRI) always is required to detect, e.g., lesional patterns of the brain. In case of negative cranial imaging, consider spinal neuroimaging to exclude, e.g., malformations, tethering, tumors, and inflammation. In case of foreign materials (e.g., ventriculo-peritoneal shunt, intrathecal baclofen pump, deep brain stimulators), ensure whether these are compatible with the magnetic field of the MRI. In doubt, use cranial CT to exclude acute reasons for spasticity (bleeding, ischemia, thrombotic infarction, tumor, etc.).

Neurophysiology may help to detect involvement of the second motor neuron of affection of the sensory nervous system in cases of peripheral neuropathies. Also muscular disorders may present with toe-walking mimicking spasticity, which should be differentiated using the abovementioned clinical assessments already. In case of affected family members, consider testing for hereditary spastic paraplegias, of which multiple genetic origins have been reported (for further information visit www.ncbi.nlm.nih.gov/omim or www.wemove.org).

Thrombophilia or increased risk of bleeding should be excluded in case of typical lesional MRI findings suggesting thrombosis or hemorrhage.

Radiographs are necessary to detect bone or joint dysfunction (e.g., hip subluxation, patella alta).

18.2.3 Recommended Interventions

The prerequisite for the successful treatment is a clear understanding of etiology, primary and secondary factors, and a clinical decision making in which the whole range of treatment options is tailored to the patient. The modern approach to

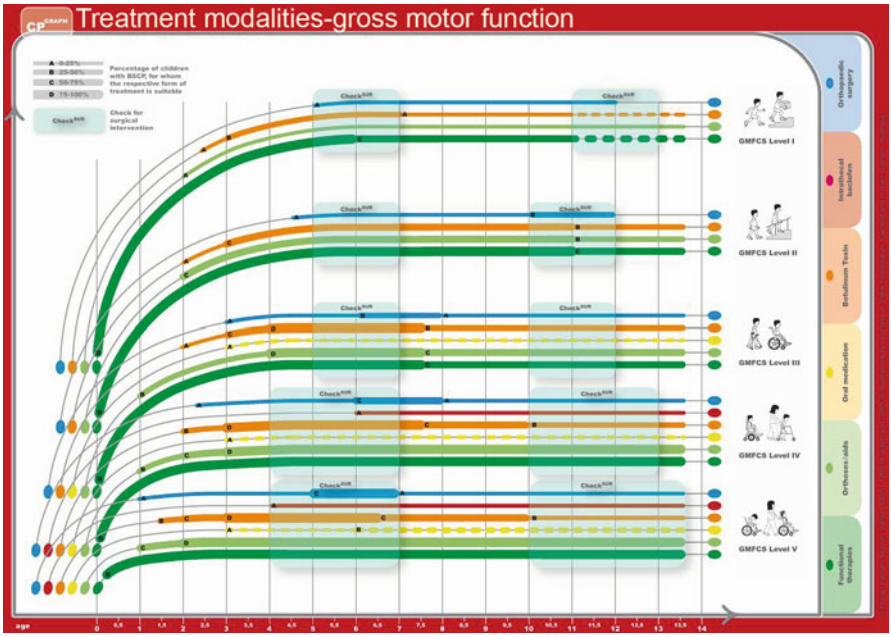

Fig. 18.1 CP-graph treatment modalities—gross motor function. This graph is not an evidence-based treatment guideline; it aims to facilitate communication between parents, therapists, and medical doctors concerning (1) achievable motor function, (2) realistic goal setting, and (3) treatment perspectives for children with spasticity [19]

spasticity therapy is based on the integrative, bio-psycho-social model of the ICF ("International Classification of Functioning, Disability and Health" of the WHO). In this approach, singular measures are coordinated with the aim to optimize time course and intensity of treatment for each individual patient. This helps in achieving the best possible therapeutic outcome [15–17].

Treatment of spasticity at the ICF level of "body functions" primarily aims to lower spastic muscle tone in the affected motor segments on passive muscle stretching as well as on active movement. In addition, it is important to attain normal muscle length (ICF Level "body structure") in order to improve active motor competence through biomechanical relief.

The Gross Motor Function Classification System (GMFCS) based on the motor development curves [18] can be expanded to provide a graphical framework on how to treat spasticity and motor disorders in general in children with CP (Fig. 18.1). This graph is not an evidence-based guideline; it aims to facilitate communication between parents, therapists, and medical doctors concerning (1) achievable motor function, (2) realistic goal setting, and (3) treatment perspectives for children with spasticity [19].

To treat spasticity, local and systemic approaches are available [19–22]:

- Physical therapy (e.g., stretching, positioning, thermal stimulation)
- Classic kinesitherapy (e.g., neurodevelopmental treatment/NDT)
- Self-control techniques (e.g., biofeedback)

- Neuromodulation therapy (e.g., forced-use/constraint-induced movement therapy)
- Repetitive motor exercises (e.g., treadmill therapy)
- Systemic pharmacotherapy (e.g., baclofen, tizanidine, dantrolene)
- Neurosurgical intervention (e.g., neurotomy and baclofen pumps)
- Neuro-orthopedic surgery (e.g., myotomy, tenotomy)
- Focal denervation (botulinum toxins, phenol, alcohol)
- Robotic therapy (e.g., Lokomat®, Armeo®)

Systemic and (multi)focal pharmacotherapy resemble therapeutic options, which can be used temporarily to modulate spasticity. Unfortunately, patients with oral medication frequently show habituation; therefore, drug discontinuation should be attempted in conjunction with the patients' situation to test whether it is still effective. Continuous oral first-line medication is *baclofen administered orally*. It is an agonist of the neurotransmitter GABA B. It inhibits transmission of both mono- and polysynaptic reflexes at spinal cord level. Systemic use of baclofen can increase hypotonia of the trunk, sedation, and decline in swallowing. Asymmetric muscle tone can aggravate scoliosis. Aggravation or induction of seizures/epilepsy has been reported. For indication and management of intrathecal baclofen (see Table 18.2 and Sect. 18.5.1). For management of baclofen withdrawal syndrome (see Sect. 18.5.3).

Due to significant habituation *benzodiazepines* are first-line medications only helpful for intermittent use (e.g., over weeks to maximum months during acute aggravation of symptoms).

Due to limited effectiveness in only selected cases, second-line medications are rarely used. Here, *tolperisone* resembles the most effective oral medication. It is a centrally acting muscle relaxant, which usually shows less sedation compared with baclofen. Adverse events can be vertigo, dizziness, dry mouth, hypotension, or increased paresis. *Dantrolene* can cause severe liver dysfunction; therefore, regular laboratory checks are necessary. Dosages of first- and second-line systemic medication to treat spasticity are presented in Table 18.2.

Please note that for children almost, all available medication is used off-label. Dosages are examples and may vary according to the individual needs of the patient. If there is not an urgent need, follow the rule "start low, titrate slow" to avoid side effects, e.g., dizziness or drowsiness.

Management of *(multi)focal spasticity* using botulinum toxin is well established. Focal treatment with *botulinum (neuro)toxin (BoNT)* can be indicated by high treatment efficacy, low incidence of side effects, the adaptive possibilities, and compatibility of BoNT with all the other treatment options listed above.

BoNT is produced by Clostridium botulinum—a sporiferous, gram-positive, anaerobic bacterium that requires special conditions for growth (pH 4.5, protein-rich growth medium, 40 °C). There are seven known, immunologically distinct serotypes of botulinum toxins. BoNT is a zinc-dependent endopeptidase composed of a light (50 kD) and a heavy (100 kD) chain held together via a disulfide bond. BoNT does not cross the blood–brain barrier or pass through the skin. It is not cytotoxic but inhibits cholinergic neuromuscular and neuroglandular transmission.

Table 18.2 First- and second-line systemic medication to treat spasticity

First-line medication	*Baclofen*	Orally: Start with 0.5 mg/kg divided into 3 doses, increase weekly by 0.5 mg/kg. Maintenance: 2–5 mg/kg /day divided into 2–4 doses (max. 60 mg/day)
	Tetrazepam	Orally: Start with 2 mg/kg/day. Maintenance: 4 mg/kg/day
	Diazepam	Orally: Start with 0.25–0.5 mg/kg/day. Maintenance: up to 1 mg/kg/day divided into 2–3 doses
	Lorazepam	Orally: Start with 0.05 mg/kg/day. Maintenance: up to 0.2 mg/kg/day divided into 2–3 doses
	Intrathecal baclofen	Usual daily dose of 150–2,000 μg/24 h via implanted catheter pump *Management of Baclofen withdrawal syndrome* (see Sect. 18.5.3)
Second-line medication	*Tolperisone*	Orally: (Divided into 2–3 doses/day) 6 months–2 years of age (5–12 kg): 25–50 mg/day 3–5 years of age (13–19 kg): 50–75 mg/day 6–9 years of age (20–29 kg): 75–100 mg/day 10–12 years of age (30–43 kg): 100–125 mg/day 13–14 years of age (44–52 kg): 150 mg/day Adolescents above 14 years of age: 150–450 mg/day. Higher dosages can be necessary in some individuals according to tolerability
	Dantrolene (Dantrium)	Orally: Start with 0.5 mg/kg/day and increase weekly by 0.5 mg/kg. Maintenance: 2–8 mg/kg/day divided into 3–4 doses (max. 400 mg)
	Others	Tetrabenazine, tizanidine

The molecular mode of action at the cholinergic nerve endings involves three main steps:

1. *Binding*: After injection, the toxin accumulates on glycosidic receptors near the preterminal nerve endings. The C-terminal end of the toxin's heavy chain specifically binds to SV2 (synaptic vesicle 2), a vesicular membrane protein presented on the surface of the terminal axon during acetylcholine release. Binding and uptake of BoNT require the presence of active vesicles and thus currently active neuromuscular transmission.
2. *Internalization*: BoNT enters the axon terminal by means of energy-dependent, receptor-mediated endocytosis and ends up in the endosomal compartment. Under the acidic conditions inside the endosome, BoNT undergoes conformational changes leading to separation of heavy and light chain and transfer of the latter from the endosomal compartment into the cytosol.
3. *Toxic action*: The light chain irreversibly cleaves the membrane-associated fusion complex (SNARE complex) responsible for exocytosis of acetylcholine.

The fusion complex consists of three proteins: VAMP (vesicle-associated membrane protein), SNAP-25 (synaptosomal-associated protein), and syntaxin. BoNT types A, C, and E cleave SNAP-25; types B, D, F, and G cleave VAMP; and type C cleaves syntaxin. As a result, the release of acetylcholine into the synaptic cleft is blocked for a certain length of time depending on the type of BoNT involved.

Clinically, 3–10 days after BoNT injection, the injected muscle begins to show signs of a dose-dependent incomplete paresis with neurogenic atrophy and inhibition of the disinhibited tonic stretch reflex. The maximum effect is reached after 2–4 weeks, remains at this level for a certain time, and then slowly decreases. In striated muscles the clinical effect is usually apparent for about 3–6 months [19–21]. Eventually the neurotoxin will be proteolytically degraded in the preterminal axon. This allows the fusion complexes that are necessary for exocytosis to be newly formed so that synaptic function is resumed as could be shown in an animal model [23]. Nevertheless, in humans the focal morphological effect of neurogenic atrophy of the muscle is outlasting the functional effect [24] and the relevance of the discrepancy between clinical efficacy (3–6 months) and structural changes (more than 12 months) is still under debate [25].

BoNT doses are specified as units of biological activity (mouse units, MU). One MU corresponds to an amount of toxin that—after intraperitoneal injection of female Swiss Webster mice with a body weight of 18–20 g—causes 50 % of these mice to die. This dose is also called lethal dose 50 or LD 50. Clinical efficacy and the adverse effects profile of different, commercially available BoNT preparations are not directly comparable on the basis of the respectively stated mouse units. The use of fixed conversion factors between preparations proved unsatisfactory; therefore, products are generally not interchangeable. Four preparations are generally available on the European and American market. To avoid misunderstanding, the required terminology for botulinum toxins type A (BoNT/A) changed to onabotulinumtoxinA (preparation Botox®), abobotulinumtoxinA (preparation Dysport®), and incobotulinumtoxinA (preparation Xeomin®) and for botulinum toxin type B (BoNT/B) to rimabotulinumtoxinB (preparation Myobloc/Neurobloc®). Due to the individual potency, each preparation needs its own dose calculation. Dose calculation includes (1) the number of muscles to inject, (2) the dose/muscle, (3) the dose per injection session, and (4) dose modifiers. Below 25 kg body weight (BW), dose calculations follow a BW upper dose limit; above 25 kg BW, adult dosages should be used (see Fig. 18.2). For dose recommendations of the four different BoNT preparations, see Table 18.3. The following dose modifiers are important to consider:

- Severity of CP according to GMFCS.
- Accompanying diagnoses (e.g., dysphagia, aspiration pneumonia, hypopnea).
- Predominant type of movement disorder (spastic versus dyskinetic).
- Activity of the injected muscle (dynamic versus fibrotic compounds of the muscle).
- Muscle bulk size.
- Nutritional status, body mass index.

Fig. 18.2 Dosing loop botulinum toxin. Check and balance carefully between dose variables and cofactors. In a multi-muscle/multilevel injection protocol, it might be necessary to reduce the number of muscles in order to maintain adequate dose/muscle. This dosing loop botulinum toxin helps to stay focused on formulating specific treatment goals

Table 18.3 Dose recommendations for the four available botulinum toxin preparations

Botulinum neurotoxin type A (BoNT/A):	*Recommended upper dose limit*
Up to 25 kg body weight (see Fig. 18.2); for patients >25 kg BW, refer to adult dose recommendations	
1. OnabotulinumtoxinA (Botox®):	25 units/kg and/or 400 units/session
Large muscles: 3–6 units/kg	100 units/muscle
Small muscles: 0.5–2 units/kg	50 units/injection site
2. AbobotulinumtoxinA (Dysport®):	25 units/kg, and/or 1,000 units/session
Large muscles: 10–20 units/kg	250 units/muscle
Small muscles: 5–10 units/kg	125 units/injection site
3. IncobotulinumtoxinA (Xeomin®):	25 units/kg and/or 400 units/session
Large muscles: 3–6 units/kg	100 units/muscle
Small muscles: 0.5–2 units/kg	50 units/injection site
Botulinum neurotoxin type B (BoNT/B):	*Second-line BoNT for spasticity*
4. RimabotulinumtoxinB (Myobloc/Neurobloc®):	400 units/kg and/or 10,000 units/session
Large muscles: 100–150 units/kg	2,500 units/muscle
Small muscles: 30–50 units/kg	1,250 units/injection site

- Knowledge about the distribution of motor endplates in the injected muscle.
- Experience from previous BoNT injections. Dilution can be adapted to body region and muscle size (e.g., forearm: lower dilution, lower leg: higher dilution).

Potential adverse events (AE) include:

- Local AE: to strong weakness of the injected muscle
- Distant focal AE: bladder dysfunction, constipation, strabismus, swallowing difficulty
- Systemic AE: flue-like symptoms, headache, generalized weakness
- Procedural AE: injection pain, hematoma, adverse events due to analgo-sedation/anesthesia

Depending on the definition of adverse events in published literature, adverse events vary significantly. Generally they are rare and temporary. The risk of AE increases with increased total dose or increased severity of impairment. Isolated cases with fatal outcome in timely connection with BoNT treatment have been reported but are not conclusively understood. Health authorities in the USA and Europe have not concluded that there is a causal connection, but the ongoing discussion concerning safety and licensing of BoNT needs to be followed carefully by each treating physician.

Due to the elective and repetitive nature of BoNT injection in patients with spasticity, especially children have the right for a pain-free procedure. Therefore, depending on the local prerequisites, some sort of analgesia has to be available for the patients. To assure correct injection into the targeted muscles, guiding techniques are necessary. Bony landmarks and palpation proved to be insufficient [26]. In pediatric neurology ultrasound has evolved to be the method of choice to assure accurate injection of muscles with BoNT[27].

18.3 Dystonia

18.3.1 Description of Presenting Symptoms

Dystonia is clinically characterized by involuntary sustained or intermittent muscle contractions, which cause twisting and repetitive movements (hyperkinetic), abnormal postures (dystonic), or both [3]. Childhood dystonias represent a heterogeneous group of movement disorders and etiology ranges from inherited disorders to dyskinetic cerebral palsy. Generalized dystonias predominate and cause significant disability. Dystonia is commonly triggered or exacerbated by attempted voluntary movement and may fluctuate in presence and severity over time. The severity and quality of dystonic postures may vary with body position, specific tasks, emotional state, or level of consciousness [3]. Dystonia may cause hypertonia as a result of dystonically co-contracting agonists and antagonists, but hypertonia is not always present in dystonia. Dystonia may be limited to specific regions of the body, leading to a more specific dystonic syndrome (e.g., torticollis). In general, the location of dystonia is characterized as focal when it affects a single body part, segmental when

it affects 1 or more contiguous body parts, multifocal when it affects 2 or more noncontiguous body parts, generalized when it affects 1 leg and the trunk plus 1 other body part or both legs plus 1 other body part, and hemidystonia when it affects only one half of the body [3]. Athetosis, poor dexterity, abnormal patterns of muscle activation, eye movement, and oromotor abnormalities are frequently associated with dystonia.

The anatomic localization of lesions that lead to dystonia has not yet been identified with certainty, but pathophysiologically, a dysfunction of the striato-pallido-thalamo-cortical motor loop is thought to play a key role with a reduced globus pallidus internus activity, which leads to disinhibition of thalamus and therefore increased stimulation of motor cortex. This is the rationale for deep brain stimulation therapy of globus pallidus internus. It is likely that many forms of childhood dystonia are attributable to lesions in the basal ganglia [3], but a genetical reason has to be considered, when lesions are not present. Multiple genetic loci and genes have been described in conjunction with dystonia (DYT1 … DYT 16). For details see www.ncbi.nlm.nih.gov/omim, www.wemove.org.

Besides the classification with respect to the affected body parts, several dystonic phenotypes can be differentiated:

1. Primary generalized dystonia
2. Paroxysmal kinesiogenic/non-kinesiogenic dystonia
3. Dopamine-responsive dystonia
4. Heredodegenerative/secondary dystonia
5. Focal/segmental dystonia
6. Dystonic storm/status dystonicus
7. Acute dystonic reaction

The following differential diagnoses have to be kept in mind in patients presenting with dystonia:

- Seizures/epilepsy (focal/tonic)
- Sandifer syndrome
- Spasmus nutans
- Benign paroxysmal torticollis
- Psychogenic movement disorder
- Alternating hemiplegia
- Tic disorders

18.3.2 Recommended Assessments

18.3.2.1 Clinical Assessments

Dystonia may be action induced or posture induced; therefore, it is essential to test for dystonia in all mentioned positions and actions. Dystonia and spasticity may

Table 18.4 Diagnostic workup in childhood dystonia

Blood
Blood smear (acanthocytosis?)
Calcium, phosphate, copper, ceruloplasmin, urea
GOT, GPT, ammonia
Lactate, carnitine, amino acids
TSH, T3
Antistreptolysin titer, anti-DNase titer
Genetic testing for generalized torsion dystonia (DYT1)
Urine
Organic acids
Lactate, creatine metabolites
Copper in 24 h. Urine sample
Oligosaccharides, mucopolysaccharides
Neurophysiology
EMG: Co-contractions?
EEG: Epileptic discharges?
Liquor
Lactate, biogene amines
Dopamine substitution test
Ophthalmologic examination
Neuroimaging
Cranial MRI
MR spectroscopy for detection of lactate peaks in the basal ganglia or creatine deficiency
Cranial CT when calcification of basal ganglia is suspected (discuss with your radiologist, whether modern MRI sequences will detect calcification)

occur in the same limb, and distinction requires determining the velocity-dependent, action-induced, and posture-responsive components.

Video documentation is necessary to compare outcome of any intervention with baseline, as well as potentially natural progression.

The *Barry-Albright Scale (BAS)* assesses dystonia on a 5-point ordinal scale, which rates severity in eight body regions. It can be used in all ages [28]. This scale produces a reliable total score for children with generalized dystonia, but reliability of scores of individual regions is less.

The *Burke-Fahn-Marsden Dystonia Rating Scale (BFM)* assesses dystonia in ten body regions with inclusion of provoking factors and severity weighting. It is well established and can be used at all ages [29].

The *Global Dystonia Rating Scale (GDS)* is a third rating scale for dystonia and was rated to be the most useful dystonia rating scale in adult neurology [30].

18.3.2.2 Diagnostic Workup

For diagnostic workup, see Table 18.4.

Table 18.5 Oral medication in primary generalized dystonia

Dopamine agonists: Levodopa/carbidopa	Start with 1 mg/kg BW/day (max. 25 mg), and increase in 25 mg steps/week to the maximum of 10 mg/kg divided into 3 doses/day
Anticholinergics: Trihexyphenidyl	Start with 0.5 mg, and increase by 0.5 mg/week (>5 years of age use 1 mg steps). Maintenance: 10–20(−60) mg/day divided into 3–4 doses/day
Baclofen	Start with 0.5 mg/kg divided into 3 doses, and increase weekly by 0.5 mg/kg. Maintenance: 2–5 mg/kg/day divided into 2–4 doses (max. 60 mg/day)
Others	
Clonazepam	
Dopamine depleting agents	
Dopamine receptor blockers	

Table 18.6 Oral medication for paroxysmal dyskinesias

Kinesiogenic	*Carbamazepine* (Tegretol, Timonil)	Start with 5(−10) mg/kg BW. Usually low doses suffice to be free of symptoms
Non-kinesiogenic	*Clonazepam* (Rivotril)	1.5–3 mg/day in infants, 3–6 mg/day in school-aged children, 4–8 mg/day in adolescents

18.3.3 Recommended Interventions

Multidisciplinary supportive care is necessary as in spasticity management. It comprises functional therapies, orthotics, oral medication, focal medication, neurosurgery, and sometimes orthopedic surgery.

The therapeutic window for oral medication is narrow and side effects limit clinical use. In persisting focal dystonia with limitations in daily activities, consider additional therapy with botulinum toxin. Best choice of medication remains trial and error.

For *dopamine-responsive dystonia* (Segawa syndrome), *L-Dopa*: levodopa/carbidopa (Madopar, Sinemet) is very effective. Administered orally start with 1 mg/kg body weight (BW) per day (max. 25 mg) and increase in 25 mg steps/week. Very good and sudden response to low dose L-Dopa is common. In rare circumstances, there is a late response (>3 weeks), or higher doses (>100–150 mg L-Dopa) are needed.

For oral medication in *primary generalized dystonia*, see Table 18.5. If the patient experiences nonresponse, check early the indication for deep brain stimulation (DBS) of internal pallidal globe (esp. in DYT1 positive dystonia).

For oral medication in *paroxysmal kinesiogenic and non-kinesiogenic dyskinesia,* see Table 18.6.

Very low doses of carbamazepine are often sufficient to treat the disorder completely. Carbamazepine may worsen myoclonus and myoclonic epilepsy. While the

Table 18.7 Management of acute dystonic reaction

Life threatening	*Oxygen* administration	
	Diazepam: Orally/rectally	5–10 mg
	Lorazepam: Orally, I.M, I.V.	0.1(–0.2) mg/kg Maximum: 4 mg as single dose
	Biperiden: Slowly I.V.	0,05–0,1 mg/kg Maximum 5 mg/6 h
Severe	*Biperiden*: Slowly I.V.	0.05–0.1 mg/kg
	Promethazine: I.V.	0.5–1 mg/kg

dose is being increased, side effects include nausea and mild sedation. Carbamazepine may cause a decrease in the white blood cell count (WBC) and increases in markers for liver disease. Clonazepam usually is less effective.

In *heredodegenerative and secondary dystonia*, treat etiology if possible. Oral medication worth full trying could be *L-Dopa and trihexyphenidyl* (for dosage see Table 18.5). Additionally *tetrabenazine* (Nitoman) can be administered orally with a starting dose of 12.5 mg per day increased weekly in 12.5 mg/day steps. Maintenance dosage usually ranges between 100 and 200 mg divided into 3–4 doses per day. Additionally baclofen and botulinum toxin could be helpful (see Tables 18.3, 18.5).

In *focal dystonia*, Botulinum toxin has proven to be effective (torticollis, writer's cramp, etc.). Second-line medication would be *trihexyphenidyl* or *tetrabenazine* (see above).

Status dystonicus (dystonic storm) describes a life-threatening condition seen in dystonic patients (e.g., patients with posttraumatic dystonia or near drowning). It is characterized by severe generalized muscle contractions being extremely painful. They are triggered by infection, stress, trauma, surgery, fever, zinc or penicillamine therapy in Wilson's disease, abrupt introduction, withdrawal, or change in medical treatment, including lithium, tetrabenazine, and clonazepam. Management has to be initiated promptly on intensive care unit and requires basic supportive therapy (fluid balance, analgesia, antipyretics, ventilatory support, hemodynamic monitoring) and indication for deep sedation under muscle paralysis and assisted ventilation has to be checked early. Medications regularly used are midazolam and propofol. It may require a more invasive approach with intrathecal (or intraventricular) baclofen infusion. Bilateral pallidal deep brain stimulation can be considered in rare cases (e.g., pantothenate kinase deficiency); in the majority of patients, DBS remains an experimental approach.

Complications of status dystonicus are hypercreatine kinesemia, rhabdomyolysis, hyperpyrexia, muscle exhaustion, pain, dehydration, acute renal failure, and respiratory insufficiency. An important differential diagnosis is the neuroleptic malignant syndrome (see Chap. 7) and malignant hyperthermia (see Chap. 4).

Acute dystonic reactions can be life threatening (very rare) or severe. For acute treatment, see Table 18.7.

Explicitly ask for intake of antidopaminergic medication (e.g., antiemetics), serotonin reuptake inhibitors, biperiden (relapse?), cocaine, previous dystonic reactions, and HIV.

If symptoms persist for more than 3 min after first biperiden dosage, repeat biperiden dosage once.

If symptoms persist after 60 min, change medication**.** Dose escalation should only be performed on intensive care unit under vital parameter monitoring. In persisting nonresponse check the diagnosis.

18.4 Other Movement Disorders

The spectrum of movement disorders in pediatrics is wide. A brief overview will be presented in tabulated form for the following movement disorders:

- *Tic disorders*: intermittent, repeated, stereotyped movements or sounds that occur infrequent or almost constant (Table 18.8).
- *Restless legs syndrome*: spontaneous, continuous urge to move the legs associated with unpleasant paresthesias especially at rest that improve with movement (Table 18.9).
- *Ataxia*: lack of coordination while performing voluntary movements leading to disturbance and unsmooth, disjointed, jerky movements (Table 18.10)
- *Opsoclonus-myoclonus(−ataxia) syndrome (OMS, OMA)*: opsoclonus: ocular motility disorder with spontaneous, arrhythmic, conjugate saccades occurring in any direction of gaze without a saccadic interval (dancing eye). Myoclonus: brief, shock-like, involuntary movements caused by muscular contractions of inhibitions (Table 18.11)
- *Tremor*: rhythmic back-and-forth or oscillating involuntary movement about a joint axis with a relative symmetric velocity in both directions (Table 18.12)
- *Chorea*: ongoing brief, random-appearing sequence of one or more discrete involuntary movements or movement fragments (Table 18.13)

18.5 Management of Patients with Intrathecal Baclofen (ITB) Therapy Overdose and Withdrawal Syndrome

18.5.1 Introduction

Lioresal (baclofen) is an agonist of GABA B receptor and is regularly used as a drug to reduce spasticity or dystonic hyperactivity. It acts at the spinal cord and reduces reflex activity thereby lowering muscle tone. Actions at supraspinal site may contribute to its clinical effect.

It can be administered intrathecally if oral dosages are not sufficient to relieve hypertonia or side effects occur. The pivotal factor for better efficacy and tolerance is the fact that intrathecally administered dosages are by factor 100–1,000 smaller compared to oral dosages.

Table 18.8 TIC disorders

Presenting symptoms	Recommended management		Additional recommendations
Simple: Vocal or focal movements	Transitory symptoms (<1 year)	No or defensive pharmacotherapy; education and establishment of coping strategies is important	Involuntary movements can be suppressed for only a certain period of time
Complex:		Habit reversal training	Sense of relief after the execution of tic
Words, phrases, stereotype sequences of movements			
Tourette syndrome		Tiapride (Tiapridex) orally:	Tics usually aggravate during stress
Multiple motor tics	Strong psychological strain	7–12 years: 50–100 mg per dose up to 2–3 times/day (not available in the USA)	*Etiology*
At least one vocal tic		Risperidone (Risperdal) orally: 0.5–4(−9) mg daily divided in 1–2 doses	Primary
Start before 21 years of age		Pimozide (Orap) orally:	Drug induced (amphetamines, Ritalin, caffeine, carbamazepine, steroids, neuroleptics, CO)
Symptoms wax and wane over the years		2–12 years: 0.5–4 mg daily 12–18 years: 2–10 mg daily	Parainfectious: postencephalitic, PANDAS (still controversial)
		Haloperidol (Haldol) orally:	Others: neuroacanthocytosis, Huntington's disease, Wilson's disease, pantothenate kinase syndrome, autism spectrum disorders
		0.25–0.5(−5) mg daily divided in 1–2 doses	Adverse event: tardive dyskinesia (persistent, repetitive involuntary movements usually involving the lower face). These may not be fully reversible, especially in children

Table 18.9 Restless legs syndrome

Presenting symptoms	Recommended management	Additional recommendations
Intermittent	Nonpharmacologic therapy	Usually primary, can be secondary
Daily	Iron replacement	Iron deficiency
Refractory	Mental alerting activities	Vitamin B12 or folic acid deficiency
	Avoidance of aggravating factors	Thyroid dysfunction
	Improvement of sleeping hygiene	End-stage renal disease
	Increase frequency of hemodialysis in patients with renal replacement therapy	Diabetes mellitus
	Pharmacotherapy	Multiple sclerosis
	Dopamine agonists: (Pramipexole and ropinirole: no pediatric dosage established—refer to adult neurology)	Rheumatic diseases
	L-Dopa (levodopa/carbidopa 100/25 mg) single dose 1 h before sleep time	Venous insufficiency
	Others:	Plus…
	Benzodiazepines and opioids (refer to adult neurology guidelines)	Dopamine agonists seem to be superior to L-Dopa
		Problems with L-Dopa
		Augmentation
		Rebound of RLS in the morning
		Recurrence in second half of the night

Intrathecal baclofen is administered via an implanted pump-catheter system, with the pump implanted abdominally and a spinal catheter placed intrathecally. Usually, the tip of the catheter is on the thoracic or cervical level.

As with every implanted system, there is a risk of dysfunction due to several reasons. The most vulnerable part of the system is the catheter itself that can occlude, dislocate, or disconnect. In addition there is a small but significant risk of infections.

Patients with a baclofen pump have often concomitant diseases or varying symptoms such as drowsiness, dizziness, constipation, and seizures. Secondly these symptoms may or may not be associated with baclofen therapy as a side effect or symptom of malfunction of the system.

If there is a significant change in health status of a patient with an implanted baclofen pump, it is important:

- Not to overlook that the patient has an implanted system—several case reports in the literature describe a harmful delayed identification of the pump.
- That dosages and recent changes in dosages are checked—preferentially by looking at printouts from last refill visits documenting status and changes of the system.
- That a dysfunction of the system is ruled out [31–33].

Table 18.10 Ataxia

Presenting symptoms	Recommended management	Additional recommendations
Congenital nonprogressive ataxia:	Search for specific metabolic disorder with specific therapy	Ask for
Pontocerebellar hypoplasia	Functional therapies as foundation of a multidisciplinary treatment strategy	Variation of severity during the day
Agenesis or hypoplasia of the cerebellar vermis	L-Dopa (for dosage see Table 18.5)	Relation to meal intake
Cerebral palsy	Idebenone (Catena): orally 15–45 mg/kg BW per day	Symptoms become worse, when child is tired, hungry, or ill
Acute nonprogressive ataxia	Coenzyme Q 10: orally 400 mg/day	Stable or progressive ataxia
Virus infection, (varicella, see Chap. 17)	Topiramate (Topamax): orally 0.5–2 mg/kg BW per day	Restitution in between ataxic episodes
Basilar migraine		Family history
Episodic ataxia		See also: http://ghr.nlm.nih.gov/, www.wemove.org
Familial, AD inheritance		
"Channelopathies"		
Nonprogressive chronic ataxia		
Stroke, trauma, HIE, tumor, etc.		
Progressive ataxia		
Metabolic/chemical		
Degenerative/demyelinating		
Tumors/paraneoplastic		

The last step can only be performed certainly by a physician with experience in ITB therapy. Therefore, it is recommended to get in touch with the responsible physician as soon as the symptoms of the patient raise suspicion of system malfunctioning, even if the patient's signs and symptoms seem to be mild.

18.5.2 ITB Overdose

18.5.2.1 Presenting Symptoms

Patients with ITB overdose present with pronounced muscular hypotonia, nausea and vomiting, headaches, drowsiness, dizziness, somnolence, nystagmus, arterial hypotension, respiratory depression, seizures, urinary retention, constipation, and pseudo-obstruction. Drowsiness can progress to somnolence and finally loss of consciousness and coma.

Table 18.11 Opsoclonus-myoclonus (−ataxia) syndrome (OMS, OMA)

Presenting symptoms	Recommended management	Additional recommendations
Ataxia	Immunologic therapy Pulsed steroid therapy Methylprednisolone I.V.: 20–30 mg/kg/day (max 500–1,000 mg daily) for 3(−5) days Dexamethasone orally: 1–2 mg/kg/day over 3(−5) days (max. daily dose 16–32 mg)	Intervals between weeks and months depending on clinical course (Necessary overall treatment time for the repeated pulses can be years)
"Dancing eye syndrome" Age: 1.5–3 years of age Drooling	Continuous prednisone orally: 2 mg/kg/day Cyclophosphamide (Endoxan) orally: 2–8 mg/kg/day Immunoglobulins I.V.: 0.4 g/kg/day during 4 days Alternative: 1 g/kg/day during 2 days	Prolonged taper over several months (not preferred by the authors)
Loss of ambulation Speech impairment	Plasma exchange Rituximab	Intensive care unit Potential add-on, not established
Insomnia Behavioral problems ("rage attacks") Depression Hyperkinetic disorder Attention deficit	Rage attacks Trazodone (Desyrel) orally: 1.5–2 mg/kg/day divided into three doses (not more than 6 mg/kg/day)	

Overdosing can occur especially during testing and dose adjustment periods when still trying to find the optimum dosage for the individual patient. Frequent causes are:

- Errors in pump programming
- Confusion of available infusion solutions
- Inadvertent injection into subcutaneous tissue during refill procedure
- Direct injection into the catheter through the catheter access port

18.5.2.2 Assessments

Investigations include a thorough clinical investigation to delineate a hypothesis for further workup of the patient. Then pump-catheter system has to be checked by an experienced team. This check includes the following steps: check the remaining volume within the pump, puncture the side port to aspirate spinal fluid, administer contrast medium, examine the patient radioscopically after cranial and caudal tilting, and use CT to assess epidural distribution of the contrast medium and MRT to assess a possible involvement of granuloma at the catheter tip.

Table 18.12 Tremor

Presenting symptoms	Recommended management	Additional recommendations
Primary tremors:		Tremor analysis:
(Enhanced) physiological tremor: typically in "clumsy" children with the diagnosis of developmental coordination disorder (DCD)	No therapy, education, concept of variety of motor development	Frequency Amplitude Aggravation Associated symptoms
Essential tremor: Isolated postural tremor, aggravates during stress, might interfere with activities of daily life	Propranolol orally: 20–60(−320) mg daily divided in 1–3 doses, standard adult dose 3 × 20 mg/day	Therapeutic window for oral medication is narrow and side effects limit clinical use
		Small amounts of alcohol improve symptoms in 50–70 % of cases (caution about self-treatment even in adolescents)
		Exclude secondary tremors and check especially for: Thyroid function Electrolytes Hypoglycemia Medications Wilson's disease (if clinically suspectable)
	Primidone (Mysoline)orally: 1–10(−20)mg/kg daily, titrate slowly on individual basis	
Cerebellar tremor: Intention tremor with increasing amplitude, frequency <5 Hz	Topiramate (Topamax) orally: 0.5–2 mg/kg daily	Check for oculomotor dysfunction, evaluate indication for deep brain stimulation (BDS)
Dystonic tremor: Focal, sensory trick	Botulinum toxins: see above	Video documentation might help to assure the diagnosis, consider deep brain stimulation (DBS)
Psychogenic tremor: Irregular tremor	Multimodal therapy	Exclude secondary tremors

Palatal tremor with or without ear click. Ear click can be primary or secondary due to brainstem infarction	Botulinum toxin	Consult ENT specialist, neuroimaging
Spasmus nutans	Spontaneous remission, usually 6–12 months of age (–3 years), Uni- or bilateral nystagmus (essential feature: disconjugacy)	Ophthalmologic consultation to exclude other reasons for strabismus, refractory errors, amblyopia, and other forms of congenital nystagmus
Ocular oscillation (Horizontal nystagmus)		
Head nodding		Cranial MRI to exclude underlying tumor (1 % of cases)
Head turning (torticollis)		
Jittering: High frequency, low amplitude (typical symptom in 50 % of neonates)	No therapy, exclude drug withdrawal, hypoglycemia, hypocalcemia	Typical region: chin
Shuddering attacks	No therapy	Excitement, concentration induced
Secondary tremors	Treat underlying cause	Refer to pediatric textbooks
Endocrine		
Medication		
Intoxication		
Metabolic		

Table 18.13 Chorea

Presenting symptoms	Recommended management	Additional recommendations
Sydenham chorea (SC, chorea minor) one major clinical features of rheumatic fever	Penicillin orally: 100,000 IE/kg daily for 10 days (max. 1,200,000 IE/day) followed by prophylaxis with 200,000 IE daily up to months/years (duration is a controversial)	Most common acquired chorea in childhood; 1–8 months following group A streptococcal infection
	Chronic state Tetrabenazine (Nitoman) Valproate Steroids Immunoglobulin I.V.	Molecular mimicry of antibodies cross-reacting with hosts antigens
PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections)		Expanded neuropsychiatric clinical spectrum compared to SC, still controversial
Benign hereditary chorea: Autosomal dominant inheritance Chromosome 14q, mutation in TIFT 1 Gen	Clobazam Clonazepam Haloperidol Others	Pharmacotherapy rarely helpful, "benign" is sometimes misleading with respect to severity and course
Others Metabolic Genetic Infections Vascular	Treat underlying cause	Refer to pediatric textbooks

18.5.2.3 Interventions

- Treat the patient symptomatically on the intensive care unit (including controlled artificial respiration if necessary).
- Check dosage and refill plan of the patient.
- Check the patient's medical record or with the patient's physician to confirm the drug or drug concentration within the pump reservoir.
- Seek information from an ITB-experienced physician: how long/how much to lower the ITB dose or to empty the pump (undertake this action on your own only in case you have the appropriate equipment; otherwise, you may damage the pump or catheter).
- Be aware of withdrawal symptoms if the dose was lowered significantly.
- According to the personal opinion by the authors, early drawing of cerebrospinal fluid (with the aim to lower the baclofen concentration in CSF) or parenteral administration of physostigmine is not suitable, although described by others [34].

Measuring baclofen levels in plasma or CSF is neither necessary nor useful.

Please note that it is inadvisable to stop the pump completely, because it will damage devices irreparably (e.g., Medtronic®).

18.5.3 ITB Withdrawal

18.5.3.1 Presenting Symptoms

Increasing muscle tone, rebound spasticity, feeling restless, vomiting, fever, insomnia, clouded consciousness, pruritus without rash, convulsions, multiorgan failure, and rhabdomyolysis are symptoms of ITB withdrawal. The condition may resemble autonomic dysreflexia, sepsis, malignant hyperthermia, and neuroleptic malignant syndrome.

Withdrawal of baclofen is caused by:

- Malfunctions in the catheter system
- Disconnection of the pump-catheter or catheter-catheter (2-piece catheter) systems
- Dislocation of catheter tip
- A kink in the catheter
- The level of the infusion solution in the pump is too low or the reservoir is empty
- The battery is expired
- Filling or programming was incorrect
- Infection
- An intrathecal mass at the tip of catheter

18.5.3.2 Assessment

Please refer to ITB overdose (Sect. 18.5.2). In addition, consider a possible microbial contamination of pump pouch and catheter system if patient with ITB treatment presents with fever and other signs of an infectious disease.

18.5.3.3 Interventions

- Monitor and treat the patient in the intensive care unit
- Contact a physician experienced in ITB treatment
- If a physician experienced in ITB is unavailable or if restoration of intrathecal baclofen at the same dose as before is not possible or delayed, the following is recommended (unless otherwise contraindicated):
  - High-dose oral or enteral baclofen in combination with
  - Preferentially intravenous (or oral or enteral) benzodiazepines (e.g., diazepam) by continuous or intermittent infusion. Titrate the dosage until the desired therapeutic effect is achieved.
  - Thereafter, organize thorough checkup of the pump-catheter system by an ITB-experienced team.

In case an infection is assumed:

- Check for signs of meningitis.
- Do an inspection and palpation of pump pouch and lumbar fixation of the spinal catheter.

- Perform a lumbar puncture to collect CSF (be careful not to damage the catheter!).
- Aspirate CSF via puncture of the side port/catheter access (undertake this action only in case you have the appropriate equipment and experience; otherwise, you may damage the pump or catheter).

Please note that under special circumstances, e.g., when the tip of the catheter is dislocated, there may be an inconstant flow of baclofen, and therefore, symptoms of overdose may alternate with symptom of withdrawal, which can be a puzzling situation. In this case stabilize vital parameters on the ICU and contact ITB-experienced physicians.

When dealing with a patient with an ITB pump, the following notes may also be helpful:

- Collect useful information:
  - Pump type
  - Catheter type
  - Pump volume
  - Type and concentration of the drug
  - Dose per day
  - Date to which the reservoir alarm is set
  - Date for the next refill
- MRT in patients with baclofen pump implanted:
  - Cranial MRT is without problems up to a field strength of 3.0 T (observe manufacturer-dependent specifications).
  - Following MRT, some pumps must be (telemetrically) checked for a possible rotor stop.
- Decommissioning the pump:
  - If a child with a pump implant dies, check if the pump has to be decommissioned to avoid any acoustic alarms in the future.

The full prescribing information includes a detailed description of the therapy and can be found at http://www.medtronic.com/patients/severe-spasticity/full-prescribing-information/index.htm (accessed November 11, 2012).

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Chapter 19
Acute Pain

Stefan Lundeberg and Alyssa A. LeBel

Abstract Pain is a common symptom and still undertreated in children despite better knowledge. Safety has improved with the development of new drugs and fuller understanding of their pharmacokinetics and dynamics in children. For successful treatment, the mechanism of pain has to be analyzed. A multimodal analgesic treatment strategy is suggested, and analgesics should be used with appropriate complementary methods. Where complex analgesia is needed, consulting an acute pain treatment team with pediatric expertise is the most helpful approach.

Keywords Pain • Nociceptive • Neuropathic • Procedural pain • Pain management • Pediatric

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19.1 Introduction

19.1.1 Overview of the Ontogeny and Neurobiology of Pain

Over the past 40 years, the practice of pediatric pain management has advanced from a stage of anecdotal report to a research-supported standard of care in developed and many developing countries. Statements, such as the one delivered by Swafford and Allan in a textbook of pediatrics from 1968, are now considered blatantly false: "Pediatric patients seldom need medication for the relief of pain. They tolerate discomfort well. The child will say he does not feel well, or that he is uncomfortable or that he wants his parents but often will not relate this unhappiness to pain." However, challenges in pediatric pain assessment, cognitive and behavioral changes in a developing patient population, and limitations of controlled and randomized investigations in vulnerable subjects still influence the field. Fortunately, clinicians no longer assume that "neurologic immaturity" limits an infant or child's appreciation and experience of pain. Anatomic, neurochemical, and neuroimaging studies describe a functional pain transmission system present during the fetal period and maturing throughout childhood. Neuromodulatory systems present predominantly after birth and still demonstrate robust neuroplasticity into late adolescence.

More specifically, sensory nerve terminals for cutaneous nociception are present in the fetal perioral areas at 7 weeks GA (gestational age), with spread to the entire body by 20 weeks GA. At the level of the dorsal horn of the spinal cord, A-fibers enter prior to C-fibers at 8–12 weeks GA. A and C fiber territory overlaps at birth in the developing substantia gelatinosa. Ascending pain pathways are completely myelinated in the spine and brainstem between 22 and 30 weeks GA. Myelination extends to the thalamus at 30 weeks and to the cortex at 37 weeks to term. Descending inhibitory pathways develop post-term.

Excitatory neurotransmitters and neuromodulators develop early in the fetus, at 8–10 weeks GA, including CGRP (calcitonin gene-related polypeptide), SP (substance P), somatostatin, and NMDA (*N*-methyl-D-aspartate) systems. VIP (vasoactive intestinal peptide) and enkephalin appear at 10–14 weeks. Catecholamines are present in late gestation, and serotonin systems develop 6 weeks post-term. Receptors for excitatory neurotransmitters are numerous and widely distributed in the neonate, regressing to a more adult distribution during the postnatal months. In the late fetus, GABA (gamma aminobutyric acid) and glycine may act as excitatory neurotransmitters. NMDA and NK-1 (neurokinin-1) receptor density are maximal in the late fetal period.

At the cortical level, near-infrared spectroscopy shows hemodynamic and oxygenation changes in the neonatal brain following touch and noxious stimulation of a limb that may relate to cortical processing of tactile and painful stimuli, such as venipuncture. Stress responses are present in the neonate and may generate morbidity through stress-induced hyperglycemia, lactic acidosis, catecholamine release,

and substrate mobilization. Neuroendocrine pathways between the hypothalamus and pituitary function at 21 weeks gestation; cortisol and beta-endorphin have been assayed following intrauterine sampling for exchange transfusion. Norepinephrine is present in paravertebral ganglia and adrenal chromaffin cells at 10 weeks gestation and is released with intrauterine stress (asphyxia). In a landmark paper by Anand and Hickey in 1987, the metabolic effects of pain in the fetus and neonate were delineated, providing a scientific basis for the treatment of neonatal pain.

The influence of early pain responses on later pain behaviors is provocative in many animal studies and increasingly replicated, with some controversy, in human reports. One study by Grunau compared 18 preterm infants, subject to repeated painful procedures in the NICU (neonatal intensive care unit), with matched full-term infants regarding their somatic complaints at 18 months. Twenty-five percent of mothers of preterm infants with prolonged NICU stays noted a significantly increased number of somatic complaints in their toddlers as compared to mothers of full-term infants who had brief normal nursery stays.

In summary, the neonatal pain transmission system is anatomically present, readily excitable, with the potential for central sensitization. Neonates and infants feel pain, but the cortical modulation of noxious stimuli is still under investigation.

19.2 Presenting Symptoms and Recommended Assessment of Pain

There is no objective, generic measurement of pain. It is a complex and multidimensional sensation that is modulated by previous pain experience, affect, attention, family beliefs, and environment. Pain is best assessed by questioning the patient directly, a challenge for infants and nonverbal children who must rely on their caregivers to interpret and report signs of pain and distress.

For verbal and school-aged patients, questions about pain quality, location, duration, and severity are possible, as well as a past history of relieving and exacerbating factors. Severity may be most reliably determined using a numeric rating scale, choosing numbers from 1 to 10, or VAS (visual analog scale), making a mark along a 10 cm line from “no pain” to “worst pain imaginable.” Patients with less appreciation of numeric ranking may substitute a faces scale. Location may be colored onto a figure.

Additional measures for more comprehensive assessment may include an inventory of symptoms, the CDI (Children’s Depression Inventory; 1982 by Maria Kovacs PhD), the Revised Children’s Manifest Anxiety Scale (RCMAS-2; 2008 by Western Psychological Services), and the Pain Response Inventory [1].

Pain assessment methods for infants and preverbal children often combine behavioral and physiologic indices. Scales are based on behavioral features such as facial expression, crying, and posture and behavioral variables such as heart and respiratory rate, blood pressure, and sweating (Table 19.1). Limitations in the use of

Table 19.1 FLACC (Face, Legs, Activity, Cry, Consolability)

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

From Merkel et al. [2]. ©The Regents of the University of Michigan. Used with permission
The scale has five criteria which are each assigned a score of 0, 1, or 2. The scale is scored between a range of 0–10 with 0 representing no pain

these measures include distinguishing between pain and distress, such as hunger or fear. Physiologic changes may represent sepsis, hypoxia, or medication effects rather than pain. However, regular use of these scales is indicated in this patient population.

For children with developmental delay, nurses have recently developed a modification of behavioral and physiologic observation, with the assistance of the primary caretakers, the INRS (individualized numeric rating scale).

In pediatric care, cognitive development influences communication of pain as well as coping strategies. Children as young as 18 months may indicate the location of pain, but pain intensity is difficult to elicit before 3 years. At 3 years, children can grossly estimate "no pain; a little pain; and a lot of pain." Concrete measures, such as "poker chips" and "pieces of hurt" may also be used to convey intensity. The use of more abstract self-report measures, such as the faces scales, is not valid for most patients under 5 years of age. Simple self-report measures are recommended for children older than 6 years, such as the NRS and VAS. Many adult scales are appropriate for adolescents.

Coping strategies are also determined by cognitive levels. Children at 18 months may indicate an awareness of ways to eliminate pain through structured play sessions. They may seek hugs and kisses and ask for medicine. Children who are 3–4 years of age may spontaneously use distraction and also report that play makes them feel better. Deliberate distraction and self-initiated cognitive strategies present at approximately age 5 years. Cognitive and behavioral strategies, such as relaxation and biofeedback, are usually most effective after age 6–7 years.

19.2.1 Pain Classification

Pain is often described in relation to time (acute vs. long term) or underlying etiology as:

- Nociceptive
- Inflammatory
- Neuropathic
- Functional (psychogenic)
- Idiopathic (without known origin)

Pain is often a mixture of different types, such as nociceptive and neuropathic. It is of major importance to analyze what kind of pain the patient is suffering from in order to prescribe the most beneficial treatment and analgesics. Nociceptive pain and neuropathic pain are the two most common pain types in infants, children, and adolescents. Psychogenic pain is now best described as neuropathic central pain. Idiopathic pain usually has a physiologic origin, yet to be defined.

19.2.2 Acute and Chronic Pain

Pain, as defined by IASP (International Association for the Study of Pain), is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." Clinically, patients present four different types of pain, primarily based on the time course of symptoms but also reflective of underlying nociceptive mechanisms (nociceptors, primary afferent fibers, ascending nociceptive tracts) and the ultimate distribution and memory of neural activation and modulation throughout the pain transmission system (cortical and subcortical centers, descending modulatory systems). These four patterns are:

- Transient pain – activation of nociceptors in the absence of tissue damage (venipuncture, lumbar puncture)
- Acute pain – tissue injury, regional activation of nociceptors and their dorsal horn and central connections, and restoration of normal nociceptive function with tissue healing (trauma, surgery)
- Chronic pain, cancer related – ongoing tissue injury due to disease and/or repetitive treatments with sustained nociceptive activation/hyperalgesia and central modulation of the pain signals by cortical regions involving discrimination, attention, affect, emotion, memory, and motor control (surgery, radiation, chemotherapy)
- Chronic pain, nonmalignant disease – persistent pain due to complex central and peripheral neuronal changes that outlast the original nociceptive stimuli, such as injury and disease, or are generated directly by nervous system dysfunction (peripheral neuropathy, spinal cord injury, somatoform disorder)

Pain treatment is guided by recognition of these pain categories, and all temporal patterns may overlap in a single patient, such as a pediatric cancer patient with metastatic osteosarcoma, post-amputation, undergoing radiation and chemotherapy, as well as multiple transient procedures.

Regarding procedural pain, noninvasive options include distraction, parental involvement, choice, cognitive techniques in children developmentally older than 4–5 years, sucrose in infants less than 6 months, and topical anesthetics.

For acute pain, acetaminophen (paracetamol) and nonsteroidal anti-inflammatories, opioids, and possible regional anesthesia will likely be effective until resolution of tissue injury. Opioids are the standard of care for severe acute pain.

For chronic pain, malignant and nonmalignant, recognition of the complex network of pain transmission and modulation is essential, as well as any pain contribution from nerve injury, persistent inflammation, and environmental stress. Treatment may include use of short-acting symptomatic opioids and nonsteroidals, but generally emphasizes long-acting preparations; prophylactic neuropathic pain medications, such as tricyclic antidepressants and antiseizure agents; management of expected side effects; and functional restoration techniques, such as biobehavioral treatment, physical and occupational therapy, reconditioning, and complementary adjuvants. Chronic pain is a multidimensional experience and requires multimodal therapy. Recent brain imaging techniques suggest an extremely distributed system of pain transmission in patients with chronic pain, such as complex regional pain syndrome (Fig. 19.1).

19.2.3 Nociceptive Pain

Activity in pain fibers is evoked by stimulation of pain receptors at the nerve endings, nociceptors. The pain receptors may be sensitive to temperature, mechanical, or chemical stimuli. Pain signaling generates two separate experiences depending upon the type of nerve fiber (A-delta or C-fibers) which is transmitting the input. A-delta fibers, which are myelinated, transmit the impulses faster and are projected to a high degree on the sensory cortex. The effect is a sharp, distinct, and well-localized pain. In contrast, activity in the slower transmitting C-fibers reaches the thalamus and from there more diffusely spreads to multiple brain structures, generating a sensation of a more general pain experience (Fig. 19.2).

From a clinical point of view, nociceptive pain is the most common origin of pain in pediatric patients. An example of nociceptive pain is postoperative pain which is directly related to surgery. Pain develops as a result of tissue damage and the arising inflammatory process. Within minutes after the surgical damage, secondary hyperalgesia develops and pain is amplified via segmental reflexes within the spinal cord. Postoperative pain diminishes because of the healing process, and pain treatment is usually needed for 3 or 4 days. Another example of an acute pain condition is a tendon or a muscle strain due to a trauma. Pain is usually caused by

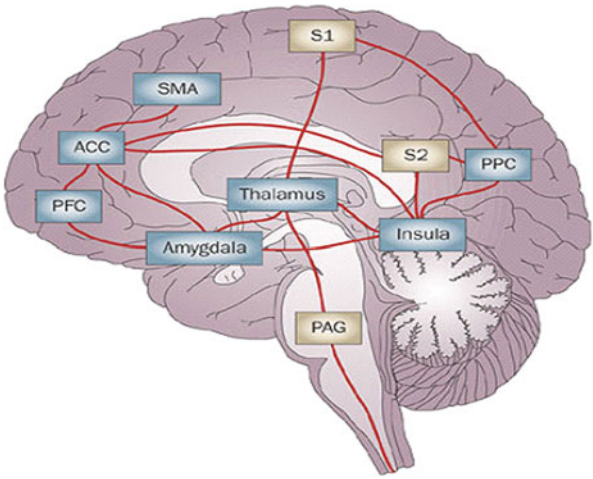

Fig. 19.1 Brain areas active in pain processing as seen with fMRI. Discrimination: thalamus; SSC (I and II, both nociceptive and allodynic), Motivation/affect: anterior cingulate; amygdala, hippocampus (anxiety), Motor control: cingulate; pre-central gyrus; cerebellum, Memory of pain: insula, Modulation *PAG*, Pain/temperature *DM* nucleus of thalamus, Reward/emotional salience: nucleus accumbens *PAG*

mechanical pressure from bleeding in the area. Ischemia develops secondary to the damage and may prolong pain, suffering, and the healing process. Nociceptive pain conditions usually respond to analgesic treatment.

19.2.4 Neuropathic Pain

Neuropathic pain is generated as a direct effect of a lesion or a disease in the somatosensory nervous system. The somatosensory system includes the central nervous system and peripheral nerves. The pain experience is many times not in proportion to the damage. Neuropathic pain can develop at the time of an injury but also weeks to months after a trauma. Interestingly, infants and younger children seldom develop neuropathic pain due to a nerve lesion, such as brachial plexus trauma following birth trauma. Clinical evidence suggests that pain caused by nerve lesion is more likely appreciated after 8–10 years of age.

Pain can be spontaneous (continuous or intermittent) or induced by stimuli and is often described as very intense, sharp, and burning by the patient. On examination, the patient can show signs of hyper- or hyposensitivity to one or several types of stimulation. Pain induced by a non-nociceptive stimulus as touch is called allodynia.

Visceral tissue and organs have complex neurogenic innervations. Conditions and diseases within the visceral system can create severe and complex pain situations. Visceral neuropathic pain is not specifically localized and is often projected to the somatic areas (referred pain).

Treatment with analgesics often has a limited effect on neuropathic pain. Pain reduction can be achieved but seldom total pain relief.

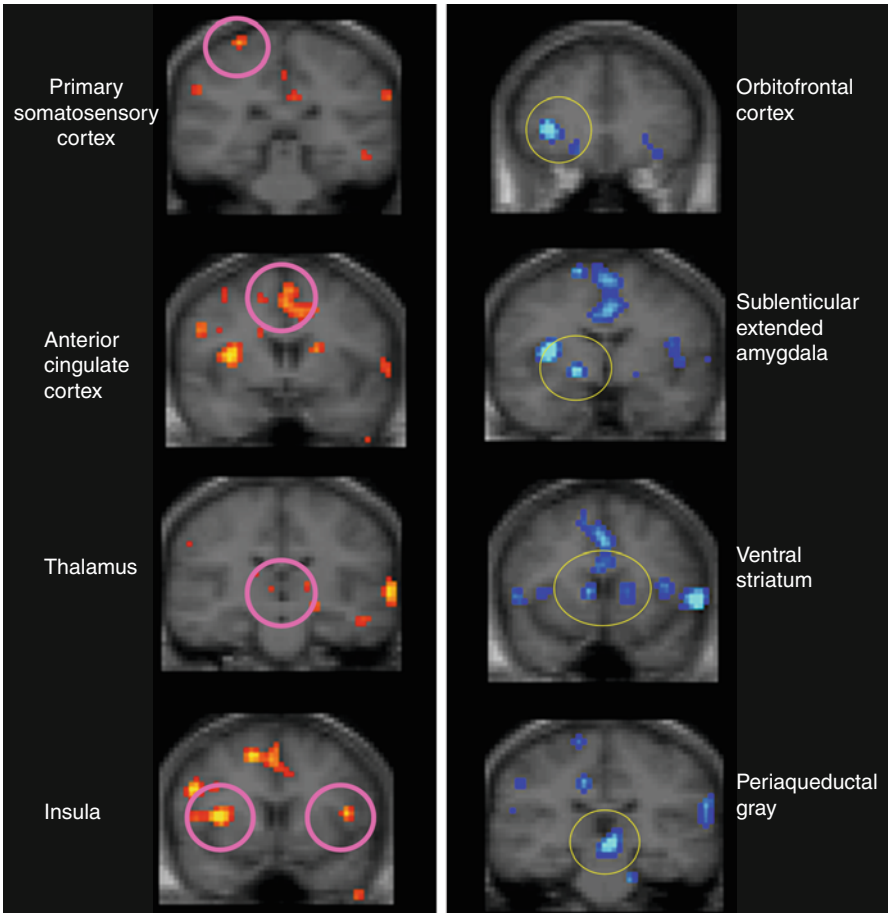

Fig. 19.2 fMRI brain regions of activation after noxious stimulation. (*Left*) Sensory regions; (*right*) emotional regions (From Becerra et al. [3])

19.3 Recommended Treatment

19.3.1 Strategies in the Treatment of Pain

The aim of pain management is to achieve acceptable levels of pain for each individual child with the least side effects possible. Realistic goals are to recognize pain in children with clinical feasible assessment tools, to minimize moderate and severe pain safely, and to prevent pain where it is predictable. Prophylactic treatment in elective surgery and before planned procedures limits the total amount of analgesics needed. A safety web is needed for rapid control of breakthrough pain and to handle

Table 19.2 Treatment strategy

1. Analysis of possible pain mechanisms
2. Assess pain intensity at rest and movement
3. Use a multimodal analgesic technique to achieve an acceptable pain level from the patients standpoint
4. Prescribe analgesic for breakthrough pain
5. Combine analgesic treatment with physical and psychological strategies when possible

Table 19.3 Analgesics

Type of pain	Analgesic
Nociceptive	Local anesthetics
	Acetaminophen (paracetamol)
	NSAIDs
	alpha$_2$-agonists
Neuropathic	Tricyclic antidepressants
	Gabapentin
	Pregabalin
	Topiramate
	Zonisamide

undesirable side effects. Analgesics, such as opioids, cause negative side effects, and it is important to treat side effects promptly when they are problematic (Table 19.2).

The underlying mechanism causing pain should be determined as management of nociceptive and neuropathic pain differs to a large extent. A multimodal analgesia approach is often recommended, especially for neuropathic pain. A combination of analgesics often reduces the need of high doses and related side effects (Table 19.3). Functional pain is seldom reactive to analgesic treatment alone.

Analgesic treatment may be combined with complementary physical and psychological approaches when possible. The importance of involving the child and parents in the treatment plan is essential. Reducing fear, discomfort, and creating patient control are major features for treatment success.

19.3.2 Treatment of Nociceptive Pain Conditions

Many pediatric pain services use techniques of parallel or co-analgesia based on up to six groups of analgesics, namely, local anesthetics, acetaminophen (paracetamol), NSAIDs (nonsteroidal anti-inflammatory drugs), opioids, α(alpha)$_2$-adrenergic receptor agonists, and, to some extent, NMDA blockers, such as ketamine. In particular regional analgesic methods should be used in all cases unless there is a specific contraindication. Analgesics, such as acetaminophen and NSAIDs, should be given on a regular basis and not only when pain becomes troublesome. Analgesic

combinations from different classes of drugs are important to achieve a successful pain management.

Regional/local anesthesia is discussed later in this chapter.

19.3.2.1 Acetaminophen (Paracetamol)

Several mechanisms in the central nervous system are responsible for the analgesic effect. The analgesic potency is relatively low and a ceiling effect has been shown in studies. The i.v. formulation of mannitol-solubilized acetaminophen (paracetamol) has shown to be clinically useful, and it is speculated that the higher effect site concentration achieved in the brain may result in higher analgesic potency. Acetaminophen (paracetamol) is absorbed from the small bowel, and the oral route should therefore only be used when the g.i. (gastrointestinal) function is normal. Of note, both pain and postoperative conditions reduce g.i. motility. Rectal administration is slow and incomplete and therefore the least effective route of acetaminophen (paracetamol) therapy. Time to peak analgesia after i.v. administration is about 1 h and, after oral administration, 2 h.

Dosing regimens for acetaminophen (paracetamol) have been revised in the last years on basis of age, route of delivery, loading dose, maintenance dose, duration of therapy, and liver function to ensure a balance between efficacy and safety. It is recommended to use i.v. administration during the first 24 h to optimize the analgesic effect and, thereafter, switch to oral formulations if the g.i. motility is normalized. If the oral route is used from the beginning of therapy, a loading dose is often used. This is not necessary when using i.v. acetaminophen (paracetamol). Normal dosing in healthy pediatric patients is 60–80 mg kg/day i.v. and 80–100 mg kg/day p.o. divided on four doses. Dose reduction should be performed after 2–3 days of therapy and in younger infants, preterm neonates, and sick children. For more detailed dosing, please consult textbooks of pain pharmacology or the Internet.

19.3.2.2 NSAIDs

NSAIDs are important in the treatment and prevention of mild and moderate nociceptive pain. The site of action is within both the peripheral and central nervous system. In studies in adults, the combination of NSAIDs and opioids results in an opioid-sparing effect of about 30–40 %, and from a clinical point of view, similar findings are observed in pediatric patients. NSAIDs in combination with acetaminophen (paracetamol) produce better analgesia than either alone. NSAIDs are especially effective in pain emerging from fractures and bone processes. Concerns have been raised about the effect of NSAIDs on bone healing after orthopedic surgery in children, but the benefits of short-term use outweigh the risks. NSAIDs can be given to a majority of children with asthma. Only about 2 % of children react negatively with increased obstructive symptoms when receiving NSAIDs. COX-2 inhibitors are alternatives to nonselective NSAIDs if the patient has a bleeding disorder or thrombocytopenia.

Table 19.4 Opioid dosing[a]

Opioid	Oral	Intravenous
Morphine	0.2–0.3 mg/kg 4 times daily	0.05–0.1 mg/kg every 2–4 h 0.02 mg/kg/h infusion
Oxycodone	0.1–0.2 mg/kg 3–4 times daily	0.05–0.1 mg/kg every 2–4 h 0.02 mg/kg/h infusion
Hydromorphone	0.04–0.08 mg/kg 4–6 times daily	0.02 mg/kg every 2–4 h 0.006 mg/kg/h infusion
Fentanyl	NA	0.5–1 μg/kg every 2–4 h
Methadone	0.2 mg/kg 3–4 times daily	0.1 mg/kg q every 4–8 h
Codeine	0.5–1 mg/kg 4 times daily	NA

[a]Titrate to patient's need

Most commonly used NSAIDs are ibuprofen, diclofenac, ketolorac, and celecoxib (selective COX-2 inhibitor). Recommended dose of ibuprofen is 4–10 mg/kg 4 times daily and diclofenac 1 mg/kg 3 times daily in children aged older than 3 months. Intravenous ketolorac dosage is 0.3 mg/kg 4 times daily. The use of ketolorac should not exceed 5 days.

19.3.2.3 Opioids

There are several opioids used for the treatment of nociceptive pain. The idea that some opioids are weak (i.e., codeine) and others are strong (i.e., morphine) is not accurate. Most opioids are capable of treating pain in spite of its intensity if the dose is adjusted correctly. At equipotent doses, most opioids have comparable effect and side effects. The individual response to an opioid can differ. Opioid rotation is sometimes a useful tool when the patient is troubled by nausea and vomiting. Therefore, it is reasonable to have the option of several opioids to choose from in management of pain. Codeine is metabolized into morphine which is responsible for most of codeine's analgesic effect. Children, especially under the age of 6, are to large extent poor metabolizers of codeine and, as a result, lack analgesic effect upon administration. Further, a small proportion of people are "ultra-rapid metabolizers" who convert an appropriate dose of codeine into potentially fatal level of morphine in the blood. Codeine is not usually recommended for pain treatment in children.

In acute pain conditions, opioids should be administered by the intravenous route for most rapid effect and for the opportunity of easy titration. If repeated doses are required, it is advantageous to use an opioid infusion. Among opioids, morphine is the most common choice. Morphine infusions of between 10 and 30 μg/kg/h provide sufficient analgesia with an acceptable level of side effects with the appropriate level of monitoring. Oxycodone, hydromorphone, methadone, and buprenorphine may be offered as alternatives to morphine (Table 19.4). Pethidine (meperidine) is

not recommended in children because of the adverse effect of its main metabolite, norpethidine, which may increase cortical excitability.

In appropriately selective cases, the subcutaneous route of administration is a useful technique to the i.v. route. Other methods of opioid delivery are oral, transdermal, sublingual, and intranasal routes.

When pain is under control, opioids may be switched to the oral route. The oral dose is often considerably higher because of limited bioavailability compared to the i.v. dose. For example, the morphine dose given orally has to be about three times higher than the i.v. dose for equivalency. In opioid naïve patients, an initial oral dose of morphine is approximately 0.2–0.3 mg/kg. In neonates and young infants, the dose should be reduced to 0.05–0.1 mg/kg. Time to peak analgesic effect of oral morphine administration is about 30–40 min after intake.

Opioid agonists do present undesirable side effects such as nausea and vomiting, constipation, pruritus, urinary retention, sedation, and, most significantly, respiratory depression. Sedation and respiratory function must be monitored carefully when opioids are administered i.v. and during the initial phase of opioid treatment. Safety protocols and management protocols for side effects are necessary. Most side effects diminish with time, except for constipation. Constipation by itself creates stomach pain and increases the risk of nausea and vomiting. Laxatives and oral mixture of naloxone (opioid antagonist) may be recommended when opioid treatment is used. Naloxone administered orally has a local effect on the opioid gastrointestinal receptors without a central antagonist effect because of an almost first passage effect in the liver. An alternative for severe cases of constipation is subcutaneous injection with methylnaltrexone. The treatment should begin with a limited dosage because of the prompt effect on intestinal motility which can cause intestinal colic.

Withdrawal of opioids is discussed later in this chapter.

19.3.2.4 Alpha$_2$-Adrenergic Receptor Agonists

Clonidine and dexmedetomidine are the two most clinically used alpha$_2$-agonists. Clonidine can be administered by several routes, as oral, i.v., and as an additive to local anesthetics. Dexmedetomidine is most frequent used as an i.v. drug for sedation and to a lesser extent as an analgesic. The intranasal application of dexmedetomidine, on the other hand, has promising possibilities both for procedural pain and sedation.

Alpha2-agonists reduce pain transmission in the spinal cord and have effect on both nociceptive and neuropathic pain. In supraspinal areas alpha$_2$-agonists produce sedation and affect the vasomotor center. The vasomotor effect is vasodilatation and increased bradycardia in smaller children. Historically, clonidine was earlier used for treatment of hypertension. From a clinical point of view, hypotension and bradycardia are seldom problems in infants and children. There is no ventilatory depression or major constipation effects of alpha$_2$-agonists as compared to opioids, an important advantage in respect to safety issues.

The effect on pain and sedation is dose dependent, with greater effect when higher dosage is used. Several pediatric pain treatment services have been using clonidine as part of the multimodal treatment approach with analgesic benefit. Clonidine administered i.v. has an immediate effect, but time to peak effect after oral administration is about 60–90 min. Oral bioavailability is fairly high, about 80 % but with individual variation. A normal analgesic dose is 1 μg/kg i.v. and 1–2 μg/kg p.o. three times daily. Higher dose is often required in more severe pain conditions.

19.3.2.5 NMDA Blockers

Ketamine or the isomer S-ketamine (more potent with less side effects) is a possible drug to use for decreasing windup in and following complex surgery. It is used as a continuous infusion and should be started before surgical incision and continued postoperatively for a couple of days. In higher doses there is a risk for developing unpleasant dreams and hallucinations. Close patient monitoring is essential to identify these side effects. Acute neuropathic pain is another area for the use of NMDA blockers.

19.3.3 Treatment of Neuropathic Pain

The treatment of pain that is initiated or caused by a primary lesion or dysfunction within the nervous system itself presents significant challenges. When the peripheral and central somatosensory and cortical and spinal pain modulatory regions are the symptom generators, medications such as opioids and nonsteroidal anti-inflammatory agents are often ineffective, even in significant increased dosage. More appropriate pharmacologic choices directly target neuromodulatory neurotransmitters (tricyclic antidepressants, TCAs), neuronal membrane channels (antiseizure medications, local anesthetics, and receptors responsible for central nervous system excitation, such as *N*-methyl-D-aspartate receptors (NMDA antagonists)). For complex and chronic neuropathic disorders, such as intractable headache, CRPS (complex regional pain syndrome), and visceral hyperalgesia, a multidisciplinary approach is warranted, combining neuropathic pharmacology with physical, cognitive, and complementary therapies.

In pediatric practice, studies supporting interventions for neuropathic pain are more limited than for nociceptive pain and are predominantly case studies and clinical series with rare subject control. Placebo effects are not often reported due to ethical concerns, and medication effect is likely altered by central pain-processing changes throughout pediatric development. Interestingly, some common neuropathic pain disorders in the adult population, such as diabetic peripheral neuropathy, brachial plexus neuralgia, radiculopathy, trigeminal neuralgia, and post-herpetic neuralgia, are rare in children. However, there are disorders somewhat unique to

pediatrics, such as hereditary and metabolic neuropathies (Fabry's disease, mitochondrial disorders, lead exposure) and primary erythromelalgia. Adult pain conditions present in children may have a more favorable prognosis, such as CRPS, trauma, and postoperative neuropathic pain.

Medication choice is frequently based on adult studies, despite developmental limitations, and on the safety and efficacy information for medication used for non-painful disorders, such as epilepsy and depression. However, a specific safety concern, suicidal ideation, has been highlighted by the FDA regarding the use of all antiseizure and antidepressant agents in children and adolescents, necessitating appropriate discussion with families when initiating treatment. Fortunately, current data (please see References) supports the thoughtful use of these agents in pediatric patients with and without depression. Parents may appropriately be referred to the websites of the European and American Psychological and Psychiatric Associations for additional information.

Regarding antidepressant agents most frequently used for pediatric pain, amitriptyline is often the initial choice, as this medication has a relatively long record of safety and efficacy in patients with headache and chronic abdominal pain. In general, the starting dose is low, 0.3 mg/kg, with an increase to 1–2 mg/kg/day. A baseline ECG may be useful in patients who are at risk of cardiac arrhythmia or a prolonged QTc. Adverse effects also include sedation, constipation, weight gain, and anticholinergic autonomic effects. Nortriptyline may have less associated orthostatic hypotension and sedation but greater risk of palpitations. Efficacy is attributed to blockade of NE (norepinephrine) and 5-HT (serotonin) reuptake at synapses in the endorphin-mediated pain modulation pathways at central (descending) and spinal cord levels. Newer agents with similar effects, such a duloxetine and venlafaxine, have not been well studied in children. Serotonin reuptake inhibitors (SSRIs) have not shown reliable relief of neuropathic pain.

Dosing of amitriptyline/nortriptyline. Initial 0.05–2 mg/kg at bedtime p.o.; may increase dose over 2–3 weeks, to effect; max 2 mg/kg/day

Antiseizure medications provide a clinical level of comfort for prescribers, due to information available through pediatric epilepsy trials. However, the use of these agents for pediatric neuropathic pain is limited, with gabapentin as the most studied medication in reports of children and adolescents with CRPS, phantom pain, and postoperative trauma. Dosage is weight based, and serum levels do not correlate well with pain response. Adverse effects and potential toxicity guide periodic evaluation of the serum level. Possible side effects are multiple and vary according to the selected agent. Unacceptable symptoms include rash, sedation/mental clouding, renal calculi formation, and severe gastrointestinal distress. Hematologic and hepatic changes seen with some of the older antiseizure medications are less frequent with newer agents (Table 19.5). These newer formulations also potentially bind to a greater variety of receptors within the pain transmission system, expanding from sodium and calcium channel binding to include NMDA and GABA receptors.

Table 19.5 First- and second-generation antiseizure drugs

First generation	Second generation
Carbamazepine (CBM)	Gabapentin (GBP)
Clonazepam	Lamotrigine (LTG)
Phenytoin (PHT)	Topiramate (TPM)
Primidone	Zonisamide (ZNS)
Valproate (VPA)	Pregabalin (PGB)
	Levetiracetam (LEV)

19.3.3.1 Dosing of Antiseizure Medications

Gabapentin. Initial, 5 mg/kg/dose at bedtime; day 2, increase to 5 mg/kg/dose, twice daily; day 3, increase to 5 mg/kg/dose 3 times/day; titrate to effect; usual dosage range, 8–35 mg/kg/day divided into 3 doses/day.

Pregabalin. Initial, 150 mg/day in divided doses (50 mg 3 times/day); may be increased within 1 week based on tolerability and effect; maximum dose, 300 mg/day (dosages up to 600 mg/day were evaluated with no significant additional benefit and an increase in adverse effects).

Topiramate. Children <12 years: initial, 1–3 mg//kg/day (maximum, 25 mg) given nightly for 1 week; increase at 1- to 2-week intervals by 1–3 mg/kg/day given in 2 divided doses; titrate dose to response; usual maintenance, 5–9 mg/kg/day given in 2 divided doses. Adolescents ≥17 years and adults: initial, 25–50 mg/day given daily for 1 week; increase at weekly intervals by 25–50 mg/day; titrate dose to response; usual maintenance, 200 mg twice daily; maximum dose, 1,600 mg/day.

Zonisamide. Initial, 1–2 mg/kg/day given in two divided doses/day; increase dose in increments of 0.5–1 mg/kg/day every 2 weeks; usual dose, 5–8 mg/kg/day. Adolescents >16 years and adults: adjunctive treatment of partial seizures, initial 100 mg/day; dose may be increased to 200 mg/day after 2 weeks. Further dosage increases to 300 mg/day, and 400 mg/day can then be made with a minimum of 2 weeks between adjustments, in order to reach steady state at each dosage level. Doses of up to 600 mg/day have been studied; however, there is no evidence of increased response with doses above 400 mg/day.

Additional pharmacologic considerations for treatment of neuropathic pain include agents that bind to the NMDA receptor, such as ketamine, and alpha2-agonists, such as clonidine, described in the previous section on treatment of nociceptive pain. Local anesthetics will be presented in the next section. Representative dosing for ketamine is as follows: p.o. 6–10 mg/kg per dose, i.m. 3–7 mg/kg per dose, and i.v. 0.5–2 mg/kg per dose. Ketamine is most frequently used for sedation during procedures or anesthesia induction. Short-term infusions are currently being studied for the treatment of severe neuropathic pain. Adverse effects include increased salivation, g.i. distress, sedation and short-term memory loss, increased intracranial pressure, cardiac dysrhythmia, and respiratory depression. Clonidine dosing is 2–4 μg/kg 4 times daily, with use limited by potential hypotension and sedation. If clonidine is used for greater than 2 weeks, a sudden discontinuation may be associated with rebound hypertension.

Table 19.6 Local anesthetic dosing

Local anesthetic	Maximal doses	mg/kg
Drug	Epidural	Peripheral
2-Chloroprocaine	10–30	8–10
Lidocaine	5–7	5–7
Bupivacaine	2–3	2–3
Levobupivacaine		
Ropivacaine	2.5–4	2.5–4

Of note, for some pediatric patients with pain resistant to pharmacology, such as those with limb pain due to CRPS, physical and cognitive interventions, which activate the diffuse pain-processing system, may be more effective than pharmacologic choices. In a study by Lee in 2002, 28 patients with CRPS of the lower limb participated in physical therapy once vs. three times per week, with cognitive-biobehavioral therapy once per week, for a total of 6 weeks. Outcome measures included pain scores, gait testing, stair climbing, psychological inventories, regional and systemic autonomic examination, and quantitative sensory testing. Results showed that both groups had a greater than 50 % improvement in pain scores (VAS), improved gait and stair climbing, and no need of assistive devices by 6 weeks.

19.3.4 Local Anesthesia

Local anesthetics reversibly block voltage-gated sodium channels and, therefore, initiation and propagation of neural impulses along peripheral and central nerve pathways. They are generally used for regional anesthesia for procedures, surgery, and as adjuvant therapy for some chronic neuropathic pain disorders (CRPS, cancer pain). Amide agents lidocaine and bupivacaine are most commonly used. An oral analog of lidocaine, mexiletine, may be used for neuropathic pain, but little data is available regarding efficacy in children. The dose is 2–3 mg/kg/day, divided bid-tid. Intravenous lidocaine may be administered in bolus dosing or brief continuous infusion for intractable nerve pain and headache, maintaining a serum level less than 5 μg/mL to avoid cardiac and central nervous system toxicity. The i.v. dosage is 20 μg/kg/min to achieve an analgesic level of 102 μg/mL.

For regional anesthesia, such as epidural and brachial or lumbar plexus blockade, dosing is decreased due to application of drug in proximity to the target receptor (Table 19.6). This technique may, therefore, overcome the limitations of local anesthesia, such as low potency, toxicity near therapeutic dose, and other local actions with spread non-sodium nerve channels, mitochondria, and cellular membrane components. Binding, potency, and potential neurotoxicity of the drug are enhanced by acidosis, previous nerve injury or neuropathy, hypotension, and local vasoconstriction. Acute cardiac toxicity may be reversed by intravenous administration of a lipid emulsion, such as Intralipid 20 %, at 0.25 mL/kg/min. Local anesthetic effectiveness may be decreased by technically poor delivery, tachyphylaxis,

Table 19.7 Topical anesthetics

	EMLA®	LMX-4®	Synera® / Rapydan®	LET (lidocaine, epinephrine, tetracaine, open wound)
Time to use (min)	60–180	20–30	20–60	20
Duration	4 h	1 h	3 h	21 min
Issues	Methemoglobin; use in patients >37 weeks	Tegaderm occlusion; no methemoglobin	Heating agent; use in patients >3 years	Need to mix solution

EMLA®: eutectic mixture of 2.5 % of lidocaine and prilocaine
LMX-4®: liposomal delivery system of 4 % lidocaine
Synera®: mixture of 7 % tetracaine and lidocaine in a heated patch

infection, and genetic variation. Patients with chronic neuropathic pain show the greatest resistance, possibly due to the distributed nature of pain in these patients. Recent research is focusing on developing sensory selective blocking agents derived from biologic nerve toxins, such as tetrodotoxin and saxitoxin.

Of note, some neuropathic medications have local anesthetic effects, such as tricyclic antidepressants, ketamine, clonidine, and methadone (D-isomer is an NMDA antagonist).

The pharmacology of local anesthetics in neonates and infants may precipitate overdosage in these patients, warranting careful titration due to delayed hepatic degradation and prolonged elimination half-live of amide anesthetics. Neonates and infants also have reduced serum levels of albumin and alpha1-acid glycoproteins that bind local anesthetics, leading to increased levels of free and unbound drug. However, neonatal volumes of distribution are also increased compared to older children, offsetting potential systemic toxicity. Ester local anesthetics, such as chloroprocaine 1.5 %, are often used for epidural analgesia in neonates due to its rapid metabolism by plasma cholinesterase.

Topical anesthetics have clearly advanced the treatment of pediatric procedural pain, with many dosage forms available, including gels, sprays, creams, ointments, and patches. Depending upon the preparation, absorption through the skin for dermal afferent binding is enhanced by eutectic mixture, liposomal preparation, and iontophoresis (EMLA®, LMX-4®, Synera®). Direct placement of a combination of lidocaine, epinephrine, and tetracaine (LET) into open lacerations/wounds may obviate the need for local injection (lidocaine 20 %, racemic epinephrine 2.25 %, and tetracaine 2 %) (Table 19.7).

19.3.5 Procedural Pain Treatment

Procedural sedation and analgesia is the use of sedative, analgesic, and dissociative drugs to provide analgesia, anxiolysis, and sedation during painful or unpleasant

Table 19.8 Procedural pain – drug classes and drugs

Analgesic without sedative effect	Analgesic and sedative effect	Sedative without analgesic effect
Local anesthetics	alpha$_2$-agonists	Midazolam
Acetaminophen (paracetamol)	Opioids	Diazepam

diagnostic and therapeutic procedures (Table 19.8). Progression from minimum sedation to general anesthesia does not lend itself to random partition. Low doses of opioids or sedative-hypnotics induce mild analgesia or sedation respectively, with little danger of adverse events. Higher doses provide progressively deeper sedation, increasing the risk of respiratory and airway compromise. Procedural guidelines are intended to regulate the procedure and most importantly enhance patients' safety. Continuous observation of patients by a health-care provider capable of recognizing adverse sedation events is essential. This person must be able to continuously observe the patient's degree of sedation and vital organ functions. Procedural sedation and analgesia personnel should be proficient at maintaining airway patency and assisting ventilation if needed when sedatives are used.

A multimodal analgesic-sedative approach is recommended for best efficacy. Analgesic drugs should always be combined with distraction techniques and the highest degree of patient self-control. The environment should be relaxing and calming, and adding music is a useful option.

Knowledge of pharmacodynamics is essential. Time to peak analgesic effect of acetaminophen (paracetamol) and NSAIDs is about 2 h after oral intake. For clonidine, peak effect is about 60–90 min and for morphine 30–40 min. If the i.v. route is used, the effect is often faster and more prominent. Nasal application, preferably as an aerosol, of analgesics and sedatives is a novel and an increasingly popular technique when the patient lacks an i.v. line. Drugs used in awake children should not give rise to a painful or discomforting experience. It is therefore important to use buffered solutions of local anesthetics and avoid mixtures which taste bitter or create unpleasant sensations upon administration, i.e., midazolam.

Generally safe sedatives that also produce analgesics include acetaminophen (paracetamol), NSAIDs and local anesthetics, alpha$_2$-agonists, S-ketamine (ketamine), and opioids. As mentioned previously, higher doses produce an elevated degree of sedation, requiring adjustment by the attending staff. Inhaled nitrous oxide is another attractive alternative for procedural pain, in doses up to 50 % mixture in oxygen. The onset is fast and the effect is short-lasting when the gas is turned off. It is often an advantage to use systems that offer the possibility to titrate nitrous oxide mixture up to 50 %. In teenagers, loss of self-control can be especially troublesome, and in children experiencing nausea, the nitrous mixture could be lowered, resulting in fewer side effects.

Diazepam, midazolam, chloral hydrate, barbiturates, and propofol are pure sedative-hypnotic drugs without analgesic properties. These drugs should never be used without analgesics when performing a painful procedure. The use of sedatives alone is sadly still quite common at many hospitals and institutions taking care of children. Midazolam has gained a widespread use because of its fast-acting and

relatively short-acting effect. Midazolam is also considered to have amnesic properties and is for that reason popular among clinicians. This is partly true and only applicable for the explicit memory (conscious memory). The implicit memory (unconscious memory) which registers discomfort and unpleasant episodes is unchanged or even enhanced when midazolam is used. The effect could lead to distressing behavior for the child, especially when used at repeated procedures. However, some degree of amnesia may be beneficial during procedures. Of note, several children's hospitals have recently eliminated the use of midazolam for painful procedures.

19.3.6 Complementary Methods

19.3.6.1 Physiotherapy

The aim of physiotherapy is to restore the patient's best possible motor function. Simultaneously, with increased activity, the endogenous opioid system is activated, leading to reduced pain.

19.3.6.2 Sensory Stimulation

TENS (transcutaneous electric nerve stimulation), acupressure, and acupuncture often create effective pain relief in children. It is of importance that these techniques are introduced cautiously in children and adapted to the age of the child. Dorsal column electric stimulation is occasionally needed in complex pain conditions.

Other forms of sensory stimulation as cold and heat therapy as well as massage have been increasingly used in children during the last decades. Cold therapy is used regularly at the time of joint surgery to reduce pain and decrease inflammation.

19.3.6.3 Distraction and Self-Control

There are several beneficial distraction techniques to be used, including guided imagery, individual muscle relaxation, and self-hypnosis. Effective distraction reduces significantly pain perception. Distraction is especially important to use in painful procedures. High level of patient self-control is further more an important tool to reduce fear and increase compliance with the treatment.

19.3.7 Withdrawal of Opioids and Benzodiazepines (Midazolam)

After prolonged exposure to opioids and midazolam, children develop both tolerance and withdrawal. These issues are especially seen in younger age groups and

develop commonly during critical illness in the pediatric intensive care unit. A problem with withdrawal often arises when the patient is transferred to a regular ward and the previous drug doses are quickly reduced. It is important to monitor the patient closely to discover early signs of withdrawal and plan a slow reduction of opioids and midazolam. Early signs of withdrawal are changes in sleep pattern, such as short periods of sleep and easily disturbed sleep, and feeding problems. Late signs are the more classic features of withdrawal and for the child include the distressing autonomic symptoms of sweating, jitteriness, and tachycardia. Several scales designed to measure withdrawal problems rarely contain the early signs of withdrawal.

The strategy for management of withdrawal is to prevent oversedation and the development of the need of high dose and prolonged use of opioids and midazolam. The reality is still often that the patient is referred to a regular ward with high doses with opioids and midazolam administered i.v. Close monitoring of withdrawal symptoms and slow reduction of doses are necessary to achieve a successful weaning. As a rule, it takes about as long or double the time to wean a patient compared to how long the drugs have been used. Switching to oral route as soon as possible and using long-acting opioids (i.e., methadone, buprenorphine) are suggested. The use of clonidine, often higher doses than for pain treatment, can help to more rapidly decrease opioids and midazolam.

19.3.8 Pain Emergencies

The most common emergent problem in pediatric pain is severe breakthrough pain. Symptomatic treatment may include rapid-acting opioids and NSAIDs, especially in an i.v. formulation, as well as adjuvant medications for sedation, anxiolysis, and muscle spasm. Intravenous methadone is an alternative for patients who do not respond to the first-line opioids. (For drugs and doses, see treatment of nociceptive pain.)

For sedation and anxiety:

- Midazolam: infusion 0.05–0.02 mg/kg/h i.v.; oral single dose 5–10 mg/kg
- Lorazepam: i.v. 0.05 mg/kg q 3–4 times daily; oral 0.05 mg/kg 4 times daily
- Ketamine, s-ketamine: i.v. 0.5–2 mg/kg; oral single dose 3–7 mg/kg
- Hydroxyzine: i.v./oral 0.5–1 mg/kg 4 times daily
- Diphenhydramine: i.v/oral 1–2 mg/kg 4–6 times daily

For muscle spasm – oral antispasmotics (see also Chap. 17):

- Diazepam: GABA A agonist at spinal cord; sedation due to reticular activating formation binding
- Dantrolene: inhibits calcium ion release in muscle fibers; decreases muscle contraction
- Baclofen: GABA B agonist; inhibits presynaptic release of excitatory transmitters
- Tizanidine: alpha2-agonist; inhibits release of aspartate and glutamate

Additional emergent conditions related to pain include:
Hypotension:

1. Administer supplemental oxygen.
2. Establish i.v. access for bolus of 250–500 mL of lactated Ringer's solution (weight >40 kg).
3. Monitor vital signs and verbal communication.
4. Elevate lower extremities or place patient in Trendelenburg.
5. Administer vasopressors, only if necessary: ephedrine:

   (a) Children <12 years: i.m., i.v., s.c.: 3 mg/kg/day in 4–6 divided doses
   (b) Children ≥12 years and adults: i.m., s.c.: 25–50 mg (range: 10–50 mg); may repeat with a second dose of 50 mg; not to exceed 150 mg/24 h. Intravenous: 10–25 mg; may repeat with a second dose in 5–10 min of 25 mg; not to exceed 150 mg/24 h

Anaphylaxis:

1. Assess airway and administer oxygen.
2. Establish i.v. access for NS or LR bolus of 20 mL/kg.
3. Primary treatment is epinephrine: < 10 kg 1:1,000, 0.01 mg/kg i.m.; 10–25 kg, 0.15 mg i.m.; 26–100 kg, 0.3 mg i.m.
4. Secondary treatment includes diphenhydramine 1 mg/kg po/IV, max 50 mg; methylprednisolone 1 mg/kg i.v., max 50 mg; and possible ranitidine 2 mg/kg i.v., max 50 mg.

Opioid overdose:

1. Support ventilation.
2. Administer incremental naloxone IV; start at 0.05 mg with 0.4 mg as total dose.
3. Consider naloxone infusion if long-acting opioid given; 0.25–0.5 μg/kg/h.

Opioid withdrawal:

1. Resume opioid treatment.
2. Consider clonidine.
3. Treat associated nausea with p.o. prochlorperazine, 0.4 mg/kg/day divide in 4 doses, or i.v. ondansetron. Children <10 kg, 0.5 mg every 8 h as needed; children ≥10 kg to <30 kg, 1 mg every 8 h as needed; children >30 kg and adults, 2 mg every 8 h as needed.
4. Treat muscle pain with NSAIDs.
5. Fluid replacement for diarrhea.

19.4 Conclusion

Children in all ages can experience pain. Pain conditions are most often nociceptive or neuropathic. It is essential to analyze the cause of pain in order to achieve an effective treatment. The aim of pain management is to reach acceptable levels of pain for each individual child, and a multimodal treatment approach is suggested.

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