Chapter 11
Children with Neurodegenerative Development Disorders in Uganda

Angelina Kakooza-Mwesige and Dirk M. Dhossche

Abstract Neurodegenerative disorders in childhood are a miscellaneous group of severe disorders characterized by regression and progressive neurological degeneration with impairment of vision, hearing, speech or movement often associated with seizures, feeding difficulties and impairment of intellect. The course can be acute, rapidly progressive or slowly progressive, only disclosing its full impact over time. Neurodegenerative diseases have multiple causes including metabolic, viral, immunopathic, environmental and epileptogenic, but many lack an identifiable biochemical or metabolic cause or mechanism. Neurodegenerative disorders are an important source of childhood impairment in developing countries like Uganda due to the high prevalence of specific causes such as human immunodeficiency virus, cerebral malaria, sub-acute sclerosing panencephalitis due to measles, and the emergence of poorly understood entities such as Nodding Syndrome. Knowledge on this extremely varied group is expanding along with biochemical and genetic advances but there is currently a paucity of data in most low and middle income settings including Uganda on the number of children affected by neurodegenerative disorders and their demographic characteristics. The detection and diagnosis of childhood neurodegenerative disorders is complex and fraught with pitfalls. There is need to incorporate a rigorous history, including family history, and physical examination as an indispensable component of the diagnostic evaluation. Neurodegenerative disorders may be mistaken at the disease onset for unexplained psychiatric disturbance, cerebral palsy, epilepsy or cognitive impairment. Laboratory investigations, neuroimaging and specific tests assist in making an accurate diagnosis which is important for appropriate therapy, prognosis, and genetic counseling. Often the treatment is symptomatic but dietary restrictions may be useful in certain diseases as well as specific treatments to counteract the offending metabolites, improve or decrease abnormal enzyme function, or to off-set metabolic dysfunction. It may be possible

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_11

in the future to target specific pathways with somatic gene therapy but this will require more technological advances and discoveries. A referral for genetic counseling is important due to heritability of many neurodegenerative disorders. Public health initiatives should focus on the risk of consanguineous marriages as a way to raise awareness of a preventable cause of a neurodegenerative disorder in childhood.

Keywords Neurodegenerative disorders • Neurodevelopmental disorders • Childhood • Regression

Abbreviations

BBB	Blood-brain barrier
CNS	Central nervous system
CSF	Cerebral spinal fluid
ECG	Electrocardiogram
EEG	Electroencephalogram
ERG	Electroretinogram
HAART	Highly active antiretroviral therapy
HIC	High income countries
LMIC	Low and middle income countries
NDDD's	Neurodegenerative developmental disorders
NS	Nodding syndrome
SSPE	Subacute sclerosing panencephalitis

Introduction

Neurodevelopmental disorders have been singled out as one of the greatest challenges to improving global public health by the World Health Organization (WHO) [1]. Neurodevelopmental disorders comprise a miscellaneous group of chronic conditions, often severe, that commence during neurological development and typically persist throughout the life of an affected child. These include the following specific conditions: cognitive impairment, learning disorders, cerebral palsy, autism spectrum disorders, epilepsy, attention deficit hyperactivity disorders, hearing impairment, visual impairment and neuromuscular disorders.

A small group of children is afflicted with neurodegenerative disorders, a severe type of disorder characterized by regression and progressive neurological degeneration that can occur acutely, rapidly progressive, or slowly progressive only disclosing its full impact over time. Neurodegenerative diseases have multiple causes, including metabolic, viral, immunologic, environmental and epileptogenic, but

many lack an identifiable biochemical or metabolic cause or mechanism. Knowledge on this extremely varied group is expanding along with biochemical and genetic advances and will be discussed in this chapter.

Neurodegeneration denotes the progressive loss of structure and function of neurons from the central or peripheral nervous system [2]. This evolving loss of neurons produces the neurodegenerative developmental disorders (NDDD's) by causing the child's brain to degenerate and results in severe cognitive impairment or death [3]. These neurodegenerative disorders of childhood include a large, diverse group of diseases that develop as a consequence of certain genetic and biochemical defects, chronic viral infections, and miscellaneous unidentified causes.

There is paucity of data in most low and middle income settings including Uganda on the number of children affected by NDDD's and their demographic characteristics. Furthermore the diagnosis of these conditions is often impeded by the perplexing nature of presentation which is comparable to the common pediatric problems such as failure to thrive, recurrent vomiting, feeding problems, sepsis and/or developmental delay [4]. In addition, NDDD's may be mistaken at their onset for unexplained psychiatric disturbance, cerebral palsy, epilepsy or cognitive impairment. This implies that one has to have a high index of suspicion and sum up all the important clinical information so that the appropriate investigations are carried out. Furthermore it stresses the importance of obtaining a thorough history and physical examination as a precondition to undertaking extensive investigations in these disorders. The aim of this chapter is to present an overview of some of the causes of neurodegenerative disorders and their presentation as seen in Ugandan children.

Epidemiology

Neurodegenerative disorders are a small but severe subgroup within the neurodevelopmental disorders. Research on neurodegenerative disorders in childhood is limited in Uganda and in most other developing countries yet there are emerging data on the whole group of neurodevelopmental disorders. The available data on some neurodevelopmental disorders will be presented here. Data on specific and common etiologies such as human immunodeficiency virus, cerebral malaria, sub-acute sclerosing panencephalitis, and Nodding syndrome will be presented later in the text.

Neurodevelopmental disorders among children have been extensively researched in High Income Countries (HIC) but there is limited information on them in Low and Middle Income Countries (LMIC) because there are hardly any studies measuring the prevalence of these disorders, and none measuring changes over time. It is believed that neurodevelopmental disorders are more common in Low and Middle Income Countries (LMIC) than in the High Income Countries (HIC) due to multiple known risk factors such as malaria, HIV and other infectious diseases. However with the advent of effective prevention and treatment of infectious diseases, control of toxic exposures and nutritional deficiencies there has been a significant lowering of the childhood mortality over the last decade [5]. This implies that there will likely

be an expected increase in prevalence of children with neurodevelopmental disorders as the mortality is higher in such children compared with the typically developing ones [6]. This hypothesis however needs to be supported by further studies.

A three stage community based survey conducted in rural and urban areas of Uganda to study the prevalence of neurodevelopmental disorders screened 1,169 children aged 2–9 years focusing on seven conditions namely: cognitive impairment, cerebral palsy, autism spectrum disorders, epilepsy, speech and language disorders, hearing impairment and vision impairment. A prevalence of 10.3–12.8/100 population was reported [7]. Of these the most common neurodevelopmental disorder was moderate-severe cognitive impairment (26.2 %), followed by epilepsy (10.6 %) and speech and language impairment (8.6 %). The estimated prevalence for Autism was 1.2/100–1.3/100 children in this population [7] There is scanty information on the basic descriptive epidemiology of neurodegenerative developmental disorders (NDDD's) in childhood, particularly in LMIC. Currently available data from LMIC is often based on case series from referral hospitals or designated community studies and as such, is neither representative of the larger geographic region, nor of the whole spectrum of NDDD's.

In general, NDDD's are rare in the pediatric population and are estimated to occur in 1/10,000–1/500,000 of the population in the HIC [8]. In the few studies done earlier in Africa focusing on varied disease conditions the prevalence ranged from 4.8/100,000 to 10/100,000 [9, 10]. The varied aspects regarding these conditions among children in Uganda remain obscure. Nevertheless, it is known that as a group of diseases they confer an enormous burden in terms of human suffering and economic cost on the child, the family and the community [11].

Diagnosis

A specific biochemical or genetic defect does not wholly ascertain the diagnosis of a NDDD. There is need to incorporate a rigorous history and physical examination as an indispensable component of the diagnostic evaluation. The characteristic of a neurodegenerative disorder is regression and progressive deterioration of neurologic function with impairment of vision, hearing, speech or movement often associated with seizures, feeding difficulties and impairment of intellect. Reaching a specific diagnosis is important for providing appropriate therapy, prognosis and genetic counseling. The inheritance pattern of several neurodegenerative disorders is autosomal recessive, and therefore consanguinity is considered a risk factor that should be addressed when counseling families and raising awareness through public health policy [12]. Examples of some neurodegenerative disorders, the time of presentation, inheritance pattern and associated features are shown in Tables 11.1, 11.2, and 11.3.

Table 11.1 Some neurodegenerative disorders in neonates showing the principal systems affected, neurologic/psychiatric/behavioral abnormalities and their inheritance patterns

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Infantile Refsum's disease	Peroxisomal disorders	Rapid, jerky eye movements (nystagmus); progressive muscle weakness and wasting; poor balance and coordination (ataxia); hearing loss	Austosomal recessive
Zellweger syndrome	Peroxisomal disorders	Weak muscle tone (hypotonia), feeding problems, hearing loss, vision loss, and seizures	Austosomal recessive
Neonatal adrenoleukodystrophy	Peroxisomal disorders	Hypotonia, vision problems, hearing loss, liver dysfunction, developmental delay, intellectual disability	Austosomal recessive
Ornithine transcarbamoylase deficiency	Urea cycle disorders	Feeding difficulties, lethargy, and respiratory distress, irritability, temper tantrums, inconsolable crying, ataxia, seizures, hyperactivity	X-linked recessive
Argininosuccinicaciduria	Urea cycle disorders	Feeding difficulties, lethargy, mental retardation, recurrent generalized convulsions, ataxia, poorly controlled breathing rate or body temperature	Austosomal recessive
Arginosuccinate lyase deficiency	Urea cycle disorders	Lethargy, poor feeding, neurocognitive deficiencies (attention deficit hyperactivity disorder) [ADHD], developmental disability, seizures, and learning disability	Austosomal recessive
Pyruvate carboxylase deficiency	Mitochondrial disorders	Weak muscle tone (hypotonia), abnormal movements, seizures, and coma	Autosomal recessive
Glutaricaciduria type II deficiency	Mitochondrial disorders	Poor feeding and decreased activity, and vomiting	Autosomal recessive
Carnitine palmitoyltransferase deficiency type II	Mitochondrial disorders	Seizures, cardiomyopathy, respiratory failure, seizures, liver failure, cardiomyopathy, and an irregular heartbeat (arrhythmia)	Autosomal recessive
Maple syrup urine disease	Amino acid and organic acid disorders	Intermittent periods of ataxia, drowsiness, behaviour disturbances, and seizures	Autosomal recessive
Nonketotic hyperglycemia	Amino acid and organic acid disorders	Lethargy, profound hypotonia, intractable generalized or myoclonic seizures, apnea, feeding difficulties	Autosomal recessive

(continued)

Table 11.1 (continued)

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Methylmalonic acidemia	Amino acid and organic acid disorders	Hypotonia, lethargy, recurrent vomiting, profound metabolic acidosis, spastic quadriparesis, dystonia, and severe developmental delay	Autosomal recessive
Menkes kinky hair syndrome	Copper transport system	Weak muscle tone (hypotonia), sagging facial features, seizures, developmental delay, and intellectual disability	X linked recessive
Spinal muscular atrophy type 1	Peripheral nerves	Muscle weakness, respiratory failure, a weak cry; problems feeding; recurrent episodes of pneumonia, excessive sweating (hyperhidrosis), loss of bladder and bowel control, and an irregular heartbeat (arrhythmia)	Autosomal recessive
Smith-Lemli-Opitz syndrome	Cholesterol metabolism	Microcephaly, moderate-severe intellectual disability, Autistic behaviours, hyperactivity, aggressiveness and self injurious behaviours weak muscle tone (hypotonia), feeding difficulties, sleep cycle disturbance	Autosomal recessive
Galactosemia type I	Carbohydrate metabolism	Poor feeding, delayed development, clouding of the lens of the eye (cataract), speech difficulties, and intellectual disability	Autosomal recessive

Table 11.2 Some neurodegenerative disorders in infancy showing the principal systems affected, neurologic/psychiatric/behavioral abnormalities and their inheritance patterns

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Farber's disease	Lysosomal storage diseases	Paralysis of the arms and legs (quadriplegia), seizures, loss of speech, involuntary muscle jerks (myoclonus), and developmental delay	Autosomal recessive
Krabbe's disease	Lysosomal storage diseases	Irritability, muscle weakness, feeding difficulties, episodes of fever without any sign of infection, stiff posture, and slowed mental and physical development, vision loss and seizures	Autosomal recessive
Tay-Sachs disease	Lysosomal storage diseases	Loss of motor skills such as turning over, sitting, and crawling exaggerated startle reaction to loud noises, seizures, vision and hearing loss, intellectual disability, and paralysis	Autosomal recessive

(continued)

Table 11.2 (continued)

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Alexander disease	Leukodystrophies	Megalencephaly, seizures, spasticity, intellectual disability and developmental delay	Autosomal dominant
Canavan disease	Leukodystrophies	Feeding and swallowing difficulties, seizures, and sleep disturbances, developmental delay, hypotonia, macrocephaly, abnormal posture, and intellectual disability	Autosomal recessive
Pelizaeus-Merzbacher disease	Leukodystrophies	Impaired intellectual functions, such as language and memory, delayed motor skills, such as coordination and walking	X linked recessive
Leigh disease	Mitochondrial disease	Hypotonia, involuntary muscle contractions (dystonia), ataxia, peripheral neuropathy, weakness or paralysis of the muscles that move the eyes (ophthalmoparesis); rapid, involuntary eye movements (nystagmus); or degeneration of the nerves that carry information from the eyes to the brain (optic atrophy), severe breathing problems, and hypertrophic cardiomyopathy	Autosomal recessive/X linked recessive/ Sporadic
Medium-chain acyl CoA dehydrogenase deficiency	Mitochondrial disease	Lethargy, vomiting, seizures, breathing difficulties, liver problems, coma, and hypoglycemia	Autosomal recessive
Phenylketonuria	Amino acids and organic acid diseases	Profound intellectual disability, developmental delay, microcephaly, seizures (e.g., tonic-clonic, myoclonic, infantile spasms), tremors, athetosis, and spasticity, autistic behavior and attention-deficit–hyperactivity disorder	Autosomal recessive
Glutaric aciduria type I	Amino acids and organic acid diseases	Macrocephaly, muscular spasms, jerking, rigidity, or decreased muscle tone	Autosomal recessive
Lowe syndrome	Central nervous system and eyes and kidneys	Delayed development, impaired vision, moderate to severe intellectual disability, Kidney abnormalities, seizures, weak muscle tone from birth (neonatal hypotonia), feeding difficulties and problems with breathing	X linked recessive
Biotinidase deficiency	Enzymes that depend on Vitamin biotin	Seizures, weak muscle tone (hypotonia), breathing problems, and delayed development, hearing loss, eye abnormalities, loss of vision, problems with movement and balance (ataxia), skin rashes, hair loss (alopecia)	Autosomal recessive

Table 11.3 Some neurodegenerative disorders in childhood and adolescence showing the principal systems affected, neurologic/psychiatric/behavioral abnormalities and their inheritance patterns

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
Charcot Marie tooth disease	Peripheral nerves	Balance difficulties, clumsiness, and muscle weakness in the feet, loss of sensation and wasting (atrophy) of muscles in the feet, legs, and hands	Autosomal dominant
Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness) [DIDMOAD]	Multisystem	Depression, paranoia, auditory or visual hallucinations, violent behavior, dementia, suicide	Autosomal recessive
Symptomatic progressive myoclonic epilepsies (such as Unverricht-Lundborg disease (ULD) and Lafora disease)	Central nervous system and for Lafora disease in addition-affects heart, liver and muscle	Myoclonic jerks and tonic-clonic seizures visual hallucinations (occipital seizures), progressive neurologic degeneration including cognitive and/or behavioral deterioration, dysarthria, and ataxia	Autosomal recessive
Metachromatic leukodystrophy	Central and peripheral nervous system	Anxiety, depression, emotional lability, social withdrawal, schizophrenia, poor memory	Autosomal recessive
Late-onset GM2 gangliosidosis	Lysosomal disorder	Dystonia, intention tremor, dementia, obsessional paranoia, hallucinations, acute psychosis, dysarthria	Autosomal recessive
Juvenile Huntington's disease	Basal ganglia	Rapid, significant drop in overall school performance, depression, gait disturbances, tremors or slight involuntary movements, seizures, obsessive compulsive disorder, mania, sexual inhibition or inappropriate sexual behaviours	Autosomal dominant
Fabry's disease	Lysosomal storage disorder	Pain, particularly in the hands and feet (acroparesthesias); a decreased ability to sweat (hypohidrosis); cloudiness of the front part of the eye (corneal opacity); ringing in the ears (tinnitus); and hearing loss	X-linked recessive
Kearns-Sayre syndrome	Mitochondrial disease	Cardiac conduction defects, ataxia, muscle weakness, deafness, kidney problems, and a deterioration of cognitive functions (dementia)	Variable
MELAS syndrome, NARP	Mitochondrial disease	Recurrent stroke-like episodes in the brain, migraine-type headaches, vomiting and seizures, general muscle weakness, exercise intolerance, hearing loss	Variable

(continued)

Table 11.3 (continued)

Neurodegenerative disorder	System involved	Neurologic/psychiatric/behavioral abnormalities	Inheritance pattern
MERRF syndrome	Mitochondrial disease	Myoclonus (muscle jerks), seizures, ataxia, muscle weakness, hearing impairment	Variable
Juvenile neuronal ceroid lipofuscinosis	Lysosomal storage disorder	Inappropriate behavior, thought disorder, paranoia with hallucinations, delusions	Autosomal recessive
Subacute sclerosing panencephalitis	Central nervous system	Deterioration in learning or schoolwork, involuntary movements, deterioration in the thought processes, myoclonic jerks, epileptic seizures may or may not occur	Sporadic
Adrenoleukodystrophy	Central nervous system and the adrenal glands	Difficulty reading or writing, obsessional behavior, irritability, social withdrawal, dementia	X-linked recessive
Variant Creutzfeldt–Jakob disease	Central nervous system	Dementia, blurred vision, gait changes, disorientation, hallucinations, lack of coordination, myoclonic jerks or seizures, personality changes, sleepiness, speech impairment	Unknown
Wilson disease	Multisystem especially liver, brain, and eyes	Antisocial behavior, anxiety, depression, manic depressive psychosis, clumsiness, tremors, difficulty walking and mood swings	Autosomal recessive
Multiple sclerosis	Central and peripheral nervous system	Overwhelming fatigue, visual disturbances, altered sensation and difficulties with mobility, muscle stiffness (spasticity), exaggerated reflexes (hyperreflexia), or poor bladder control	Unknown
Friederich's ataxia	Central and peripheral nervous system -spinocerebellar degeneration	Ataxia, gradual loss of strength and sensation in the arms and legs, muscle stiffness (spasticity), impaired speech, hypertrophic cardiomyopathy, impaired vision, hearing loss, or an abnormal curvature of the spine (scoliosis)	Autosomal recessive
Gaucher's disease type III	Lysosomal storage disorder	Hepatosplenomegaly, Anemia, Thrombocytopenia, Bone disease (bone pain and fractures), seizures and slowing of horizontal eye movements	Autosomal recessive

Regression and Progressive Neurological Deterioration Are Cardinal Features

The presentation of a child with a neurodegenerative developmental disorder has varied manifestations. Some children may present with a history of regression in previously acquired developmental milestones, or history of a delay in acquisition of milestones, history of no further attainment of milestones following previously normal progress or a history of total loss of previously acquired milestones. This is graphically illustrated in Fig. 11.1 that demonstrates the possible developmental trajectories of child development. Child (A) depicts the normally developing child who attains the neurodevelopmental milestones at the appropriate successive age. Child (B) shows a child having a fairly stable developmental progress however this is made at twice the successive age and is a picture typical of children with cognitive impairment. Child (C) shows an initial developmental progress which then levels off with hardly any more variation. This represents a child with a neurodegenerative disorder even in the absence of developmental regression. Child (D) initially exhibits a similar trend as is seen in child (C) nonetheless this is followed by gradual loss of developmental skills and is a picture that typifies "classic" neurodegenerative disorder. Child (E) on the other hand shows that this gradual loss of skills is not necessarily a smooth uninterrupted process but may proceed in intermittent bursts of deficits which may denote stress arising from the effects of injury or illness.

In certain circumstances it can be challenging to differentiate between a plateauing of skills, a pseudo-regression and real onset of a neurodegenerative condition in a child with a pre-existing neurological deficit. In such situations it is important to review the authenticity of the original diagnosis and institute the appropriate measures where possible to reverse the condition. Some causes of pseudo-regression

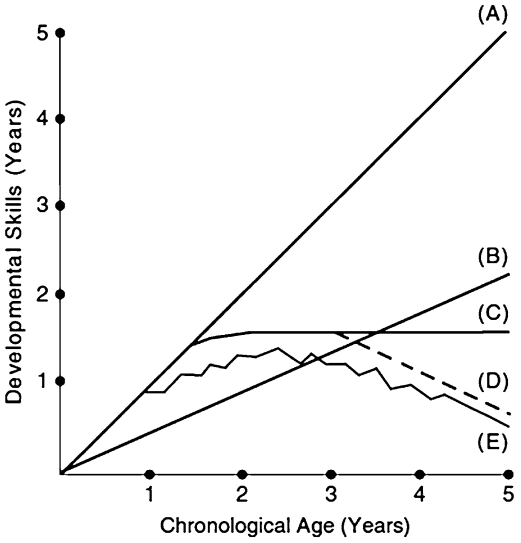

Fig. 11.1 Graphic representation of childhood development (Reproduced with permission from Goldstein E. M, & Holden K.R, (2009), Neurodegenerative Disorders: Variable Clinical Presentation of Cognitive Decline, in Bernard L. Maria (ed.), Current Management in Child Neurology (4th Edition, pp. 322–336), Shelton, CT: People's Medical Publishing House, (PMPH-USA))

may include: depression especially in adolescents, poorly controlled and subtle epileptic seizures as is seen in unrecognized absence seizures or non-convulsive ("subclinical") status epilepticus, acquired hypothyroidism, substance abuse, lead encephalopathy, repeated traumatic brain injury and in children deprived of emotional contact as seen in prolonged hospitalizations [13] or in those who witness domestic violence [14].

Initial Evaluation of Children Suspected of Suffering from Neurodegenerative Disorders

A comprehensive history taking followed by detailed physical examination is paramount when evaluating children with suspected neurodegenerative disorders [4, 12, 15]. A thorough history taking is essential for the assessment of any child with developmental regression in order to exclude other disorders that may mimic neurodegenerative disorders. Following an uneventful pregnancy and delivery of a normal full term child, the child with suspected neurodegenerative disorder may either present with an acute and rapidly progressive or a vague and slowly progressive course. For the latter course it is crucial that it should be distinguished from a static non-progressive disorder. The slowly progressive course primarily affects the white matter and can commence in infancy, childhood or adolescence. Usually the acute onset predominantly affects the gray matter and is seen in neonatal or early infancy with the symptoms commencing a few days after birth.

Following an in-depth history, a formulation of differential diagnoses is made to come to a diagnostic hypothesis directing subsequent laboratory investigations. A classic distinction in the group of neurodegenerative disorders involves those with predominant white matter involvement (such as Multiple Sclerosis, Adrenoleucodystrophy, Alexander Disease, Canavan Disease, Krabbe Leukodystrophy, Metachromatic Leucodystrophy) versus those with predominant gray matter involvement (such as Mitochondrial Encephalopathies, Neuronal Ceroid Lipofuscinonis, Progressive Infantile Poliodystrophy, and the Symptomatic Progressive Myoclonic Epilepsies) [16].

White matter disorders typically feature onset in late childhood, with initially normal cognitive functions, but early and prominent spasticity and cerebellar signs, gait difficulties, and early peripheral neuropathy due to demyelination. Later signs occasionally include focal neurologic deficits, seizures and megalencephaly. Other signs are absence of exaggerated reflexes and optic atrophy. The electroencephalogram (EEG) shows diffuse delta slowing, the electromyogram (EMG) shows slowed nerve conduction velocity and evoked potentials are prolonged or absent.

Disorders primarily affecting white matter can be subdivided into two broad categories, demyelinating and dysmyelinating/hypomyelinating. Demyelination occurs when immune-mediated inflammatory responses, toxic exposure, or vascular injury destroys previously normal myelin, as for example in multiple sclerosis, acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis and

myelinoclastic diffuse sclerosis of Schilder. These white matter disorders likely have an immunological basis but their mechanisms are not completely understood. Disorders that involve dysmyelination or hypomyelination include metabolic diseases affecting the nervous system such as galactosemia, pyridoxine-dependent seizures, infantile Refsum's Disease, metabolic disorders of lipid metabolism (e.g., Metachromatic Leukodystrophy, Krabbe's Disease, and diseases affecting myelin proteins (e.g., Pelizaeus-Merzbacher) (see Tables 11.1, 11.2, and 11.3).

In contrast, gray matter disorders manifest typically in early infancy with microcephaly, early severe seizures, and progressive dementia. Later features are axonal loss, retinal degeneration, progressive spasticity. The reflexes remain normal or become exaggerated. The EEG shows epileptiform discharges, the EMG and evoked potentials are usually normal. The main localization of grey matter loss is specific in some disorders. The basal ganglia are mainly involved in Juvenile Huntington Disease or Wilson Disease. Friedreich Ataxia involves spinocerebellar degeneration; in Spinal Muscular Atrophy, a genetic defect causes targeted death of neuronal cells in the anterior horn of the spinal cord with subsequent system-wide muscle wasting (see Tables 11.1, 11.2, and 11.3).

It is conceded that many neurodegenerative disorders have mixed white and gray matter involvement, or both grey and white matters are involved in a later stage of many of the disorders. Classification schemes may use the type of underlying molecular and genetic defect and change as such due to advances in identifying these defects. Examples are the group of Peroxisomal Disorders that include Adrenoleucodystrophy and Zellweger Syndrome, and the group of Lysosomal Disorders including Krabbe Leukodystrophy and Metachromatic Leukodystrophy).

Postnatal complications such as kernicterus, sepsis, meningitis, and head trauma should be investigated in the history as non-supportive of a neurodegenerative disorders. On the other hand, a positive family history of neurological disorders or early and unexplained deaths may suggest the presence of an undiagnosed inherited neurodegenerative disorder. Other confounders mimicking neurological regression and deterioration such as medical disorders, visual impairment, hearing loss, epilepsy, autism spectrum disorders, intellectual disability, attention-deficit hyperactivity disorders, or child abuse and neglect need to be considered when taking the history.

The clinical examination should include head circumference to detect megalencephaly, an important feature in Canavan, Tay-Sach's, Sandhoff's and Alexander Disease, or microcephaly that is a usual feature of many gray matter disorders due to progressive neuronal loss. Dysmorphic features need to be assessed as facial dysmorphisms are associated with some neurodegenerative disorders such as Zellweger Syndrome and mucopolysaccaridoses. A thorough neurological examination permits us to further define which specific nervous system functions or systems are deranged. In particular one should also assess ocular abnormalities that are prevalent in neurodegenerative disorders, in the form of optic atrophy in white matter disorders and retinal degeneration in grey matter disorders.

More specifically during the eye examination, look out for evidence of cortical blindness as in MELAS syndrome, abnormal movements (as in Ataxia telangiectasia,

Gaucher's disease, types 2 and 3, Kearns-Sayre syndrome and Pelizaeus-Merzbacher disease), corneal clouding (as in Wilson's disease and Hurler's disease), lens opacities (as in Fabry's disease, Galactosemia, Lowe syndrome,) optic atrophy (as in Canavan disease Metachromatic leukodystrophy, Adrenoleukodystrophy and Pelizaeus-Merzbacher disease) or a Cherry Red Macula (as seen GM1 gangliosidosis, Tay-Sachs disease, Sialidosis type I).

Specific clinical findings give clues to the diagnosis. For example, hepatomegaly and/or splenomegaly are prominent in mucopolysaccaridosis, sphingolipidosis, peroxisomal and mitochondrial disorders. Progressive renal failure is found in Fabry Disease and Lowe Syndrome. Abnormalities of the hair (seen in Menkes syndrome, Biotinidase deficiency and mucopolysaccaridoses), the kidneys (as in Zellweger syndrome). Mucopolysaccaridosis, Friedreich Ataxia, and mitochondrial disorders are associated with cardiac disorder.

Investigations for Neurodegenerative Disorders

As a general rule, findings on history and physical examination should guide the selection of laboratory investigations as many neurodegenerative disorders have unique genetic, metabolic, or enzymatic markers. Facilities for a comprehensive workup for most neurodegenerative disorders are currently unavailable in Uganda with most assays having to be performed by overseas laboratories.

Initial laboratory studies should include blood analysis covering complete blood count, glucose, calcium, anion gap, electrolytes, renal function tests, ammonia, aminotransferases, lactic acid, pyruvic acid, uric acid and ketones. Urine analysis is done for ketones, pH, aminoaciduria, organic aciduria, homocystinuria, mycopolysaccharides and oligosaccharides. Serum ammonia, lactate, pyruvate, amino acids, and urine for amino acids and organic acids would screen for most amino acids disorders, organic acidopathies, and urea cycle abnormalities. Chest X-ray may show cardiomegaly in mitochondrial disorders, Friedreich Ataxia, and mucopolysaccharidosis. Conduction abnormalities may be present on electrocardiogram (ECG). Skeletal survey may reveal specific bony abnormalities such as dysostosis multiplex in mucopolysaccharidosis.

Children with dysmorphic features should have genotyping and chromosomal studies. Other investigations that bring important information are EEG often showing bilaterally synchronous paroxysmal discharges in grey matter disorders versus continuous non-paroxysmal slow wave activity in white matter disease. In diseases involving both the grey and white matter, the pattern may be mixed with both bilaterally synchronous paroxysmal discharges and markedly increased recordings of slow wave activity. The electroretinogram (ERG) may provide information about retinal involvement that features in several metabolic diseases. Recording of visual evoked potentials assist in documenting retinal lesions that may be more focal or restricted to retinal ganglion cells as in gangliosidosis. Brainstem auditory evoked potentials may be abnormal in a demyelinating disease or in axonal lesions. Nerve

conduction studies show decreased nerve conduction velocity in demyelinating neuropathy, and decreased amplitude of the motor or sensory action potential in axonal neuropathy. Abnormal neurogenic changes can be differentiated from myopathic changes by analysis of the electromyogram.

Specific diagnostic tests and enzyme assays can be done to identify specific neurodegenerative disorders that often involve skin fibroblast culture, CSF examination, DNA studies, nerve, or muscle biopsies. These tests are not done routinely but only in specialized laboratory, are often expensive, and can be found in other literature [17].

Role of Neuroimaging

There are a range of neuroimaging techniques that could be employed for the early diagnosis of neurodegenerative disorders; however one needs to consider the purpose of the investigation. Early diagnosis may be used to appropriately delineate a specific disease condition from others that may present with similar clinical symptoms especially in the early stages, alternatively it may be utilized to timely identify a malfunctioning central nervous system before the clinical symptoms appear.

In Uganda there are limited diagnostic modalities with respect to brain imaging despite its significant value. Cranial computed tomography (cranial CT) and magnetic resonance imaging (MRI) brain scans are usually employed. MRI however plays a primarily vital role in diagnosis of central nervous system degenerative illnesses because it is exceptional in the visualization of many cerebral abnormalities compared to CT.

Other powerful neuroimaging techniques that permit visualization of organ structure and function with precision include: positron emission tomography (PET) and single photon emission computed tomography (SPECT) but these are currently unavailable. These utilize radio-ligands which measure in detail the functioning of distinct areas of the human brain and are beneficial in detecting and characterizing potential pathophysiological brain changes. These methods particularly PET that has the higher sensitivity are of great value in detecting early stages of the causes of cognitive impairment [18].

General Treatment Guidelines

Treatment can be directed towards the underlying disorder, associated features, and complications. Dietary restriction is useful in certain diseases such as phenylketonuria, maple syrup urine disease, adrenoleukodystrophy etc. Treatable complications include epilepsy, sleep disorder, behavioral problems, feeding difficulties, gastroesophageal reflux, spasticity, drooling, skeletal deformities, and recurrent chest infections. Specific treatments to counteract the offending metabolite (s), improve

or decrease abnormal enzyme function, or to off-set metabolic dysfunction are possible for specific diseases in addition to organ transplantation including bone marrow transplantation (when irreparable brain damage has not occurred). Bone marrow transplantation has been shown variable but promising results in lysosomal storage diseases, mucopolysaccharidoses, Gaucher's Disease, metachromatic leukodystrophy, and adrenoleukodystropy. It may be possible in the future to target specific pathways with somatic gene therapy but this will require more technological advances and discoveries. A referral for genetic counseling is important due to heritability of many neurodegenerative disorders. Public health initiatives should focus on the risk of consanguineous marriages as a way to raise awareness of a preventable cause of neurodegenerative disorders in childhood.

Common Etiologies of NDDD's Seen in Uganda

Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) belongs to the Lentivirus genus of the Retroviridae family. The UN estimates that there were 35.3 (32.2–38.8) million people in the world infected with HIV in 2012 [19]. Uganda is estimated to have 1.5 million people living with HIV-1, of whom 190,000 are children [20].

HIV-1 is the most common cause of HIV infection in Africa with mother-to-child transmission of HIV (MTCT) being the major mode of acquisition of infection in children. The estimated risk of perinatal acquisition of untreated women to their infants ranges from 13 % to 30 % with approximately 400,000 new HIV-1 infections occurring each year [20].

A very high mortality is seen in low income countries with mortality rates of over 50 % by the age of 2 years when no treatment is instituted [21] and Uganda is no exception [22].

The HIV virus has a predilection for the Central Nervous system especially the microglia with as many as 10 % of children with AIDS developing HIV progressive encephalopathy (HPE). Information from a systematic review of studies on paediatric HIV/AIDS and neurodevelopment in infancy in Sub-Saharan Africa (SSA) shows that HIV affects all spheres of child functioning. The sphere of motor development is the most noticeably affected in terms of severity, time of onset and persistence across the age groups [23]. The cognitive sphere is also significantly affected compared to their age and gender matched HIV negative peers. One study found that despite being clinically and neurologically stable, school-aged HIV- positive children (aged 6–11 years) had considerably lower cognitive scores compared with the age and gender-matched HIV negative children [24].

In contrast, an earlier long-term prospective study of HIV-infected Ugandan children followed from birth to school age, found no evidence of significant differences in neurologic, motor, and psychometric development when compared with seroreverter children or with HIV negative children who were born to HIV-negative mothers.

This was attributed to possible earlier death of the severely ill children with HIV encephalopathy in the cohort leaving survivors with a somewhat static/stable expression of the disease hence the normal range cognitive assessments [25].

Risk Factors

The timing of HIV infection is the risk factor identified so far as contributory to this condition, with significantly lower cognitive function scores noted in children testing positive in the first 3 weeks of life compared to the scores of those identified later than this [26].

Other identified risk factors based on studies also done in adults include:

- Host factors- genetic predisposition, low educational status, presence of metabolic disorders, co-infection with hepatitis C virus and IV drug abuse.
- Viral factors- the virus subtypes B, C, D and F more related than subtype A [27–29].
- Relation of host and virus- an advanced stage of HIV/AIDS, low level of CD4+ counts, presence of chronic immune activation manifesting by increased levels of cytokines, interleukins and other serum markers. e.g. monocyte chemoattractant protein 1 (MCP-1), TNF-alpha, hsCRP, raised level of HIV-DNA load in circulating macrophages and higher CSF viral load compared to serum viral load [30, 31].

Clinical Features

HIV-associated progressive encephalopathy (HPE) is a syndrome complex characterized by a triad of cognitive, motor, and behavioral features similar to features of "AIDS dementia complex (ADC)" seen in adults [32, 33].

HPE affects children in a variable, non-linear course, however three definite patterns are identified [34, 35]:

(i) The rapid progressor group,
(ii) The sub-acute (slow) group
(iii) The static neurological group.

Similarly to adult patients, HPE may occur in children in the absence of HIV opportunistic infections or with malignancies of the central nervous system. Children may present with developmental regression, behavioral disorders, microcephaly or cerebellar signs.

Pathogenesis

The pathogenesis of HIV related central nervous system (CNS) involvement is not well understood. It is however postulated that during the early course of the infection [36], HIV enters the CNS via the CD4 T lymphocytes and monocytes, which

cross the blood-brain barrier (BBB). The infected monocytes convert into perivascular macrophages in the nervous tissue, as the HIV virus spreads to infect the local macrophages (microglia). The perivascular macrophages and microglia merge to form multinucleated giant cells (MGCs). These MGCs serve as HIV reservoirs by replicating the virus and producing neurotoxic viral molecules: viral (gp-120 and tat protein) [37]. These neurotoxins activate astrocytes, which in turn release cytokines and cause BBB breakdown enhancing the movement of more HIV-infected cells from blood to brain. In addition the astrocytes damage the neurons, resulting in demyelination and neuronal loss.

Diagnosis

According to the Consensus of Pediatric Neurology/Psychology Working Group, AIDS Clinical Trial 1996, [38] a definitive diagnosis of HPE requires at least one of the options below to be present for at least 2 months in the absence of a coexisting illness other than HIV infection:

1. Failure to achieve or loss of developmental milestones, or a loss of intellectual ability, verified by normed developmental scales or neuropsychological tests;
2. Poor brain growth, or acquired microcephaly validated by head circumference measurement, or brain atrophy demonstrated with neuro-imaging with CT or MRI scans with serial imaging necessary in children less than 2 years of age; and
3. Acquired symmetric motor deficits exhibited as: hyperreflexia and/or pathologic reflexes, hypertonia, paralysis or gait disturbances.

Unlike typical neurodegenerative syndromes there is a variable degree of reversibility for HPE. Highly Active Antiretroviral Therapy (HAART) has been shown to retard/or possibly reverse the progress of HIV-associated encephalopathy [39]. However, despite the clinical stability and use of anti-retroviral medications, there is still ongoing cognitive decline mostly attributable to the HIV infection implying that HAART may not completely reverse established encephalopathy in all cases [40].

Cerebral Malaria

Malaria is an important parasitic infestation in humans with four species responsible for producing the illness. i.e. *P. vivax, P. ovale, P. malariae* and *P. falciparum*. Infection with *Plasmodium falciparum* is responsible for the severe and complicated manifestations and in children presents with a varied spectrum of signs, symptoms, and history. This ranges from a life threatening disease to an apparently asymptomatic infection, from a rapidly progressing, fulminant illness to a chronic insult. The most severe neurological complication of *P. falciparum* malaria is cerebral malaria and has been associated with case-fatality rates of 10–40 % in hospital-based studies [41].

Clinical Features

In children cerebral malaria presents with fever, seizures, coma, and brainstem signs. The characteristic feature of cerebral malaria is impaired consciousness, with coma as the most severe manifestation which may be of gradual or sudden onset. Furthermore seizures, brain oedema, retinal changes (papilledema, haemorrhages, peripheral and macular whitening) and brainstem signs (irregularities in pupil size and reaction, abnormal eye movements, abnormalities in posture and respiratory patterns) may be manifested. Some children develop life-threatening complications such as severe anaemia, electrolyte imbalance, metabolic acidosis, hyperpyrexia, hypoglycemia, shock, or encephalopathy [42].

Risk Factors

Among some of the identified risk factors associated with development of Cerebral Malaria include [43–46]:

- Child factors- such as being of an age above 2 years, higher level of parisiteamia, having a higher number of siblings (>4), presence of malnutrition, having HIV type 1 infection, initial treatment in clinics, late presentation/consultation, non-use of mosquito nets, presence of fresh abdominal scarification and presence of genetic host factors host genes including Transforming Growth Factor Beta 2 (TGFB2) and Heme oxygenase-1 (HMOX1).
- Socio-economic factors- such as low social economic class of the family, non-living together of parents, or poor access to health facilities.
- Parental factors- such as young mother, or low level of maternal education.

While an apparent full recovery is observed in more than 85 % of children who recover from cerebral malaria [41], approximately 25 % have persistent neurological sequelae such as seizures, cortical blindness, ataxia or generalized spasticity. Others survive with concealed effects such as defects in learning, behaviour, or cognition [42, 47, 48].

Pathogenesis

The pathophysiology for these clinical features results from cerebral malaria causing a disseminated vasculomyelinopathy. This results in the histopathologic changes in the brain that include: edema, neuronal degeneration, perivascular infiltrates, perivascular demyelination, ring hemorrhages, and the microglial-astroglial nodules (Dürck's granulomas) in the late stages [49, 50]. Furthermore, the high temperatures contribute to degeneration of the neurons in the cortex, cerebellum and basal ganglia [51].

Diagnosis

Usually the diagnosis of cerebral malaria is made from a suggestive history, clinical features and a positive blood smear (on microscopy). In the absence of a positive blood smear the alternative use of rapid tests such as the immunochromatographic test for P. falciparum histidine-rich protein 2 and lactate dehydrogenase or Polymerase chain reaction tests may be used however their sensitivity and specificity plus inability to estimate the parasite load are impediments [52, 53]. Based on findings from a Malawian postmortem study, the presence of Malarial retinopathy showed increased specificity in distinguishing patients with features of Cerebral Malaria from other encephalopathies. Cerebral spinal fluid (CSF) analysis usually shows mild pleocytosis and an increase in protein. Raised levels of CSF and Blood levels of lactate may be observed. Neuroimaging typically shows brain oedema [54].

Measles

Measles is an acute viral illness caused by a morbillivirus of the paramyxovirus family. Measles continues to be an endemic illness in Uganda, despite efforts to control the outbreaks through mass measles vaccination campaigns. The impact of these campaigns is usually short-lived, not lasting more than 2 years [55]. Currently less than half of the children in Uganda receive complete immunization [56]. The majority of all measles cases (93 %) and of severe cases (97 %) are among children <15 years of age [57].

Approximately three in every ten cases of measles have one or more complications. These complications are more common in children under 5 years of age with higher mortality rates observed in the immunocompromised, the malnourished and in those with vitamin A deficiency. Among the neurological complications include: convulsions (0.5 %) and encephalitis (0.1 %).

Clinical Features

Subacute sclerosing panencephalitis (SSPE) is one of the three types of measles encephalitis (the other two being acute demyelinating encephalomyelitis and measles inclusion body encephalitis).

SSPE is a neurodegenerative disease resulting from a post infectious neurologic complication of measles. A persistent infection of the brain caused by an altered form of the measles virus is implicated in the pathophysiology. The prevalence of SSPE is dependent on how successful the measles vaccination coverage was, with the higher incidence in areas having low vaccination rates. The mechanisms underlying the viral persistence and the trigger of the viral reactivation remain elusive.

It is however suspected that as a result of genetic polymorphism, those individuals who develop SSPE exhibit an altered cellular response to the measles antigen. This results in premature production of antibodies following measles infection that impairs the host's immune cells' ability to eliminate the virus and, thus, supports a chronic intracellular infection [58–60].

In most instances following an acute measles infection, the infected children remain symptom-free for 6–15 years [61]. The risk is higher in those acquiring measles before the second birthday [62]; with the risk of SSPE being 16 times greater when it occurs in children less than 1 year of age than in those over 5 years of age [63]. The prevalence of SSPE is notably more in males than females with the onset of symptoms later in the latter group as well [64, 65].

Risk Factors

Among the risk factors associated with SSPE include [66–68]:

- Child factors- such as being of a higher birth order, younger age at measles onset, having a higher number of siblings or having HIV/AIDS.
- Socio-economic factors- such as living in poverty, congested homes, or in rural areas.
- Parental factors- such as an older mother, mother with HIV/AIDS or low level of parental education.

The initial symptoms of SSPE usually present 6 years after measles infection. The affected individuals present with progressive cognitive and intellectual deterioration that may manifest in poor school performance, personality changes, and behavior abnormalities. A period of continual motor decline ensues and over a series of months, the psychological symptoms are complicated by neurologic ones that include: myoclonic jerks, focal weakness, autonomic malfunction, seizures and rigidity, finally leading to death with akinetic mutism [65, 69, 70].

Pathogenesis

The pathophysiology for these clinical features results from oedema, principally seen in the early course of this disease. Infected cells show DNA and ribonucleic acid oxidative damage coupled with lipid peroxidation in areas exhibiting early demyelination. As the disease progresses there is cortical and subcortical perivascular infiltration of inflammatory cells, spongiosis, and demyelination in the acute phase, followed by neuronal loss. In the preliminary stages, the posterior areas of the brain are the most affected, followed by spread to the anterior regions with limited involvement of the cerebellum [71].

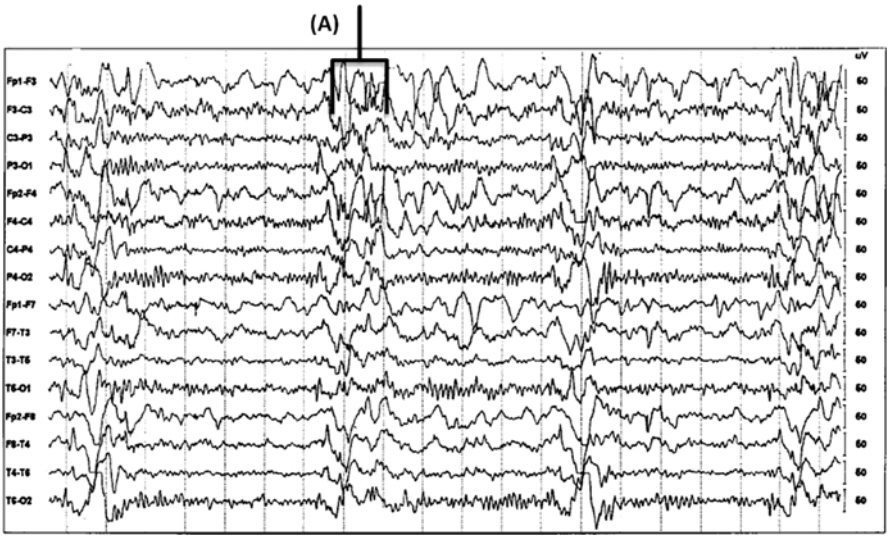

Fig. 11.2 An electroencephalogram showing a "burst-suppression" pattern highly characteristic of subacute sclerosing panencephalitis (SSPE). An example of runs of periodic bursts of high-amplitude, slow-wave complexes with a normal background rhythm apart from bifrontal slowing is shown in (*A*)

Diagnosis

The diagnosis of SSPE is accompanied by a unique set of laboratory abnormalities that facilitate its diagnosis which include: CSF analysis which shows normal cellular components, glucose and total protein, but grossly elevated values of gamma globulins and serum anti-measles antibodies. In almost all cases, the EEG reveals a "burst suppression" pattern at some point in the course of SSPE as shown in Fig. 11.2. The bursts of abnormal sharp and slow waves typically arise out of a normal background EEG activity early in the course of SSPE, but this background activity deteriorates to diffuse slow waves as the disease progresses [61].

The brain MRI may initially be normal, or may show focal abnormalities in the subcortical white matter with posterior cortico-subcortico lesions on diffusion weighted imaging (DWI) [72]. Later, diffuse cerebral atrophy, periventricular white mater T2 hyper intensities and basal ganglia are classically described [73]. A combination of the clinical features with supportive EEG and radiological findings should lead one to suspect a diagnosis of SSPE.

Nodding Syndrome

Nodding syndrome (NS) is a puzzling, often progressive, disorder that has been described in African children [74, 75]. Uganda [74, 76] is one of four African countries that have reported cases of this condition among its populations, with initial

reports coming from Tanzania [77] and subsequently Liberia [78] and South Sudan [79–81]. The northern region of the country constitutes the major area where these cases are found with the first cases reported around 1997 and peaking at the height of the political insurgency that afflicted this region for more than 20 years from 1986 and when people moved into protected Internally Displaced Peoples (IDP) camps (MOH, report). To date an estimated total of over 10,000 cases have been identified in children and adolescents from South Sudan, United Republic of Tanzania and Uganda [82]. The true burden of the syndrome in Uganda is unknown. It is currently not known if NS is a true neurodegenerative disorder due to lack of research and knowledge about etiology and mechanism. Anecdotal reports describing a down ward trend of progressive neurologic deterioration, psychiatric symptoms, physical wasting and ultimately death. Deaths from drowning/burning accidents, opportunistic infections, self-injury, persistent seizure episodes have been reported by the caregivers [84]. Whereas symptomatic improvement has been noted to occur in children with NS given nutritional and vitamin supplementation, antidepressants and/or anticonvulsants [83], no child is known to have completely recovered from nodding syndrome, and the long-term outcomes of the illness are still poorly understood [84]. It has been noted that there is parallel relationship between the nutritional status of patients with NS and the degree of severity of wasting and stunting observed in the children and the length of duration of symptoms, being most marked in those having symptoms with a longer duration [85].

Clinical Features

From the clinical descriptions of Nodding syndrome in the literature, children initially get afflicted, between the ages of 3 and 18 years (MOH report), with the 6–11 years age group being more frequently affected [86]. The children are noted to develop bouts of repetitive dropping forward of the head, termed “head nods” which are atonic seizures [74]. The head nodding is often accompanied by other seizure types such as generalized tonic-clonic, myoclonic, complex partial and absence seizures [74, 85]. Precipitants of these “head nods” include the sight of food, taste of a hot meal or cold drink [74], presence of cold weather or bathing in cold water [87] while in others no specific precipitant has been identified [85].

The head nods often precede the other seizure types by 2–4 years and continue together in some case while in others the head nods cease and the other seizures types take over.

While documented natural history studies are lacking, over the course of time following progressive brain damage, the children acquire cognitive, motor, and behavioral impairments with subsequent malnutrition and growth retardation. Focal neurological deficits are rare. There is a decline in school performance followed by eventual school drop-out [74, 85, 87]. Other reports document aggressive behavior, self-injurious outbursts, depression, visual hallucinations, loss of speech/slurred speech, upper and lower limb disfigurements with chest and vertebral bone deformities [84, 85]. A delayed sexual maturity with delayed bone growth has also been

documented [84]. NS patients also exhibit several catatonic symptoms including: slowing of movements, immobility alternating with purposeless agitation, muteness, repetitive movements, staring, posturing, grimacing, social withdrawal, negativism (including active or passive refusal to eat and drink), and urinary incontinence [83–85]. In a pilot study conducted in one of the Northern districts in Pader to determine whether NS patients meet clinical criteria for pediatric catatonia and their response to a catatonia test using lorazepam, the first-line treatment for catatonia, many of these clinical features were confirmed as well as the safety and possible benefits of Lorazepam in the treatment of NS required larger and controlled follow-up studies (Kakooza 2014, in preparation).

Pathogenesis

Regardless of previous investigations, the cause of the syndrome and the pathogenesis remain indeterminate. Possible postulations include:

- A degenerative brain disorder complicated with seizures. The origin of the degeneration could be from poorly treated infections like viral encephalitis, cerebral malaria, *O. volvulus* or traumatic brain injury resulting into repeated seizures with subsequent cognitive decline. The association with *O. volvulus* however is considered by some to be false [79, 81, 84, 86]. In addition, the screening for several viral central nervous system infections using PCR, for a possible etiological agent have proven futile [88]. Mass treatment of NS with Ivermectin and anticonvulsants, however did not control NS [84].
- An epidemiological study conducted by the Ugandan Ministry of Health and the US Centers of Disease Control found most cases and controls had low vitamin B6 levels [88], nursing the possibility that vitamin B6 deficiency may be contributory to disease pathogenesis. Since vitamin B6 is an important factor in the synthesis of neurotransmitters, any reduced levels could lead to impaired neurologic function with possible intractable seizures, the so called pyridoxine dependence seizures [89, 90]. Treatment with pyridoxine, however, did not control NS.
- Severe psychological trauma following chronic and repeated war- traumatization (both direct and indirect) in the children resulting in severe chronic Post-Traumatic Stress Disorder, coined "Developmental Trauma Disorder" (DTD) [84, 91] has been suggested. This could be complicated by chronic depression and anxiety or catatonia [92, 93] and lead to poor appetite or food refusal resulting in severe malnutrition [84].

Other etiological considerations have included depression with or without conversion symptoms, slow virus infection or prion disease, a newly discovered mitochondrial disease, neuro- toxic brain injury, chronic inflammatory brain diseases, or a mutant genetic disorder. Others have entertained that it could be as a result of a combination of any one of the previously mentioned possibilities. There is need for future multicenter studies in Uganda and other affected sites to explore possible causes/risk factors for NS and their role in this enigmatic condition.

Conclusion

Neurodegenerative disorders, although individually rare, encompass a large heterogeneous group of disorders that stem from specific genetic and biochemical defects, chronic viral infections and varied unknown causes. Comprehensive history taking followed by detailed physical examination is paramount when evaluating children with suspected neurodegenerative disorders. A high index of suspicion is necessary when any combination of the following is present:

- Regression and progressive neurological deterioration
- Changes in personality or behavior
- Symptoms of refusal to feed, lethargy, vomiting, hypotonia, coma, or seizures in the neonatal or early infancy period.
- Focal neurological deficits, spasticity, and visual symptoms and signs
- Clumsiness or difficulties in gait
- Signs of jaundice, visceromegaly
- Dysmorphic features or coarse facies
- Parental consanguinity
- Positive family history of a similar illness/death

Adequate laboratory facilities to diagnose NDDD's are scarce and lacking in Uganda leading to delays in diagnosis, treatment and hence a poor prognosis in most cases. A multidisciplinary approach involving specialists from varied relevant disciplines is recommended in the management of neurodegenerative disorders. Management is geared towards the definitive treatment of the underlying disorder, the associated features and the complications with the provision of supportive therapy where required. Making the right and timely diagnosis is of critical importance for providing appropriate therapy, genetic counselling, guiding prognosis and implementation of preventive strategies. The ongoing studies of new techniques for imaging the central nervous system, discovery of the human genome and novel therapies for clinical treatment is expected to produce significant advances in the management of neurodegenerative disorders. It is hoped that our understanding of the genetics of these complex disorders will be improved, the changes in brain structure and function associated with them made more explicit and the prevention of the progression of the disorders in certain pre-symptomatic individuals curtailed.

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