Seizures in Cerebrovascular Disorders

A Clinical Guide

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Amer Alshekhlee
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ISBN 978-1-4939-2558-2
ISBN 978-1-4939-2559-9 (eBook)
DOI 10.1007/978-1-4939-2559-9

Library of Congress Control Number: 2015939721

Springer New York Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer New York is part of Springer Science+Business Media (www.springer.com)

To Maha
MZK

To my wife Lina and my lovely 3 kids
AA

To AC and MP, my parents, and Kunal
PM

Preface

Our motivation in editing this book is to fill the gap between two major and common neurologic disorders (cerebrovascular diseases and epilepsy). These disease categories frequently overlap in clinical practice, and sufferers often evaluated by physicians from different backgrounds in neurology. This book will be an opportunity to serve health care practitioner from these backgrounds and others such as neurosurgeons and neurointensivists. Furthermore, this book can be the foundation and succinct guide to trainee in these fields of neurology.

The vast majority of the contributors to this book are renowned authorities in their fields of cerebrovascular and epilepsy disorders. The methodology in constructing the authorship for this book is somewhat unique. Each chapter was written by two or three authors, at least one of them is an expert in cerebrovascular diseases and a second author is an expert in epilepsy disorders. The editors of this book asked contributors to meld their clinical knowledge and experience. We believe this mix provides an exceptional product that hopefully serve readers or health practitioner deal with the spectrum of these diseases. The editors of this book are appreciative to the extraordinary effort and enthusiasm to each author stamped his presence in the book.

This book is divided into ten chapters according to the nature of the cerebrovascular diseases. The first chapter handles the spectrum of epidemiology of seizures and epilepsy in cerebrovascular diseases. The range of cerebrovascular diseases and epileptic disorders in pediatric population typically differs from adults; hence, this subject was handled in a separate chapter. Subsequent chapters were divided according to the type of the cerebrovascular disease; for example, Chap. 4 handles seizures in ischemic stroke, Chap. 5 handles seizures in intracerebral hemorrhage, and so on. Each chapter in the book is divided into sections including the epidemiology of seizures in that specific cerebrovascular disease category; neuroimaging section may provide a visual corroboration between these disease categories; risk factors for seizures in association with each cerebrovascular syndrome; and treatment strategies.

It is our hope that you find the chapters of this book both comprehensive and practical, and that "Seizures in Cerebrovascular Disorders" quickly become a valuable reference in your daily management of patients suffering from these disease overlap.

Contents

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Chapter 1
Epidemiology of Seizures and Epilepsy in Cerebrovascular Disease

Lawrence N Eisenman and Andria L Ford

Epidemiology of Epilepsy

Epilepsy is a very common neurologic disease with significant associated morbidity and mortality. In order to review the occurrence of epilepsy in the population, it is first necessary to clarify some definitions. Most studies are performed using the International League Against Epilepsy (ILAE) guidelines for epidemiological studies [1] which define epilepsy as two or more unprovoked seizures. Acute symptomatic, febrile, and neonatal seizures are excluded. Multiple seizures that occur within a 24-h period are considered to represent a single seizure. Anyone who has had a seizure in the last 5 years is considered to have active epilepsy while someone with a diagnosis of epilepsy who has not had a seizure within the last 5 years, with or without treatment, is considered to have epilepsy in remission.

Incidence is defined as the number of new cases in a specific population in a given period of time. It is typically expressed as the number of cases per 100,000 people per year. Cumulative incidence is defined as the proportion of a population that develops the condition being studied within a certain time. It is typically expressed as the percentage of the population that is affected at any time up to a particular age (e.g., 3% by age 75 years). Prevalence is defined as the number of patients with a disease at a given point in time. It is typically expressed as the number of cases per 1000 people. For epilepsy prevalence studies, people are considered to have active epilepsy if they have had a seizure and/or used medications to treat seizures in the past 1 or 5 years, depending on the study. As detailed below, the incidence and prevalence of epilepsy vary with age. Therefore, overall population measures of incidence and prevalence depend on the age distribution of the measured population. It is common to correct for the age distribution of the measured population to allow comparisons between studies and age-corrected values are used in this chapter.

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_1

The incidence of new-onset seizures is typically measured separately for acute symptomatic (provoked) seizures and unprovoked seizures. Estimates for the rates of provoked seizures range from 20 to 35 per 100,000 [2, 3]. Studies of unprovoked seizures typically combine both individual seizures and new-onset epilepsy (two or more seizures) resulting in incidence rates varying between 40 and 70 per 100,000 in North America and Europe [4, 5]. In studies that specifically assessed new-onset epilepsy, the rates were slightly lower. For example, in the Hauser et al. [3] classic study of the population of Rochester, MN, the rate of new-onset epilepsy was 44 per 100,000 while including single seizures increased the incidence to 61 per 100,000. The same study reported cumulative incidences of 1.2 % by age 24, 3 % by age 75, and 4.4 % by age 85 years.

The incidence of epilepsy varies with age. In general, there is a bimodal distribution with a high incidence in young children that decreases through adolescence to a minimum in young adults. Recently, it has become apparent that the incidence starts to increase again after age 50–60 years [5]. For example, in Iceland the incidence in infants was 130.2 per 100,000 in infants, 110.5 per 100,000 in adults older than 65 years, and 168.5 per 100,000 in adults aged 75–84 years [6]. In Finland, the overall incidence decreased from 71.6 to 52.9 per 100,000 between 1986 and 2002 [7]. Despite this decrease, the incidence in the elderly increased approximately 20 % [7]. It has been suggested that there are some differences between elderly men and women. Specifically, one study reported that the increase in incidence starts in men between ages 60 and 69 years while it starts later in women [2]. Recent data in the US Medicare recipients who were at least 65 years of age suggest some racial differences in the incidence of epilepsy in the elderly. White beneficiaries had incidence rates of 230 per 100,000 compared to an incidence of 410 per 100,000 in black beneficiaries, an incidence of 160 per 100,000 in Asian beneficiaries, and an incidence of 110 per 100,000 in Native American beneficiaries [8]. For all groups, incidence increased with advancing age.

Prevalence studies are typically performed with door-to-door surveys using a standardized and validated screening questionnaire. This is generally considered to be a straightforward and accurate method, although in some cases low prevalence rates have raised concerns about possible concealment. In the developed world, the prevalence of active epilepsy has been estimated to range from 4 to 7 per 1000 [5]. There are also data to suggest that prevalence increases with advanced age. For example, in Finland, the prevalence of epilepsy in those above 85 years was 9.4 per 1000 compared to the overall rate of 4.8 per 1000 [9]. The prevalence of epilepsy in adults older than 75 years increased from 1.9 per 1000 in 1940 to 14.8 per 1000 in 1980 [10]. Recent data in the US Medicare beneficiaries who were at least 65 years of age suggested racial differences in prevalence. White beneficiaries had a prevalence of 10.2 per 1000, while black beneficiaries had a prevalence of 18.7 per 1000, Asian beneficiaries had a prevalence of 5.5 per 1000, and Native American beneficiaries had a prevalence of 7.7 per 1000 [8].

Overall, the most common cause of epilepsy is idiopathic/cryptogenic, and no clear cause is identified in up to two thirds of patients [3, 6]. The most commonly identified cause in adults is cerebrovascular disease [5], a cause that is increasingly important in

older adults. For example, it has been estimated that vascular causes explain epilepsy in 32–54% of elderly patients [11, 12]. Similarly, in the Veterans Administration (VA) Cooperative trial in the elderly #428, 34.1% of patients had a history of cerebral infarction, and an additional 14.9% had a history of atherosclerosis [13, 14].

Epidemiology of Stroke

Similar to epilepsy, stroke is a common disease that carries significant societal burden both within the USA and globally. Within the USA, stroke is the fourth leading cause of death and a leading cause of serious, long-term disability, with up to 30% of survivors being left permanently disabled [15–18]. Worldwide, stroke ranks even higher in mortality as the second leading cause of death while ranking third in disability [19, 20]. In the Framingham Heart Study, a longitudinal community-based cohort study assessing cardiac and cerebral vascular risk factors and events, among ischemic stroke survivors who were older than 65 years of age, several disabilities were observed at 6 months after stroke: 50% had hemiparesis, 35% had depressive symptoms, 26% were institutionalized in a nursing home, 30% were unable to walk without assistance, 26% were dependent in activities of daily living, and 19% had some degree of aphasia [21].

Recent estimates of stroke incidence in the USA suggest approximately 795,000 strokes occur annually [17]. Of these, 75% are first-time cerebrovascular events with the remaining 25% being recurrent events. The incidence estimates are derived from several large, stroke epidemiological studies including the Framingham Heart Study [22], the Atherosclerosis Risk in Communities Study [23], the Cardiovascular Health Study [24], and the Greater Cincinnati/Northern Kentucky Stroke Study [25]. Stroke incidence globally is estimated to affect 15 million, leading to death in one third and permanent disability in one third [19]. The US prevalence of stroke (estimate for 2008) was 2.8% (affecting about seven million Americans older than 20), with slightly greater prevalence in women compared to men (3.0 vs. 2.6%, respectively) [17]. While men begin having strokes at a younger age than women, women have more strokes than men for the age group greater than 85 years and also carry an overall higher lifetime risk of stroke compared to men [22]. Women have greater disability and likelihood of institutionalization poststroke, in part due to their strokes occurring at older age [21, 22]. Age-adjusted stroke prevalence is more common in Blacks (3.9%) compared to Whites and Hispanics (2.5 and 2.6%, respectively) [26]. Much, but not all, of the increased prevalence of stroke in Blacks compared to Whites may be related to their higher prevalence of stroke risk factors [26]. Stroke is relatively uncommon in children, and prevalence increases exponentially with age: 20–39 years, 0.4%; 40–59 years, 2.0%; 60–79 years, 7.7%; and ≥80 years, 14.6% [17, 26–28].

Stroke is often divided into two broad subgroups of ischemic and hemorrhagic stroke, which account for 87 and 13% of strokes in the USA, respectively [17]. This proportion of ischemic to hemorrhagic strokes varies across the globe, however. For

example, eastern countries such as China have a higher proportion of hemorrhagic strokes (33 % of total strokes compared to 12 % in comparative white populations of European origin) [29]. Ischemic strokes are often grouped by etiologic subtype based on suspected underlying cause of thrombosis into five categories with their corresponding proportion of all ischemic strokes: (1) large-artery atherosclerosis (13–17 % of ischemic strokes), (2) small-vessel disease (16–23 %), (3) cardio-embolic (22–29 %), (4) other (uncommon causes, 1–6 %), and (5) cryptogenic/undetermined (35–38 %) [30, 31]. The large percentage of strokes falling into the cryptogenic category is in part due to not having adequate evaluation to determine its etiology in one of the other categories.

While a minority of all strokes is due to primary hemorrhage, hemorrhagic strokes are associated with high morbidity and mortality [20, 32]. Hemorrhagic strokes are often divided into intracerebral hemorrhages (including intraparenchymal and intraventricular hemorrhages accounting for about 10 % of all strokes) and subarachnoid hemorrhages (accounting for about 3 % of all strokes) [17]. Globally, hemorrhagic stroke was found to account for more disability as measured by disability-adjusted life years (DALYs) than ischemic stroke (2.5 vs. 1.6 %) due to the younger age of death in hemorrhagic stroke patients leading to more years of life lost (YLL) which is a factor in DALYs [20]. More than one third of patients with intracerebral hemorrhage die within the first month [32]. Recent data from the Greater Cincinnati/Northern Kentucky Stroke Study comparing stroke rates between 1993–1994 and 1999–2005 indicate declining incidence of ischemic strokes, but not hemorrhagic strokes [33].

Epidemiology of Seizures and Epilepsy in Stroke

Currently, it is estimated that the incidence of seizures in stroke is approximately 10 % with a very large range of estimates due to a number of factors including differences in study design, definitions, study setting (community vs. hospital), and seizure identification and classification [34]. The Seizures After Stroke Study, a prospective, hospital-based, multicenter study of consecutive stroke patients followed for an average of 9 months identified seizures in 8.9 % of patients [35]. Similarly, 9.8 % of patients admitted to the Stroke Unit of Ghent University Hospital, Belgium had seizures [36]. Community-based studies have also produced similar results. For example, patients followed in the Oxfordshire Community Stroke Project had an 11.5 % risk of having a seizure within the first 5 years following a stroke [37].

Seizures after stroke are often classified as either early or late. Early seizures are typically defined as occurring within 1 week of a stroke while late seizures are defined as occurring more than 1 week after a stroke. This distinction is important because early seizures are considered to be acute symptomatic (provoked) seizures while late seizures are considered to be unprovoked [1]. Of the 535 consecutive, new-onset stroke patients without a prior history of seizures in Rochester, MN, who

were followed for 5.5 years, 33 had a seizure within 1 week of a stroke, and 78 % of those occurred within the first 24 h. An additional 27 new-onset stroke patients had a seizure more than 1 week following a stroke [38]. In northern Manhattan, 4.1 % of new-onset stroke patients had a seizure within 7 days of having a stroke [39]. In the Greater Cincinnati/Northern Kentucky Stroke Study, 3.1 % of patients with new-onset strokes had seizures within 24 h [40]. Interestingly, in the Greater Cincinnati/Northern Kentucky Stroke Study, there was no difference in seizure incidence between patients with initial versus recurrent strokes [40].

The risk of seizures varied with stroke subtype. Specifically, many studies reported an increased risk of seizures with hemorrhagic stroke compared to ischemic stroke. In the Seizures After Stroke Study, 10.6 % of patients with a hemorrhagic stroke had seizures, while 8.6 % of patients with an ischemic stroke had seizures [35]. Over 30 % of patients in the Oxfordshire Community Stroke Project with subarachnoid hemorrhage had seizures within 5 years, and over 25 % of patients with intracerebral hemorrhage had seizures within 5 years while about 10 % of patients with an ischemic infarction had seizures within 5 years [37]. In the Greater Cincinnati/Northern Kentucky Stroke Study, 8.4 % of patients with a hemorrhagic stroke had seizures within 24 h compared to 2.4 % of patients with an ischemic stroke [40]. In the Northern Manhattan Study, 14.3 % of patients with lobar hemorrhage, 4 % of patients with a deep hemorrhage, and 8 % of patients with subarachnoid hemorrhage had seizures within 7 days compared to 5.9 % of patients with a lobar ischemic stroke and 0.6 % of patients with a deep ischemic infarct [39].

Stroke is also associated with status epilepticus which can be associated with significant mortality [41, 42]. Status epilepticus was reported in 1.1 % of patients in the northern Manhattan population [39] and 3 % of patients in the Seizures After Stroke Study [35]. Neither study showed a difference between ischemic and hemorrhagic strokes. Other investigators have reported that status epilepticus is associated with more severe strokes [43, 44]. Nonconvulsive status epilepticus has been increasingly recognized in stroke patients. It presents with a wide range of clinical symptoms ranging from confusion to coma [42]. Routine use of continuous electroencephalography (EEG) monitoring has led to the identification of subclinical seizures in stroke patients [45]. Seizures were identified in 11 % of patients with ischemic stroke, 13 % of patients with intracerebral hemorrhage, and 19 % of patients with subarachnoid hemorrhage with the majority being nonconvulsive seizures (9 , 13 , and 18 %, respectively). A significant proportion of the patients were also diagnosed with nonconvulsive status epilepticus (7 , 9 , and 13 %, respectively). Nonconvulsive status epilepticus in subarachnoid hemorrhage has been particularly associated with poor outcome [46].

The risk of developing epilepsy following stroke is less well defined, likely related to the difficulties of the long-term follow-up. It is estimated that the risk of developing poststroke epilepsy is in the range of 2–5 % [47]. In a multivariate model [48], younger age, stroke severity at onset, lesion size, intracerebral hemorrhage, and early seizures were all associated with an increased risk of developing epilepsy. Cortical lesions [49] and lobar hemorrhage [50] increase the risk of developing epilepsy. Late-onset seizures in ischemic stroke have been reported to be a bigger risk

factor than early onset seizures for the development of epilepsy [51, 52]. Late-onset seizures in hemorrhagic stroke have also been reported to be a bigger risk factor than early onset seizures [53] although this was not the case in the Seizures After Stroke Study [35].

The effect of seizures on outcomes remains an open question. In a study of 5027 Canadian stroke patients [54], patients with seizures had higher mortality at 30 days and 1 year, longer hospitalization, and worse modified Rankin scores at discharge. Since seizures are associated with more severe strokes, outcomes in patients with seizures are likely to be worse just as a result of having more severe stroke. In the Greater Cincinnati/Northern Kentucky Stroke Study [40], early seizures were associated with an increased risk of mortality at 30 days. However, after correcting for age, stroke type, and stroke severity, early seizures were not a predictor of poor outcome. In the Seizures After Stroke Study [35], seizures were associated with increased mortality at 30 days and 1 year and worse Rankin scores, but only for patients with ischemic stroke. In contrast, in northern Manhattan, early seizures were not associated with increased mortality after accounting for stroke severity [39]. Similarly, in an Italian cohort, early seizures were not associated with worse outcome [55].

Epidemiology of Seizures and Epilepsy in Select Cerebrovascular Diseases

There are several specific neurological syndromes that are clinically dominated by stroke, but also have seizures as a frequent complication. This section is not all inclusive but evaluates several conditions in which strokes and seizures commonly intersect and for which epidemiological literature is available. While the latest literature has been sought on the epidemiology of stroke and seizures related to each condition discussed below, several (such as reversible cerebral vasoconstriction syndrome (RCVS) and amyloid beta-related angiitis (ABRA)) have recently evolved and continue to evolve with respect to their respective clinical phenotypes and underlying pathophysiology.

Primary Central Nervous System Vasculitis

Primary central nervous system (CNS) vasculitis (PCNSV) is a condition of inflammation of the small- and medium-sized blood vessels involving the brain and spinal cord without any identifiable secondary cause. PCNSV affects men more than women between the ages of 40 and 60 at the time of diagnosis [56, 57]. If not properly diagnosed and left untreated, it may be fatal in up to 95% of biopsy-confirmed patients [58]. It is an uncommon condition estimated to affect 2.4 people per one million person-years based on a single population-based study from the

Mayo Clinic Olmsted County population [59]. This incidence rate was based on 101 cases of PCNSV diagnosed by clinical criteria (less than one third of cases had biopsy confirmation). While PCNSV is primarily a disease of the cerebral vasculature, symptoms due to ischemic or hemorrhagic strokes are not the most common presenting symptoms of the disease. In the Mayo Clinic cohort of 101 patients described above, the most common presenting symptoms were headache (63 %) and altered cognition (50 %) followed by hemiparesis (44 %) [59]. Patients presented with seizures in 16 % of cases. During the disease course of PCNSV, strokes affect approximately 40 % of patients whereas seizures occur in less than 25 % of patients [59, 60]. EEG data are limited to two case series. In the Mayo Clinic case series of 101 patients, EEGs were abnormal 74 % of the time (28 of 38 EEGs) with dysrhythmias in 24 and epileptogenic findings in 4 [59]. In another older case series of 39 histologically confirmed cases with 28 EEGs performed, only two EEGs were normal, and the remainder except one showed generalized slowing, several of which had "superimposed focal findings" [60]. Numerous secondary causes of CNS vasculitis due to autoimmune illness, malignancy, or infection, are commonly associated with seizures at frequencies similar to that seen in PCNSV [61].

Reversible Cerebral Vasoconstriction Syndrome

RCVS is a syndrome previously called "benign" PCNSV or Call–Fleming syndrome. Recently, greater understanding of the condition and its associations led to its new name along with proposed clinical diagnostic criteria in 2007 [62]. There are no incidence or prevalence data for RCVS, although it appears to be significantly more common than PCNSV given there are three substantial case series published since 2007 totaling 283 patients collected from only four institutions [63]. The condition affects women more than men and affects slightly younger patients than PCNSV with a median age of 42 years. The diagnosis is made by clinical presentation which typically begins with a severe thunderclap headache, and a cerebral angiogram shows focal and segmental narrowing of the cerebral arteries in the anterior or posterior circulation or both. In three case series of 67, 139, and 77 patients, strokes occurred in the form of ischemic strokes, intracerebral hemorrhage, and subarachnoid hemorrhages, leading to abnormal computed tomography (CT) or magnetic resonance imaging (MRI) findings in 12–81 % of cases (these percentages also included abnormal imaging findings related to posterior reversible encephalopathy syndrome). Seizures in these three case series ranged from 1 to 17 % [64–66]. EEG findings have not been widely reported in the literature.

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is the most common cause of lobar intracerebral hemorrhage and a major cause of cognitive decline in the elderly. Only definite

CAA can be diagnosed via postmortem demonstration of intracerebral hemorrhage in association with severe deposition of beta-amyloid protein in the small cortical and leptomeningeal arteries [67]. Therefore, the incidence of CAA is not fully established. One Japanese autopsy study evaluated 400 brains (only 26 of which had intracerebral hemorrhage) finding that 18% of men and 28% of women had evidence of CAA that increased with age such that no one younger than age 50 had CAA rising to greater than 40% in those aged more than 90 years [68]. Utilizing prospectively collected MRI data, studies have determined recurrent hemorrhage rates in patients suspected of having CAA. In a series of 94 elderly patients with lobar hemorrhage, the total number of hemorrhages at baseline predicted the risk of recurrent hemorrhage such that a 3-year cumulative risk was 14% with one hemorrhage and more than 50% with six or more hemorrhages [69]. The clinical presentation of CAA-related hemorrhage is similar to intracerebral hemorrhage due to other etiologies. Symptoms include headache, focal neurological deficits, altered consciousness, and seizures which are in association with the size and location of the hemorrhage. In a recent study by Charidimou et al. [70], 14% of 172 CAA patients also presented with symptoms termed "transient focal neurological episodes" (TFNE), often described as "recurrent, stereotyped, spreading paresthesias, usually lasting several minutes." Half of their patients had positive "aura-like" symptoms such as paresthesias, limb-jerking, or visual symptoms such as flashing lights. The other half of their patients had predominately negative "transient ischemic attack (TIA)-like" symptoms including limb weakness or dysphasia. The majority (68%) of patients had two or more stereotyped episodes with 70% lasting less than 10 min. It is currently unclear whether these episodes represent seizure activity or may be an aura due to cortical spreading depression.

Amyloid Beta-Related Angiitis

ABRA and CAA-related inflammation (CAA-RI) are recently described syndromes which are diagnosed in patients who demonstrate clinical and histological features of both CAA and PCNSV [71]. The age of presentation falls between that for PCNSV and CAA occurring commonly in the 60s. Although the cohorts of ABRA and CAA-RI cases are small, seizures appear to be more common in ABRA and CAA-RI compared to CAA and PCNSV [71–73]. In a case series of 42 patients with biopsy-proven severe CAA, clinical presentation differed between patients with and without associated inflammation on biopsy [72]. Patients with inflammation were much more likely to present with cognitive decline (43 vs. 3%) as well as seizures (57 vs. 3%), while much less likely to present with intracerebral hemorrhage (0 vs. 94%). A recent study of patients collected at Mayo Clinic between the years of 1983 and 2011 separated patients into four groups: ABRA ($n=28$), CAA-RI ($n=10$), CAA ($n=40$), and PCNSV ($n=118$; all biopsy-confirmed except for the PCNSV group which were biopsy-confirmed in one third) [73]. Comparing these four groups, seizures were most common in patients with CAA-RI (90%) followed by ABRA (39%), followed by CAA (25%) and PCNSV (16%).

Vascular Malformations

Vascular malformations are associated with a number of neurologic symptoms including seizures and strokes. They are the most common cause of intracerebral hemorrhage in young adults [74]. Vascular malformations occur frequently and are increasingly recognized as imaging quality improves. Common vascular malformations include arteriovenous malformations (AVMs), cavernous malformations (CMs), and venous malformations (VMs). AVMs are congenital abnormalities consisting of multiple arteries and veins that are directly connected without a capillary bed. They most commonly present with hemorrhage, causing about 1% of strokes. The second most common presentation is seizures, occurring in about 25% of cases [75]. They can also be identified as incidental findings on MRI at a rate of 1 in 2000 patients [76]. In a prospective study of patients diagnosed with an unruptured AVM for reasons other than seizures, it was estimated that the rate of subsequently having a seizure is about 8% after 5 years. The rate of developing epilepsy following a seizure with an unruptured AVM was estimated to be 58% after 5 years. The risk of developing a seizure from an AVM after presenting with a hemorrhage or a focal neurological deficit was 23% in 5 years and 48% in patients who had a symptomatic seizure at presentation [77].

CMs are small "popcorn-like" abnormalities consisting of a tangle of sinusoidal vascular channels. The overall incidence is estimated to be in the range of 0.4–0.9% based on both autopsy and MRI series [74]. Incidental CMs are identified in MRI scans at a rate of 1 in 625 patients [76]. It has been suggested that CMs are more likely to cause seizures than other vascular malformations [78]. Mesial temporal CMs are particularly likely to cause seizures [79]. Two prospective studies have estimated the likelihood of having a seizure following diagnosis of a CM. In 35 patients without seizures at presentation, 4 subsequently had new-onset seizures (2.4% per patient-year) [80]. Josephson et al. [77] reported that 4% of patients with incidental CMs developed seizures in 5 years and 6% of patients who presented with hemorrhage or a focal neurological deficit developed new-onset seizures in 5 years. The 5-year risk of developing epilepsy following a seizure was 94%.

VMs, also called developmental venous anomalies or venous angiomas, are thin-walled venous channels in normal brain tissue, often associated with a large draining vein. They are very commonly identified at autopsy at rates above 2% [81]. In a prospective study of VMs, 11 of 80 patients presented with seizures. Of those, ten became seizure free with medical management. It was not reported whether or not any patients subsequently developed seizures [82]. In a systematic review of 15 studies meeting inclusion criteria, 4% of patients found to have VMs presented with seizures. Again, no data on subsequent development of seizures were provided [83].

Cervico-Vascular Dissection

Dissection of the carotid or vertebral arteries in the neck is a relatively uncommon cause of stroke. The overall incidence of dissection has been reported at 2.6 per

100,000 although this likely represents an underestimate as asymptomatic cases may be missed [84]. However, it is an important cause of stroke in the young where dissection represents the cause of up to 20% of strokes [85]. Carotid dissection is much more common than vertebral dissection [84]. Diagnosis can be difficult as the classic triad of pain, Horner's syndrome, and cerebral ischemia occur in less than 50% of cases [86]. There is relatively limited data about seizures in dissection. In 33 consecutive patients with carotid dissection, 6 patients developed seizures [87], suggesting an increased risk of seizures compared to all strokes. More recently, De Reuck and Van Maele [88] compared 40 patients with strokes due to dissection to 159 patients with strokes due to atherosclerosis of the neck vessels. Of the patients with dissection, 80% had carotid dissection. A total of 3 patients with dissection (7.5%) developed seizures compared to 29 (18.2%) patients with atherosclerosis. Clearly additional studies will be required to clarify the relative risk of seizures in the setting of dissection.

Cerebral Venous Sinus Thrombosis

Cerebral venous or dural sinus thrombosis is a rare cause of stroke with a rate of up to five cases per one million per year and accounting for about 0.5–1% of strokes. It most commonly occurs in patients under 50 years of age [89]. It can be associated with anything that results in a prothrombotic state including pregnancy and oral contraceptive use, resulting in higher rates in females compared to males. Presenting symptoms are diverse and can vary from headache to coma [90]. Seizures are a common symptom of cerebral venous sinus thrombosis. In the International Study on Cerebral Vein and Dural Sinus Thrombosis, 39.3% of patients had seizures including 19.6% of patients with focal seizures and 30% of patients with generalized seizures [91]. In a more recent multicenter cohort, 32% of patients had seizures including 7% of patients with focal seizures and 29% of patients with generalized seizures [92]. Thus, seizures are much more common with cerebral venous sinus thrombosis than in arterial stroke, and the presence of seizures should prompt consideration of the diagnosis of venous sinus thrombosis [89].

Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a mitochondrial disorder originally described in 1984 [93]. It typically manifests with a variety of symptoms including strokes and seizures at a relatively young age. It is caused by any of the several single point mutations of the mitochondrial DNA, resulting in a maternal pattern of inheritance. The most common associated mutation occurs in the general population at a rate of 12–60 per 100,000. Diagnosis is typically made by a combination of MRI, muscle biopsy, and genetic testing [94].

In an early review of reported cases, 96% of patients had seizures [95]. In a recent prospective Japanese cohort, the prevalence was estimated at 0.18 per 100,000 in the general population. Stroke-like episodes, seizures, and headaches were the most common symptoms with 56% having seizures at the initial presentation, and 71% had seizures at some time during the follow-up [96].

Summary

Stroke and epilepsy are two of the most common neurologic diseases. As the population ages, stroke becomes an increasingly important cause of seizures. New-onset seizures now most commonly occur in senior adults, and stroke is the most commonly identified cause of new-onset seizures in this population. While seizures occur in a minority of patients with stroke, there are a number of cerebrovascular diseases where seizures are a much more prominent feature. The intersection of seizures and stroke remains an active area of ongoing clinical investigation.

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Chapter 2
Seizures in Ischemic Stroke

Benny S. Kim and Cathy Sila

Introduction

Stroke is the most common cause of new-onset seizures in older adults. Cerebrovascular disease accounts for 11 % of adult epilepsy, and, in older adults, stroke is the underlying cause in over a third of all cases [1]. Seizures secondary to ischemic stroke are generally categorized into early seizures (occurring up to 2–4 weeks after a stroke) and late seizures (occurring after 4 weeks). Risk factors for developing poststroke seizures generally include cortical involvement, anterior hemisphere location, early seizures, and possibly cardioembolic etiology [2]. Early seizures may be associated with increased mortality, while late or recurrent seizures may hinder long-term neurologic outcome [3]. There is a paucity of evidence for the prophylactic use of antiepileptic drugs (AEDs) in ischemic stroke without seizures. The decision to start patients on a long-term AED after their first poststroke seizure is debatable; consideration of the probability of seizure recurrence and the negative influence of some AEDs on neurological recovery must be taken into account.

Epidemiology

Cerebrovascular disease is the most commonly identified antecedent for adult epilepsy, accounting for 11 % of cases [1]. Stroke becomes an increasingly common cause of seizures when examining older populations. A population-based study in Sweden found that in patients over 60 years of age, 45 % of seizures were secondary

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_2

to stroke, followed by tumors (11%), and Alzheimer's disease (7%) [4]. Stroke is associated with a 23–35-fold increase in the incidence of seizure, and a 17-fold higher risk for the development of epilepsy [2, 5]. Stroke may also be a significant source of seizures in younger adults. A prospective cohort of 697 patients 18–50 years old who suffered a cerebrovascular event was found to have a cumulative risk of poststroke epilepsy with recurrent seizures of 8% after a mean follow-up of 10 years [6].

The timing of early seizures after stroke has been examined in a number of large studies. The Oxfordshire study found in their 545 ischemic stroke patients, 2% had suffered a seizure at the onset of stroke [5]. Labovitzet et al. found that when acute stroke patients suffered early seizures, they occurred at stroke onset in 40.5% of cases [7]. The Copenhagen stroke study reported that 86% of early seizures occurred within 3 days after a stroke, with 66% occurring within the first 24 h. Seizure subtypes included focal seizures with or without secondary generalization in 68%, and generalized tonic–clonic seizures with no clear antecedent focal seizure manifestations in 22% [8]. The frequency of early seizures occurring within a 2-week window after stroke ranges from 4.8 to 6.5% [3]. This incidence may be higher due to variability in the definition and detection methods and study setting [9].

The functional impact, underlying mechanism, and epilepsy risk of late seizures may be different than early seizures. Approximately, 3–5% of stroke survivors experience a late seizure within a year of their first episode, with 54–66% of these patients going on to develop epilepsy [3]. At 5-year follow-up, the frequency of seizure after stroke was 9.7% [10]. The risk of developing epilepsy at 5 years after a first stroke is 3.8%, and increases to 9.6% when patients suffer recurrent strokes [2]. Stroke has also been demonstrated to be a risk factor for status epilepticus in 22–32% of cases [9]. The overall poststroke incidence of status epilepticus is relatively low in large series; a single-institution study reported status epilepticus in 1.1% of a cohort of 904 acute stroke patients [7].

Risk Factors

Traditionally, certain stroke subtypes, such as embolic stroke, have been thought to be associated with an increased risk of new-onset seizures. However, seizures occur with most stroke subtypes. An increased risk of seizures after embolic strokes of cardiac origin has been shown in some studies, but not others [2, 11, 12]. The Seizure After Stroke Study (SASS), a large, prospective, multicenter study found that patients with presumed cardioembolic stroke were not at an increased risk for new-onset or recurrent seizures [13]. Interestingly, seizures have been associated with lacunar strokes in up to 3.5% of cases [14]. These seizures may develop from the release of glutamate from axonal terminals arising from injured thalamocortical neurons [12]. Consistent with this theory are studies demonstrating lateralized electroencephalography (EEG) abnormalities in 22–38% of patients with lacunar infarctions [15].

In the differential diagnosis of seizures are seizure-like involuntary movements that occur with specific stroke subtypes. Convulsive movements have been described in patients with brain-stem strokes; it has been postulated that these movements are related to ischemia of the corticospinal tract rather than a true seizure [16]. Various nonseizure transient hypokinetic and hyperkinetic movements have been infrequently described in patients with acute strokes, the most common of which are hemichorea and hemiballismus in the setting of lesions involving the basal ganglia or its pathways and the frontal lobe. Some of these movements may be delayed for months or years [17]. Kim et al. described nine patients with anterior cerebral artery strokes presenting with hemi-parkinsonism or asterixis. Symptom onset ranged from simultaneous with stroke onset to 1 month, and all patients improved [18].

Transient ischemic attacks (TIAs) have been associated with seizures in 1.8–3.7%. However, the true frequency is uncertain due to the diagnostic limitations of distinguishing some TIAs with focal seizures versus limb-shaking TIA. The latter are a particular type of seizure-like movement thought to be secondary to focal cerebral hypoperfusion due to severe stenotic or occlusive contralateral carotid disease [15]. Fischer in 1962 first described these movements as brief, arrhythmic, flailing, or jerking movements of an extremity that may be confused for a focal motor seizure or a movement disorder [19]. Clues which may help distinguishing limb-shaking TIAs from other diseases are lack of a Jacksonian march, nonepileptiform EEG, ineffectiveness of AEDs, precipitation of symptoms with maneuvers that cause cerebral hypoperfusion, and cessation of symptoms when improving cerebral perfusion. Maneuvers such as rising from a chair, hyperventilation, and hyperextension of the neck may provoke shaking movements, whereas laying supine may eliminate symptoms [20, 21].

Studies examining cerebral perfusion using positron emission tomography or transcranial Doppler have demonstrated hemodynamic failure in the contralateral hemisphere on the symptomatic side [22]. Reduced cerebral blood flow to critical watershed areas in patients who suffer limb-shaking TIAs are at a high risk for stroke [23]. In 147 patients with symptomatic internal carotid artery (ICA) occlusions, 28.6% were found to have contralateral limb-shaking symptoms. Multivariate analysis found the presence of limb shaking to be a significant independent predictor of adverse short-term and long-term outcomes when compared to patients with ICA occlusions without limb-shaking symptoms, in addition to severe National Institutes of Health Stroke Scale/Score (NIHSS) and the presence of diabetes. Symptomatic patients had a nonsignificant tendency toward increased recurrent strokes and TIAs [24]. Management may entail careful optimization of blood pressure and possible revascularization procedures to improve cerebral blood flow [20, 24].

Strokes involving the cortex have been characterized as having a high incidence of early seizures [25]. Strokes involving the anterior and posterior hemisphere, as well as the temporoparietal lobe have all been associated with increased risk of seizures, with early seizures associated with stroke in the anterior hemisphere. Cortically located strokes are twice as likely to cause seizure than subcortical strokes. Large infarcts involving the supramarginal or superior temporal gyrus have a

fivefold increased risk of developing late seizures [2, 3, 12]. Denier et al. found that a watershed mechanism of stroke was associated with a fourfold increase in early seizures compared to other cortical infarcts in 328 consecutive patients with magnetic resonance imaging (MRI)-confirmed cerebral infarctions [26]. The relationship between stroke severity and seizures has been variable. The Copenhagen stroke study found that only initial stroke severity predicted the occurrence of early seizures when using multivariate analysis [8]. Stroke disability and cortical location were found to be risk factors for developing poststroke seizures in SASS and in prospective studies specifically examining affected younger adults [6, 7, 13]. So et al. found that early seizures and recurrent strokes were the only factors predictive of developing late seizures or epilepsy. Patients who suffered an early seizure were eight times more likely to develop a late seizure and 16 more times likely to develop epilepsy. Stroke recurrence tripled the risk of suffering a late seizure or developing epilepsy [2]. Other studies found that late-onset seizures were independent risk factors for developing epilepsy after stroke [6, 13]. Hemorrhagic transformation of an ischemic stroke seems to increase the risk of seizures. An Italian study of 714 stroke patients found the incidence of seizure to be 4.2% in patients with bland infarcts, 12.5% in patients with hemorrhagic transformation, and 16.2% in patients with primary intracerebral hemorrhage (ICH) [27].

Of special note is ICH occurring secondary to cerebral hyperperfusion after surgical or endovascular treatment of a critical carotid artery stenosis. Cerebral hyperperfusion syndrome is characterized by a headache ipsilateral to the treated artery, with or without nausea, vomiting, neurological deficit, post-procedural hypertension, and seizures. Chronic low blood flow from a significant carotid stenosis may cause blood vessels distally to lose their ability to autoregulate vascular resistance. Excessive blood flow directed to an impaired vascular bed may disrupt vessels and cause hemorrhage, which may be associated with seizures. Cerebral hyperperfusion syndrome peaks between 3 and 5 days postoperatively, carrying a high morbidity when ICH develops. Transcranial Doppler may be able to predict patients who are at a higher risk for this syndrome by demonstrating increased mean flow velocity and diminished pulsatility index. In a study of 450 consecutive cases of carotid artery stenting, 0.67% had cerebral hyperperfusion syndrome with ICH. Vigilant perioperative control of systemic blood pressure may prevent this syndrome [28, 29].

Pathophysiology

The mechanism of early poststroke seizure may differ from that of late seizures. Early seizures may be secondary to biochemical dysfunction, whereas late seizures may be due to epileptogenic gliotic scarring [25]. Acute ischemia is marked by glutamate-induced excitotoxicity causing an overload of intracellular calcium and sodium, which activate variety of cellular enzymes and depolarization of the transmembrane potential, ultimately leading to neuronal loss. Glutamate has also been found to induce epileptiform type of discharges in surviving neurons [30]. Seizure activity in the acute setting of cerebral ischemia may have a deleterious effect of increasing metabolic demand in tenuous hypoxic tissue. Potentially salvageable

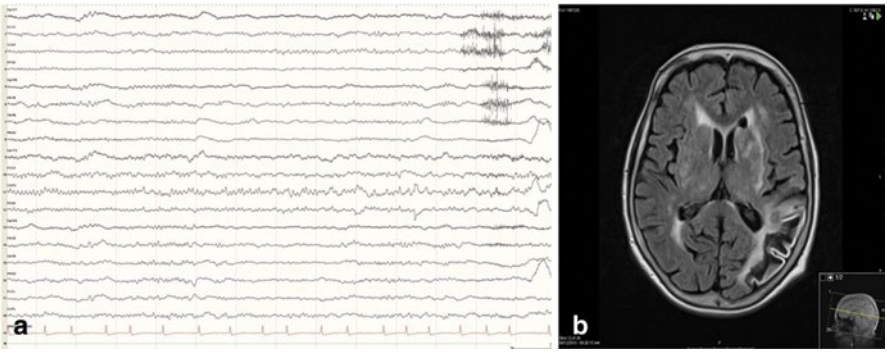

Fig. 2.1 A patient with late poststroke seizures; EEG (**a**) shows seizure pattern in left frontocentral region, onset at C3–F3 > f7–Fp1. Onset consisted of rhythmic alpha activity at F3–C3, then involved Fp1–F7, to evolve into rhythmic theta, then sharply contoured delta; seizure lasted 30–60 s. This patient suffered 18 seizures over 9 h. MRI (**b**) shows a focal encephalomalacia in the left posterior temporal and parietal lobes compatible with remote ischemic infarction

brain may be further recruited into the infarct core, leading to increased infarct size [31]. Experimental models have demonstrated transient peri-infarct depolarization in the penumbra of middle cerebral artery occlusions, and correlated the duration of depolarization with infarct volume [15]. The early phase of stroke is also accompanied by noncerebral factors such as systemic electrolyte imbalances, acid-base disturbances, and potential infections such as pneumonia which can reduce the seizure threshold [12]. Late seizures may be secondary to gliosis and development of meningocerebral scarring. Changes in membrane properties, deafferentation, selective neuronal loss, and collateral sprouting may result in hyperexcitability and neuronal synchrony sufficient to elicit seizures (Fig. 2.1a–b) [15].

Imaging

Five to thirty percent of cases identified as brain attacks may be due to stroke-mimicking conditions [23]. Winkler et al. found that of 250 consecutive patients treated with intravenous thrombolysis, 2.8 % were stroke mimics; none of whom were harmed by thrombolysis. Seizure was the most frequent diagnosis in these patients (85.7 %), with global aphasia without hemiparesis presenting ten times more frequently in the mimic than in the stroke group [33]. The clinical significance of advanced neuroimaging studies and EEG to distinguish stroke mimics from strokes before intravenous thrombolysis is unclear [33]. Furthermore, seizures may produce radiological changes that may make it difficult for a clinician to distinguish a seizure at the onset of an ischemic stroke from a seizure with postictal paresis, known as Todd's paresis. Seizure activity may lead to metabolic exhaustion of neurons within the epileptogenic focus, producing clinical paralysis. Increased regional permeability in the blood–brain barrier and edema at this site may subsequently be visualized by neuroimaging. An MRI of the brain may demonstrate focal cortical swelling, signal change in fluid-attenuated inversion recovery sequences, and

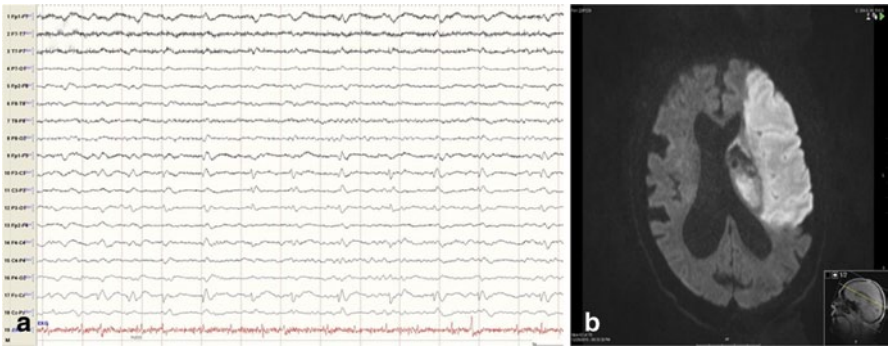

Fig. 2.2 **a–b** Periodic lateralizing epileptiform discharges (PLEDs) in a patient with acute ischemic stroke. EEG (**a**) shows intermittent PLEDs in the left parietal-central region, maximum P3 > C3, approximately 20 % of the record, lasting 3–10 s in a patient with acute ischemic stroke of the left hemisphere. MRI (**b**) shows a diffusion restriction in the left hemisphere in the distribution of the middle cerebral artery with mass effect and midline shift in an 83-year-old man who suffered acute-onset aphasia and right hemiplegia

cortical blush when contrast is administered [34]. Seizure duration may correlate with the intensity and size of these changes. Angiography after seizure may demonstrate a focal area of enhanced blood flow secondary to disruption of the blood–brain barrier [35]. Cerebral perfusion imaging may also demonstrate large areas of ictal hyperperfusion or postictal hypoperfusion. When this is observed without corresponding arterial pathology, it may be more indicative of a seizure than acute stroke (Fig. 2.2) [36, 37]. Computed tomography (CT) perfusion brain imaging has recently gained popularity as a method for evaluating penumbral tissue. Masterson et al. reported the CT perfusion changes in four patients presenting with stroke symptoms who were subsequently diagnosed with status epilepticus. Focal cortical hyperperfusion was demonstrated in all patients, with approximately 50 % increase in cerebral blood flow, 30–40 % increase in cerebral blood volume, and 40 % decrease in mean transit time. These findings were attributed to the peri-ictal phases of status epilepticus and are the opposite of perfusion changes found in acute stroke. The authors cautioned that migraines or strokes with reperfusion can produce similar results [32]. Table 2.1 demonstrates the common CT perfusion changes in ischemic infarction, penumbral tissue, and seizures.

Table 2.1 Cerebral CT perfusion changes in acute ischemic stroke and seizure

Perfusion changes	Penumbral tissue	Core infarct	Seizure
Cerebral blood flow (CBF)	↓	↓	↑
Cerebral blood volume (CBV)	Normal or ↑[a]	↓	↑
Mean transit time (MTT)	↑	↑	↓
Time to peak (TTP)	↑	↑	↓

[a] In the presence of penumbral tissue, perfusion map may show no changes in the cerebral blood volume; an important distinguishing feature for patients requiring immediate stroke intervention.
↓ indicate decrease; ↑ indicate increase

Electroclinical Manifestations of Acute Stroke

Acute ischemic stroke may have a number of EEG patterns, of which periodic lateralized epileptiform discharges (PLEDs) are of particular significance. PLEDs are electrographic phenomena characterized by widely distributed, polymorphic, and repetitive complexes of approximately 0.5–3 Hz, having one or more sharp components, present over one or more hemispheres (Fig. 2.3a) [38]. PLEDs may be an expression of dynamic brain damage in the very acute stage. While PLEDs are commonly associated with large cortical destructive processes, they may be seen in patients with subcortical, chronic lesions, or metabolic disturbances [32, 39]. Mecarelli et al. analyzed the EEGs performed within 24 h of a cohort of 232 patients admitted with acute ischemic or intraparenchymal hemorrhagic stroke. Focal

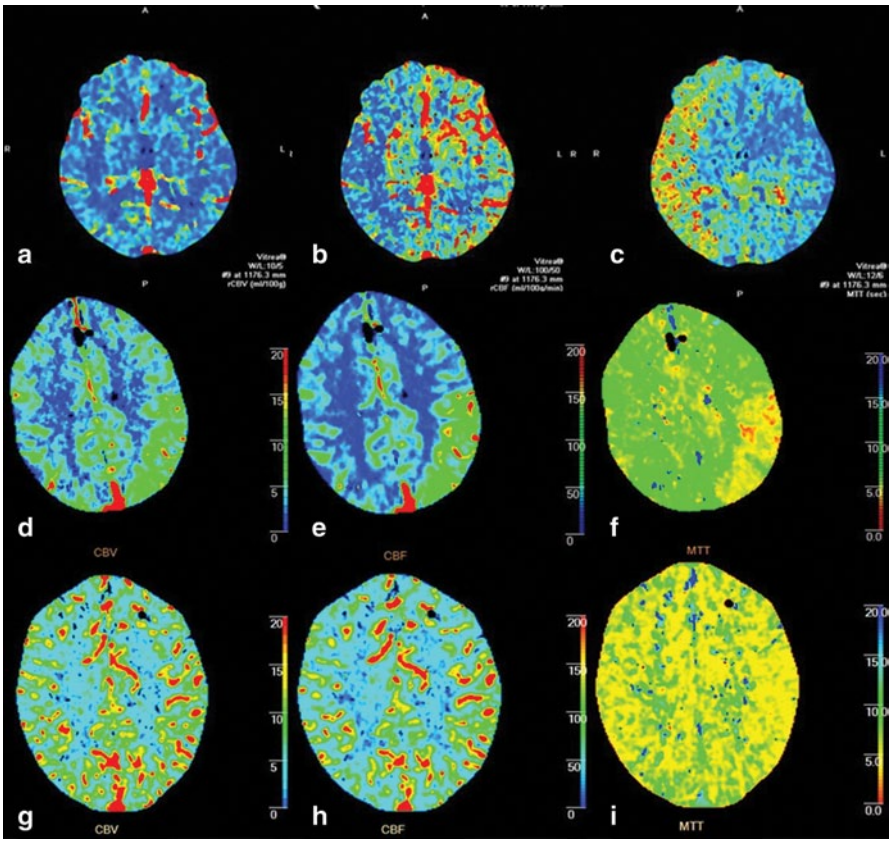

Fig. 2.3 CT perfusion analysis showing the cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) of a patient with ischemic penumbra in the right hemisphere due to a hyperacute occlusion of the right middle cerebral artery (**a** CBV, **b** CBF, and **c** MTT), and a second patient with a seizure emanating from the left hemisphere (**d** CBV, **e** CBF, and **f** MTT) followed by a complete resolution of the hyperperfusion (**g** CBV, **h** CBF, and **i** MTT)

or diffuse slowing of background was found in 84% of patients, epileptiform focal abnormalities in 10%, and PLEDs in 6%. Three out of the 23 patients with epileptiform abnormalities developed isolated partial motor seizures without secondary generalization, while none of the patients with slowing had seizures. Of the 14 patients with PLEDs, 10 had focal status epilepticus (9 convulsive, 1 nonconvulsive), and 2 had focal motor seizures. Multivariate analysis demonstrated that only early epileptic manifestations were independently associated with PLEDs [39].Various theories regarding the neurophysiology of PLEDs have been suggested. Some authors have proposed that cortical PLEDs are produced from a large external zone of hyperexcitability, which generates synchronous discharges that communicate with subcortical structures, where they are modulated and returned via corticopetal connections. In addition, subcortical lesions disrupt the basal ganglia–thalamus–cortex network, causing oscillations to be propagated through the thalamocortical projections and eventually widespread areas of cortex [38]. An EEG maybe normal in 5% of cases, and therefore, a normal EEG does not exclude epileptogenic lesions [40]. Acute ischemia may produce EEG changes within minutes of onset, providing real-time and dynamic information of the neurophysiologic state. Progressive reductions in cerebral blood flow and degree of neuronal injury lead to changes in EEG characteristics, from loss of fast beta frequencies in reversible mild ischemia, to suppression of all frequencies, or isoelectric EEG activity in neuronal death [41].

Treatment

Treatment and recurrence of seizures of varying etiology other than stroke have been studied in depth. Berg and Shinnar used a meta-analysis to study the issue of recurrence after a first unprovoked seizure. Among 16 reports, the average risk of a first unprovoked seizure was 51%. At 2 years following the first seizure, the risk of recurrence was 36% in prospective studies and 47% in retrospective studies. Recurrence risk varied depending on a number of factors, such as seizure etiology, seizure type, and electrographic findings. The recurrence risk was as low as 24% and as high as 65% [42].

The development of poststroke epilepsy occurs in 54–66% of those who experience late seizures, and less than 43% in early-seizure patients. The risk of developing a second seizure is similar to the nonstroke patient who experiences a first unprovoked seizure. In these non-stroke patients, initiating AED treatment only after a recurrent seizure does not appear to be harmful [43]. Furthermore, indiscriminate treatment of a first unprovoked seizure without regard to patient's EEG characteristics, the presence of structural lesion, or risk–benefit profile is not recommended [27, 44]. Similarly, the use of prophylactic AEDs in acute traumatic brain injury without an initial seizure is not recommended because it has been found to be ineffective in reducing mortality, functional outcome, and eventual development of epilepsy, even if it potentially reduces the likelihood of early seizures [3].

However, strokes produce a structural lesion and some authors have favored initiating AEDs after an early poststroke seizure, while others have recommended treatment only after a late seizure [1]. Labovitz and Hauser et al. suggested that the risk of epilepsy in some patients with a single-poststroke seizure is high enough to justify the initiation of AEDs before the second seizure [40, 45]. Others have suggested treating an early seizure for 1 month, then stopping the AED if seizures have not recurred during this period [40]. One approach is to initiate one AED at standard dosage if a patient has developed immediate poststroke seizure. Therapy would be continued for 1–3 months during the time of highest risk for recurrence and discontinued if no further seizures had occurred. A more conservative approach is to attempt discontinuation of AEDs only after 1 year of seizure freedom; an approach facilitated in part by the emergence of newer-generation AEDs that have more tolerable adverse effect profiles and little to no drug–drug interactions. Recurrent seizures while on AED therapy may be milder in severity and type (focal instead of secondarily generalized). Because late seizures carry higher risk of recurrence, AED therapy is recommended.

No single AED has been shown in studies to be clearly and consistently superior to another in the treatment of early seizures or epilepsy after stroke [36]. Therefore, when choosing among the different AEDs, the clinician must take into account the potential side effects of the drug, its pharmacokinetic profile, interaction with other medications, and the potential influence on the neurologic recovery process. Phenytoin, phenobarbital, and carbamazepine are hepatic enzyme inducers, while valproic acid is an enzyme inhibitor. Phenytoin and valproic acid are highly protein bound, and the former also interferes with vitamin K metabolism. These properties of older-generation AEDs may lead to difficulties in maintaining a therapeutic drug range when a patient is concurrently on warfarin. Salicylates may displace valproate from its plasma protein binding sites, leading to reduction in total plasma level. Newer-generation AEDs do not demonstrate significant interactions with warfarin or antiplatelet agents [3]. For example, levetiracetam and lamotrigine lack hepatic metabolism and have a favorable pharmacokinetic profile in terms of drug interaction, compared to older AED [35, 46]. Animal models and clinical studies suggested that older AEDs may impair the recovery after stroke. Phenytoin, phenobarbital, and benzodiazepines have been shown to impair the motor and behavioral recovery process in brain-injured rats and functional recovery in patients [15]. In contrast, vigabatrin and carbamazepine have not demonstrated negative effects on poststroke outcome [47].

Tolerability of the drug remains an important issue to consider when initiating AEDs. Studies comparing various AEDs have suggested better tolerability and retention rates for lamotrigine, gabapentin, or levetiracetam when compared with carbamazepine, a medication known to be effective in poststroke seizure [3, 46]. The long-term tolerability and efficacy of gabapentin was studied in patients who had their first seizure at least 2 weeks after stroke: 81.7% of the cohort remained seizure-free at a mean follow-up of 30 months. Side effects were reported in 38%, but were mild to moderate with only 2.8% withdrawing from the study as a result. The authors concluded that gabapentin was safe and useful for poststroke seizures [48]. Other authors randomized 106 patients with late poststroke seizures to

levetiracetam or sustained-release carbamazepine [35]. No statistically significant difference in the number of seizure-free patients was found between the two groups. At the 52-week follow-up, 94% of levetiracetam and 85% of carbamazepine were seizure free. Attention deficit, frontal executive function, and functional scales were significantly worse in the carbamazepine group. Premature discontinuation due to serious adverse effects was not statistically significant between the groups [35]. In a smaller study, 64 patients presenting with the first (early or late) poststroke seizure received lamotrigine or carbamazepine in a randomized 1:1 ratio. After 12-month follow-up, significant differences between the two groups were found in terms of efficacy, side effects, and tolerability in favor of the lamotrigine. The number of patients remaining seizure free was found to be 72% in the lamotrigine group and 44% in the carbamazepine group. Three percent of patients in the lamotrigine group dropped out because of adverse events, compared to 31% in the carbamazepine group [46].

Prognosis

Animal stroke models suggest that early seizures may be associated with increased infarct volume; however, it is unclear if early seizures have deleterious effects on the eventual functional outcome after stroke. A significant number of studies found worse outcomes in patients with late or recurrent seizures after stroke, but others failed to demonstrate this effect. The differences in these outcomes may be due to the lack of accounting for confounding factors such as stroke severity, stroke location, or AED treatment at the time of assessment, which has been shown to independently contribute to worse functional outcome with certain drugs [3, 15]. Previous studies have demonstrated increased hospital mortality rates among patients with early seizures after stroke. These studies did not account for stroke severity or rule out seizures as an independent predictor of poor outcome. It has been proposed that seizures maybe a sign of severe brain injury rather than a predictor of poor recovery [11, 49]. It is unclear if seizures independently alter functional outcome after stroke. SASS demonstrated a worse neurological score during initial hospitalization and worse Rankin scale at 9 months of follow-up in patient who had seizures after stroke; however, SASS failed to correct for stroke severity and did not analyze the role of early versus late seizures [3, 50]. Seizures do not influence the rehabilitation outcome in poststroke patients [10, 50]. Prospective studies which did account for stroke severity found no association between early seizures and outcome or mortality [7].

Status epilepticus rarely occurs in patients with acute stroke, and constitutes less than 10% of cases of poststroke seizures [9]. The clinical relevance of poststroke status epilepticus has also been inconsistent. Patients with generalized convulsive status epilepticus after a stroke have a threefold increase in mortality rate compared to stroke patients without status epilepticus [51]. This increase in mortality is seen only if the status epilepticus occurred within the first week after the stroke [9]. A

multivariate analysis found no relationship between the occurrence of status epilepticus and stroke subtype (infarction vs. hemorrhage), stroke risk factors, stroke topography, cortical involvement, lesion size, or EEG findings [9]. In addition, no difference in mortality rate was found between poststroke patients who had status and those who had seizures. The only predictor of status epilepticus was poor functional status (modified Rankin scale > 3), and the only predictor of mortality was age [52]. Status epilepticus at presentation of stroke has not been shown to predict subsequent development of epilepsy [40].

Summary

Stroke is an important cause of seizures especially in older adults. The incidence of poststroke seizure varies based on the setting and detection method. When patients suffer these seizures, they often occur at stroke onset or very soon after; however, they continue to be at risk for seizures many years later. The mechanism of early seizures may differ from late seizures. In treating these seizures, clinicians should consider the potential negative effects of some AEDs on functional outcome and the interaction with other medications especially the antithrombotic and anticoagulants.

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Chapter 3
Seizures in Intracerebral Hemorrhage

Salvador Cruz-Flores and Amer Alshekhlee

Introduction

Seizures are a complication of intracerebral hemorrhage (ICH) and they may be the presenting symptom. Although seizures occur usually at the onset of ICH, they can present late in the acute course and sometimes weeks or months after onset. Data on the incidence of seizures and risk of epilepsy in the setting of an ICH have some limitations as it derives from studies with different study designs, usually single center, often with different definitions of immediate, early, and late seizures, time of follow-up, and population studied [1].

Little information exists with regard to the role and indications of antiepileptic drugs (AEDs) to decrease the risk of recurrent seizures and epilepsy, and there are some concerns about the impact of AEDs on the outcome of patients with ICH [1]. This chapter reviews the epidemiology of seizures in the setting of intracerebral hemorrhage, their natural history and the risk of epilepsy, and the management given the current evidence.

Epidemiology

The frequency of seizures in patients with ICH varies in the different studies depending on the study design, the definition of seizures, and the time frame chosen in relation to the onset of the ICH (Table 3.1). Immediate seizures are reported in

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_3

Table 3.1 Risk of early and late seizures associated with intracerebral hemorrhage

Author	Sample size	<7 days **(%)**	<14 days **(%)**	>7 days **(%)**	>14 days **(%)**
Alberti [16]	95	5.2	–	–	–
Arntz [6]	66	6	–	10.6	–
Bladin [7]	265	–	7.9	–	2.6
De Herdt [26]	522	14	–	–	–
Garrett [20]	110	–	41.8	–	–
Giroud [34]	129	–	16.2	–	–
Haapaniemi [8]	993	11	–	9.2	–
Labovitz [22]	143	7.6	–	–	–
Madzar [23]	203	8.8	–	10.8	–
Rossi [35]	325	–	–	9.5	–
Sung [9]	1402	–	4.6	–	–
Woo [31]	263	3.4	–	4.9	–
Yang [5]	243	–	1.6	–	4.5

2% of patients when the 24-h time frame is used compared to 8.5% at 48 h, and 28% at 72 h [2–5]. Early seizures defined as seizures within 7 and 14 days have a frequency of 3.4–14 to 4.6–41%, respectively. In contrast, the frequency of late seizures is 4.9–10.8% when defined as >7 days as compared to only 2.6% when defined as >14 days. The risk of poststroke epilepsy also varies depending on the follow-up time from 2.5–11.8% at 2 years to 31% at 9 years [6–9]. Pathologically, early seizures seem to stem from the structural and biochemical disruption caused by the hemorrhage and its mass effect. In contrast, late seizures are likely related to inflammatory process and later gliosis within the lesion [7, 10].

The true incidence of seizures might be underestimated considering the fact that there are patients with subclinical or nonconvulsive seizures. In fact, the frequency of subclinical seizures can be as high as 31%. In a study of 109 stroke patients in the neurocritical care unit who had continuous electroencephalography (cEEG) monitoring within 72 h from admission, 63 of them with ICH, nonconvulsive seizures were detected in 28%, a frequency four times higher than the clinical seizures in that series. In another study of 102 patients with ICH who underwent cEEG monitoring, 31% had seizures and half were electrographic seizures; 94% of the seizures occurred within the first 72 h of onset of hemorrhage. Subclinical seizures occurred in relation to expanding hemorrhages, particularly if they involved the cerebral cortex [10]. Status epilepticus (SE) has been found in 0.3% of patients with ICH and in as many as 19–21.4% of patients with ICH who develop seizures; SE usually portends poor outcome [11–13].

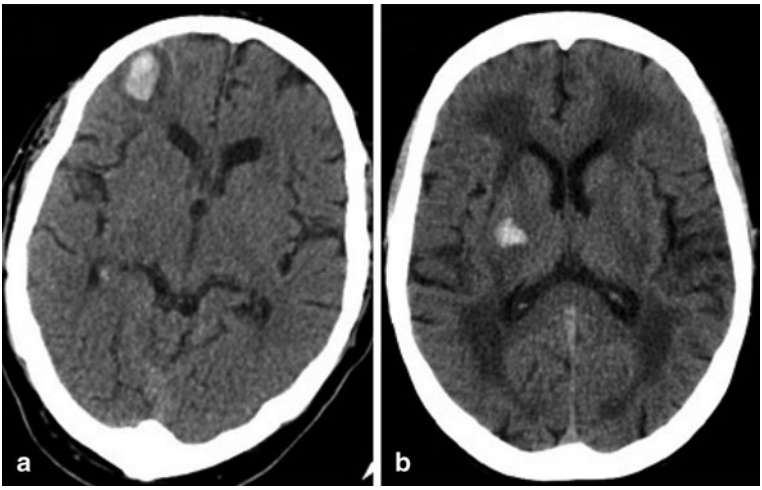

Fig. 3.1 Computerized tomography scan with spontaneous small intracerebral hemorrhage; (**a**) superficial cortical hemorrhage with minimal surrounding edema in a 46-year-old man presented with recurrent seizures and (**b**) deep putamen/capsular hemorrhage in an 80-year-old man presented with pure motor hemiparesis

Neuroimaging

Neuroimaging studies are needed to make the diagnosis and elucidate the etiology of ICH. Computed tomography (CT) is considered the gold standard (Fig. 3.1); though, magnetic resonance imaging (MRI) is more useful in elucidating the etiology of ICH (Fig. 3.2). Blood on CT appears hyperdense or isodense in patients with severe anemia, whereas blood cell degradation with time leads to altered MRI sequences. Small cerebellar hemorrhages in the posterior fossa can be missed on cranial CT unless thin cuts of the posterior fossa are obtained. CT and MRI equally perform in identifying ICH. CT may be superior in demonstrating associated subarachnoid hemorrhage, whereas MRI is certainly better in identifying an underlying structural pathology such as in those with hemorrhagic transformation of a mass lesion of arteriovenous malformation. Gradient-echo T2-weighted MRI is very helpful in demonstrating silent deposition of blood products that can be a risk factor for spontaneous ICH (Fig. 3.3). The risk of seizure varies considerably according to the size, location, and underlying etiology of the hemorrhage as well as the clinical characteristics that are discussed in detail.

Natural History

It is important to understand the natural history of seizures in the setting of ICH, as it helps deciding the type of diagnostic and therapeutic approaches. Seizures tend to present early in the course with 50–70% occurring within 24 h from onset and

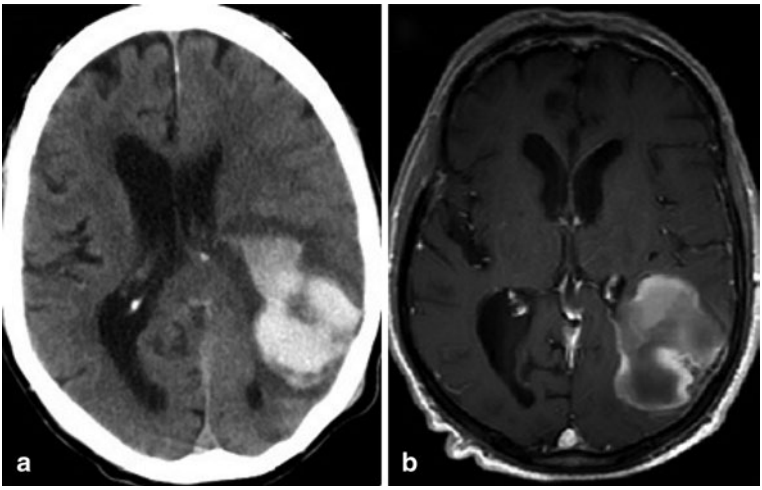

Fig. 3.2 Left parietal hemorrhage presented with status epilepticus; (**a**) *axial* head CT obtained immediately after admission; (**b**) follow-up gadolinium-enhanced T1-weighted images showed an underlying enhancing neoplasm

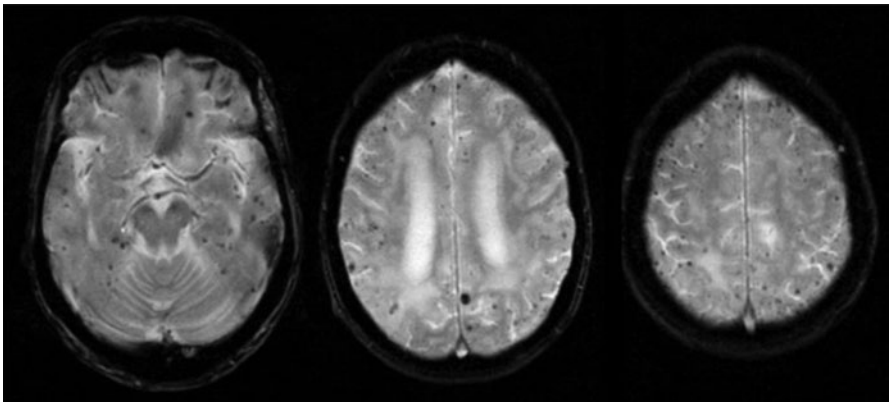

Fig. 3.3 Gradient-echo T2-weighted MRI in a 54-year-old woman with chronic severe hypertension showing silent cerebral microbleeds. Silent cerebral microbleeds are seen in 33–80 % of patients with primary intracerebral hemorrhages, in 21–26 % of patients with ischemic strokes, and in 5–6 % of asymptomatic or healthy elderly individuals. (Obtained from Neuroimaging in Neurology by Preston and Shapiro et al., with permission)

90 % by the 3rd day [4, 7, 10, 14, 15]. Earlier in the chapter, it was mentioned that early seizures occur in 14–41 % [6–9, 15], while the 30-day risk of seizures is 8 % [15] with a reported frequency of SE of 0.3 %, which represents about 20 % of those patients with ICH who develop seizures [11–13].

Some studies have identified factors associated with higher risk of developing seizures with ICH. These factors include imaging features like the volume of the

accumulated blood within the cranial cavity, the presence of hydrocephalus, involvement of the cortex and/or lobar hemorrhage, midline shift, and the presence of associated subarachnoid and subdural blood. Clinical factors predicting seizures include age, history of alcohol abuse, the presence of sepsis, severity of the neurological deficit measured by the National Institutes of Health Stroke Scale (NIHSS) or Glasgow Coma Score, in addition to the presence of significant disability as measured by modified Rankin score (Table 3.2) [2–5, 7–9, 16–25]. In a large administrative dataset from the National Inpatient Sample (NIS), Bateman et al. found that renal disease, coagulopathy, history of alcohol abuse, sodium abnormalities, and the presence of a tumor as cause of the hemorrhage were associated with SE [11].

There have been some efforts to stratify the risk of late seizures in ICH. Haapaniemi et al. created the CAVE score, "C" for cortical involvement, "A" for age < 65 years, "V" for volume > 10 cc, and "E" for early seizures < 7 days from onset. The authors utilized a cohort of 764 ICH patients who survived to 7th day from the Helsinki ICH study to derive the score and a cohort of 325 subjects from the Lillie Prognosis of Intracerebral Hemorrhage study to validate the score. The cumulative risk of seizures was 7.1, 10, 10.2, 11, and 11.8 % at 1, 2, 3, 4, and 5 years, respectively. Each item of the score has a value of 1 and the cumulative risk of seizures is 0.6, 3.6, 9.8, 34.8, and 46.7 % with 0, 1, 2, 3, and 4 points, respectively. The CAVE score was validated and found reliable in identifying patients with a higher risk for the development of seizures [8].

Risk of Epilepsy with Intracerebral Hemorrhage

Reports on the risk of epilepsy provide a variety of numbers that reflect the different definitions used in the studies and the study design. Arntz et al. prospectively studied a cohort of 697 patients with first stroke age 18–50 years, 66 of those had ICH. Authors used the definition by the International League Against Epilepsy (ILAE) of one seizure in the presence of an enduring condition that can cause epilepsy [6]. The overall risk of epilepsy in that cohort was 11.3 % including patients with ischemic strokes and transient ischemic attacks. The overall risk of epilepsy in patients with ICH was 16.7 %. When the risk projected at 5 years in Kaplan–Meier survival analysis, the risk of epilepsy was about 20 % when patients did not have recurrent seizures as compared to a risk of about 13 % for epilepsy with recurrent seizures. Importantly, the risk of seizure recurrence among patients with ICH and seizures was higher in patients with late-onset seizures (> 7 days) as compared to those with early onset of seizures (< 7 days), 6/7 patients (85 %) versus 1/4 (25 %) [6]. In contrast, Sung and colleagues reported a retrospective review of 1402 patients with ICH. A total of 64 patients (4.6 %) had seizures, and 35 (2.5 %) developed epilepsy that was defined as the presence of 2 or more seizures [9]. Several demographic, clinical, and imaging features have been evaluated as possible predictors of seizures (Table 3.2). Immediate seizures were exclusively correlated with characteristics of ICH (lobar location and small volume). Lobar location has been widely recognized

Table 3.2 Risk factors for seizures in intracerebral hemorrhage

Clinical factors
Age
Alcohol abuse
Severe neurological deficit
Poor functional status based on modified Rankin score
Sepsis
Coagulopathy
Sodium imbalance
Renal disease
Imaging factors
Hematoma volume
Cortical extension of the hemorrhage
Intraventricular hemorrhage
Subarachnoid hemorrhage
Subdural hematoma
Midline shift

as the most potent predictor of immediate seizures [9, 14, 17, 25]. Similarly, hematoma enlargement is usually associated with seizure and poor outcome. The occurrence of SE seems to be influenced by nonlesional factors such as alcohol abuse. The relations between alcohol and seizures are complex; however, both alcohol abuse and alcohol withdrawal may precipitate seizures [7]. A study by Passero et al. reported that recurrent seizures are associated with clinical events including brain infarct, hematoma enlargement, and sudden suspension of AEDs [15].

Impact of Seizures on ICH Outcomes

Reports on the impact of seizures on the functional outcome and mortality of ICH are conflicting. Some studies have shown an increased mortality or worse functional outcomes in patients with seizures. In a study by Arboix et al., in-hospital mortality rate was 37.9% in patients with ICH and ischemic stroke when seizures developed within 48 h of onset compared to 14.4% among patients with no seizures [2]. In another study of ICH and ischemic stroke, the risk of death within 30 days increases when seizures developed within the first 24 h of stroke onset (32.1 vs. 13.3%), although seizure was not an independent predictor of mortality after adjustment for other known variables that impact the outcome [3]. Madzar et al. analyzed 203 patients with ICH, 19.7% of these patients had initial seizures; favorable functional outcome as reflected by a modified Rankin scale (0–2) was found in 63.8% patients with no seizures compared to 47.5% of patients with seizures [23]. Finally, another study showed that seizures were associated with worse neurological

outcomes based on the NIHSS and a mortality rate of 27.8 % compared with 15 % in those without seizures [4]. Despite the evidence that seizures increase disability and mortality rates, other studies have not shown these associations [16, 22, 24, 26].

Seizure Semiology

With regard to the types of seizures observed in patients with ICH, most studies reported partial seizures with or without secondary generalization are the most common. In a cohort studied by Arntz et al., authors found that 27.3 % had simple seizures, 36.4 % had partial seizures with secondary generalization, and 36.4 % had generalized seizures [6]. In their case–control study, 75.7 % of the 14 patients developed focal seizures. However, Arboix et al. reported 37 % partial seizures and 62 % generalized seizures associated with ICH [2]. Electrographic nonconvulsive seizures can be found in 28–30 % in selected patients with ICH when they are monitored with cEEG. However, the actual frequency of nonconvulsive electrographic seizures in ICH is not known since there are no studies that prospectively monitor unselected patients with ICH [4, 10]. SE is rather infrequent at 0.3 % in patients with ICH, although it represents about 19 % of patients with ICH who develop seizures [11, 13]. Given the high incidence of electrographic seizures, current guidelines provide a recommendation class IIa (reasonable to perform) level B (limited populations evaluated) to perform cEEG in patients with ICH and decreased level of consciousness out of proportion to the size of injury or ICH [27].

Treatment

The current American Heart Association guidelines on the management of ICH, published in 2010, recommend treatment of all clinical seizures in patients with ICH (class I, level A) and those with electrographic seizures based on cEEG (class IIa, level B). Routine prophylaxis with antiepileptic AEDs is not recommended (class III, level B) [27]. A single center study evaluated the impact of the guidelines on practice by comparing a cohort of 30 patients treated before their publication with a second cohort of 108 patients treated after the publication of the guidelines. AEDs were used in similar proportions in both cohorts during hospital course (53.3 vs. 50 %). The proportion of patients who were discharged on AEDs was lower in the second cohort (86 vs. 59 %) suggesting that the guidelines have modified physicians' utilization of AEDs, at least in patients who did not have a clear indication [28]. To date, only one randomized controlled trial has been done to compare AEDs against placebo in patients with ICH. Gilad et al. studied 72 patients, half of those were randomized to receive valproic acid and the other half received placebo. After 1 month of follow-up, both groups had similar proportions of seizures (19.5 % in the valproic acid group vs. 22.2 % in the placebo group) [29]. In another single-center

retrospective observational study, 46 of 157 patients with ICH received prophylactic AEDs; 11% of the treated patients had seizures compared to 6.3% who did not receive AED prophylaxis [30]. Therefore, the current evidence indicates, at least in the short term, that AEDs do not decrease the risk of seizures in patients with ICH. For symptomatic patients with ICH, the choice of initial AED depends on individual characteristics, comorbidities, and potential drug interactions.

There are concerns with regard to the impact of AEDs on the functional outcome in patients with ICH. Woo et al. administered prophylactic AEDs to 216 patients with ICH, the treatment did not decrease the rate of early or late seizures; though, it was associated with worse functional outcomes measured by modified Rankin scale [31]. In a secondary analysis of 293 patients with ICH enrolled in the NXY059 trial (CHANT) that included patients within 6 h from symptom onset, AEDs administered prophylactically to 23 patients (8%) with no seizures. The administration of AEDs in this small sample was associated with worse clinical outcome after adjustment for other variables known to impact outcome [32]. Finally, Goldstein et al. analyzed a control group of patients enrolled in the Syngen Acute Stroke Study, an ischemic stroke study. Thirty-seven patients who received at least one AED were compared with 59 patients without AEDs. The motor subscores of the Toronto Stroke Scale were lower among the treated patients. In addition, they were more likely to have impairment in performing their activities of daily living [33]. Collectively, these data indicate that prophylactic AEDs may not prevent early or late seizures, and these medications can have unfavorable effect on functional recovery in patients with stroke and ICH.

Given the aforementioned limited evidence, it is reasonable to conclude that clinical and electrographic seizures should be treated with AEDs; however, the role of prophylactic therapy will have to be evaluated in a large, randomized clinical trial. Clinical trials may also assist in clarifying the duration of therapy when AEDs are implemented in the initial encounter.

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Chapter 4
Seizures in Subarachnoid Hemorrhage

Amer Alshekhlee, Sonal Mehta and L. James Willmore

Introduction

Subarachnoid hemorrhage (SAH) occurs when blood is released into the subarachnoid space surrounding the brain and spinal cord. While trauma is a common etiology of SAH, the most common cause of spontaneous SAH is rupture of a cerebral aneurysm. Ruptured aneurysms are associated with approximately 85 % of spontaneous (or nontraumatic) SAH; about 15 % are due to other causes such as ruptured arteriovenous malformation, dural fistulae, cerebral vessel dissection, infiltrative lesions, and reversible cerebral vasoconstriction syndrome [1, 2]. The incidence of aneurysmal SAH varies between 2 and 16 per 100,000 [3]. In the USA, the incidence is reported to be 9.7 per 100,000 [4]. The true incidence is believed to be higher because of increased mortality associated with aneurysm rupture, with death remitting before arrival at the hospital [4]. Aneurysmal SAHs are grades using two clinical severity grading systems; these are the Hunt and Hess score (Table 4.1) and the World Federation of Neurological Surgeons (WFNS) scale (Table 4.2) [5, 6]. Both of these grading systems are good predictors of outcomes associated with aneurysmal SAH. Despite reports suggesting improvement in outcome, the case fatality rate associated with aneurysmal SAH remains high (median mortality rate of 32 %) [4, 7, 8]. Advancements in neurosurgical techniques and intensive care

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_4

Table 4.1 Hunt–Hess clinical grading system in subarachnoid hemorrhage. [5]

Hunt–Hess grading	Clinical presentation
I	Asymptomatic or mild headache
II	Headache, stiff neck, no focal deficit other than cranial nerve deficit
III	Drowsy, mild focal deficit
IV	Stupor, hemiparesis
V	Deep coma, decerebration

Table 4.2 World Federation of Neurological Surgeon (WFNS) grading system for subarachnoid hemorrhage. [6, 76]

WFNS grade	GCS grade	Motor deficit
I	15	Absent
II	13–14	Absent
III	13–14	Present
IV	7–12	Absent or present
V	3–6	Absent or present

WFNS World Federation of Neurological Surgeon, *GCS* Glasgow Coma Scale

have reduced the overall case fatality rate from 50% to less than 30% [9]; however, cognitive deficits, depression, impaired quality of life, and seizure are frequent among survivors [10, 11].

Seizures after SAH may occur at onset or around the time of the initial hemorrhage; early seizures during the first 2 weeks of recovery after SAH or surgery; or late seizures after the first 2 weeks of recovery or following surgical treatments [12, 13]. Definitions of early and late seizures differ among authors, and there are conflicting data on whether seizures at onset predict late seizures (post-SAH epilepsy) [14, 15]. Seizures are believed to be a common complication of SAH, and may increase morbidity and mortality [16]. This increase is independent from secondary injuries inflicted by complications such as rebleeding, vasospasm, or delayed ischemic injury [17–19]. Post-SAH epilepsy is identified by a patient having spontaneous seizures separated by at least 24 h within the few months following the initial hemorrhage. In this chapter, we focus on seizures following spontaneous SAH (especially the aneurysmal type); we discuss the epidemiology, risk factors, pathogenesis, treatment, and prognosis.

Epidemiology

Seizures are commonly observed following aneurysmal SAH; the incidence varies between 6 and 24% of all nontraumatic SAH [14, 20, 21]. Between 1 and 28% of patients with spontaneous SAH develop “early” seizures (i.e., seizures within

the first 2 weeks of the onset of hemorrhage). Approximately 1–35% develop "late" seizures (i.e., seizures occur after 2 weeks of the onset of hemorrhage) [15, 22]. Factors possibly underlying the variation in the incidence of seizures include heterogeneous patient populations, practice differences in pharmacologic seizure prophylaxis, center-specific treatment guidelines, and differences in continuous electroencephalography (cEEG) monitoring and its reporting practices [21, 23]. Population-based data from patients treated in the 1950s and 1960s estimated the 1- and 5-year incidence of epilepsy after SAH at 18 and 25%, respectively [24]. A 9-year follow-up of patients in the International Subarachnoid Aneurysm Trial (ISAT) showed 10.9% risk of seizure [25]. In a review of Swedish epilepsy registry data, Adelow et al. found that hospitalization for SAH was associated with an odds ratio of 5.1 (95% confidence interval: 1.1–23.0) for a subsequent unprovoked seizure [26]. In an older retrospective series, late seizures were reported in 14% of patients, with a mean latency of 8.4 months [27]. In a systematic review of 25 studies involving 7002 patients, the prevalence of early postoperative seizures was 2.3%, and late postoperative seizures was 5.5%, with average time to late seizures was 7.45 months [28].

Epidemiological data regarding seizures in nonaneurysmal SAH is scant. In a series of 12 patients who presented with cortical SAH, seven patients (58%) had seizures, four were partial, and three generalized [29]. In a series of 34 patients who presented with cortical SAH, three patients (9%) presented with generalized tonic–clonic seizures [30]. While these are small series, they suggest that the incidence of seizures in cortical nonaneurysmal SAH may be higher than typical aneurysmal SAH, or even than those with perimesencephalic hemorrhage. This high risk of seizure in superficial cortical hemorrhage may be related to the location of blood in contact with the cerebral cortex.

Seizure Types in Subarachnoid Hemorrhage

Of the ISAT study population, 235 patients developed various clinical seizure types; 134 (57%) had secondarily generalized seizures, 39 (16%) had partial seizures, 33 (14%) had "blackouts," 4 (1.7%) had nocturnal seizures, and 25 (10.6%) had seizure of unknown type [25]. Modern techniques such as cEEG monitoring in neurocritical care units allow the identification of subtle and subclinical seizures as well [31]. Among 108 consecutive patients with aneurysmal SAH who underwent cEEG monitoring, 19% had seizures recorded on cEEG. Most of the detected seizures were nonconvulsive (95%), and a large number of patients with nonconvulsive seizures had nonconvulsive status epilepticus (70%) (Fig. 4.1) [16, 32]. The diagnosis of nonconvulsive status epilepticus should be considered in patients with poor clinical grade or clinically evident deterioration [33, 34]. Eight percent of patients with unexplained coma with SAH are found to have subclinical status epilepticus [33].

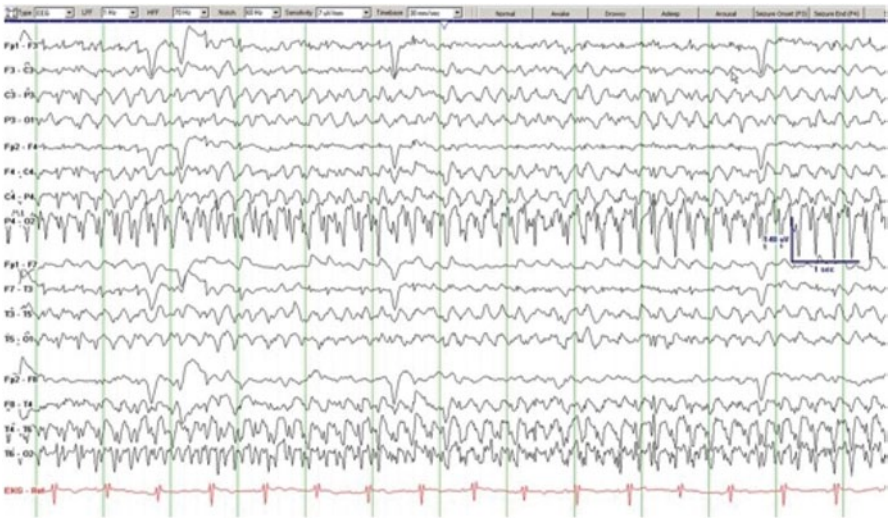

Fig. 4.1 EEG epoch demonstrates a nonconvulsive seizure in a 46-year-old woman with Hunt–Hess grade III subarachnoid hemorrhage after endovascular coil embolization of a right posterior cerebral artery aneurysm. (Abstracted from [73], with permission)

Imaging

Noncontrast brain computed tomography (CT) is the most common tool used to evaluate acute SAH. The hemorrhage is classified into three distinct patterns according to the blood accumulation within the cranial cavity: diffuse, perimesencephalic, and cortical convexity types. The initial distribution of blood based on the initial imaging remains valid for the first few days after the hemorrhage; substantial changes may occur thereafter. In the first pattern, blood layers in the suprasellar central cisterns, with diffuse peripheral extension (Fig. 4.2a). Blood distribution in this pattern is usually associated with a ruptured cerebral aneurysm located at the circle of Willis branching points. Blood layering in the Sylvian fissure usually suggests aneurysm in the middle cerebral artery distribution (Fig. 4.3a), whereas blood in the interhemispheric fissure with extension to the ventricular system may suggest an aneurysm of the anterior communicating artery (Fig. 4.3b). Blood accumulation in the posterior head region occurs with a rupture of a basilar apex aneurysm (Fig. 4.3c). The second pattern of blood layering in the perimesencephalic and interpeduncular basal cisterns (Fig. 4.2b) is considered benign and usually idiopathic (normal angiogram) and may account for approximately 10% of all SAH [35]. In the third pattern, blood products localize to a few sulci along the cerebral convexities (Fig. 4.2c), without extension to the basal cistern or ventricles. This latter pattern is less commonly recognized and has only recently been described as a distinct category of SAH [29, 36–38]. This pattern has an estimated incidence of 7% of all patients with spontaneous SAH [39]. Patients with perimesencephalic SAH have less risk of complications including rebleeding, vasospasm, and hydro-

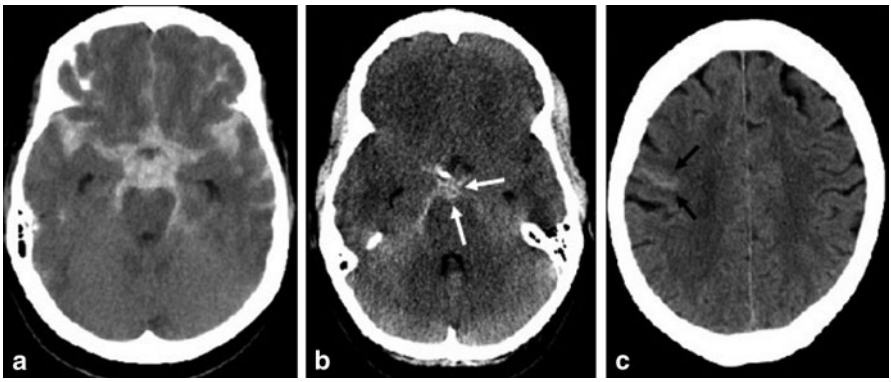

Fig. 4.2 Radiological types of subarachnoid hemorrhages. **a** Diffuse suprasellar (with evidence of diffuse cerebral edema secondary to ruptured aneurysm in the anterior communicating artery). **b** Perimesencephalic interpeduncular (*white arrows* show a small amount of blood in the basal cisterns). **c** Superficial cortical convexity (*black arrows* show blood in the right frontal convexity)

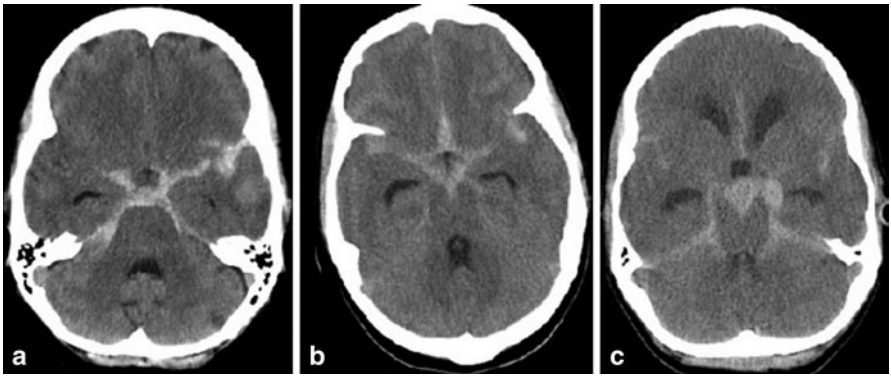

Fig. 4.3 Diffuse subarachnoid hemorrhage secondary to ruptured aneurysm in the left middle cerebral artery (**a**), anterior communicating artery (**b**), and basilar summit (**c**)

cephalus [40]. The accumulation of blood in SAH, based on noncontrast head CT, is graded according to the thickness of the blood layering in the subarachnoid space and whether leakage to the ventricular system had occurred. The Fisher grading scale (Table 4.3) perhaps is the most reliable predictor of vasospasm [41], although it does localize blood accumulation in the brain as highlighted above. Fisher scale remains subjective but with a high inter-reliability value (κ of 0.90) [42].

The risk of seizures varies with the patterns of blood distribution found on the initial head CT. The overall risk of a seizure with aneurysmal SAH is likely higher than those whose bleed is in the perimesencephalic cistern. In a review of 83 patients with spontaneous SAH with negative initial angiography, 49 of those had blood accumulation in the perimesencephalic cistern only [40]. The authors reported that none of the latter group had late epilepsy, but one patient among the diffuse

Table 4.3 Fisher grading scale in subarachnoid hemorrhage. [41]

Fisher grade	CT changes
I	No hemorrhage evident
II	A diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) less than 1 mm thick
III	Localized clots and/or vertical layers of blood 1 mm or greater in thickness
IV	Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots

CT computed tomography

SAH did develop late epilepsy [40]. In a review of 24 patients with superficial cortical convexity hemorrhage, 5 (21%) presented with seizures; all of whom were older than 60 years of age [43]. When SAH is classified by the Fisher grading system, the risk of epilepsy is higher in those with grade III and IV. In 217 patients with SAH, 17 (7.8%) developed seizures at onset, all of whom had Fisher grade III and IV. Late epilepsy in the same cohort occurred in 15 patients (6.9%), nine of whom with grade III and IV on the initial head CT [22].

Risk Factors

Numerous studies have identified the risks for early and late seizures following SAH (Table 4.4). In an earlier retrospective analysis by Ohman et al., risk factors associated with seizures in SAH included history of hypertension, presence of infarction on imaging, and the duration of coma [44]. A Korean study reported risk factors for early-onset seizures after aneurysmal SAH that included younger age (age less than 40), poor clinical and radiological grades (based on Hunt–Hess and Fisher grading systems), acute hydrocephalus, and rebleeding prior to surgical occlusion of the aneurysm [20]. Two studies evaluated the risk factors for late seizures following SAH [20, 45]. Both of these studies showed that the amount of blood within the cranial cavity, based on the initial head scan, is a consistent predictor of late seizures. In a post hoc analysis of 2143 patients enrolled in the ISAT, a Fisher grade greater than 1 on the initial head CT showed a trend in predicting posthemorrhagic epilepsy (hazard ratio 1.34, 95% CI 0.62–2.87). Another study reported a Fisher grade of 3 or greater as a risk factor for seizures [22]. Other independent risk factors for late seizures include cortical infarction and hematoma formation (intracerebral or subdural hematoma) [45]. Seizures at onset in aneurysmal SAH were believed to be an important risk factor for delayed epilepsy [14, 46, 47]. In contrast, other work reported seizures at onset are not a predictive factor for late epilepsy [48–50].

Table 4.4 Predictors of late seizures following subarachnoid hemorrhage. [20, 22, 24, 25, 44, 45, 49]

Early seizure following aneurysmal SAH
Age less than 40
Loss of consciousness greater than 1 h or low GCS at onset
Ruptured aneurysm in the middle cerebral artery
Poor Hunt–Hess grade (≥III)
Fisher grade (≥III)
Surgical clipping
Rebleed prior to surgical treatment
Ischemic infarction
Acute hydrocephalus
Hematoma formation (intraparenchymal or subdural)
Late seizure following SAH
Age less than 40
Vasospasm and cortical ischemia
Poor clinical grade at onset
Clot burden on initial head CT
Intracerebral hemorrhage
Rebleeding
Seizure at onset
Shunt dependent hydrocephalus
Aneurysm in the anterior circulation

SAH subarachnoid hemorrhage, *GCS* Glasgow Coma Scale, *CT* computed tomography

Pathophysiology

Seizure following SAH may occur by either direct injury caused by blood or blood products in the subarachnoid space or due to vasospasm. Early clinical seizures are thought to be related to large amounts of blood in the subarachnoid space and damage to the motor cortex or the insula, the combined effects of a space-occupying lesion with mass effect, focal ischemia, and blood products catalyzing the release of large amounts of glutamate and the generation of oxygen-free radicals [50, 51]. In addition to the direct pathologic effects, seizures may also worsen the extent of injury from the inciting neurologic injury by increasing metabolic, excitotoxic, and oxidative stress on at-risk brain, leading to irreversible injury. Vasospasm is a common complication that usually occurs during the acute phase of SAH and may lead to focal cerebral ischemia. Angiographic vasospasm follows a biphasic pattern, with early arterial spasm within minutes of hemorrhage and delayed phase vasospasm, which is often associated with delayed cerebral ischemia [52, 53]. Early

spreading depolarization has also been proposed as a risk factor for post-SAH seizures [54]. Spreading depolarization is a wave of massive ion translocation between the intracellular and extracellular space, near-complete sustained depolarization of neurons, glial depolarization, neuronal swelling, distortion of dendritic spines, and an abrupt, large, negative change of the slow electrical potential [55]. By contrast, epileptiform activity is characterized by a milder sustained depolarization with less pronounced disturbance of ion homeostasis up to the so-called ceiling level [56]. Whereas sustained depolarization remains below the inactivation threshold for the generation of action potentials during epileptiform activity, this threshold is exceeded during spreading depolarization. Therefore, during seizures, neurons typically fire synchronous action potentials at a high frequency, while silencing (spreading depression) of spontaneous activity is observed during spreading depolarization [57]. Late seizures may occur in the setting of superficial siderosis, blood in subarachnoid space resulting hemosiderin deposition in the subpial layer of the brain [58]. Besides late seizures, superficial siderosis is usually characterized by the presence of progressive ataxia and hearing loss.

Nonconvulsive seizures are associated with elevations in glycerol, presumably because of cell membrane breakdown [59, 60]. One theory regarding cause is that seizures in acutely injured brain have marginally maintaining homeostasis that leads to excessive metabolic demand and increased blood flow thereby compromising at-risk brain tissue leading to additional brain injury with cell death. An alternative hypothesis is that electrographic seizures or periodic epileptiform patterns (Fig. 4.4) are surrogate markers for more severely injured brain. However, most authors agree that prolonged seizures may damage the brain and are associated with secondary injury [61].

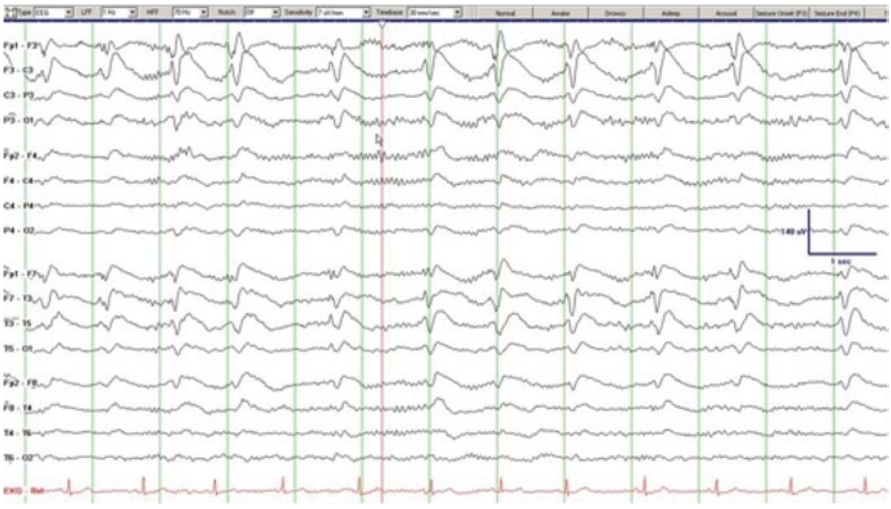

Fig. 4.4 EEG epoch shows period-lateralized epileptiform discharges in a 42-year-old woman with Hunt–Hess grade I subarachnoid hemorrhage after clipping of anterior communicating artery aneurysm. (Abstracted from [73], with permission)

Treatment

The treatment for ruptured cerebral aneurysms has changed over the past two decades. The ISAT showed significantly better outcomes associated with endovascular coiling compared to surgical clipping performed through craniotomy [62]. The same observations were confirmed in the Barrow Ruptured Aneurysm Trial (BRAT) [63]. In addition to minimal invasive surgery to secure a ruptured aneurysm, critical care and seizure detection technology have improved over the last decade [31], allowing for early treatment and prevention. Along with these changes, the recommendations for seizure treatment with primary and secondary prevention have changed.

Long-term follow-up of patients enrolled in the ISAT and other examples suggested a significantly lower risk of seizures in patients treated with coil embolization when evaluated at 2- and 14-year follow-up, compared to those treated with surgical clipping [25, 64]. Currently, no randomized clinical trials have investigated the benefit and outcomes of seizure prophylaxis following SAH. The administration of prophylactic antiepileptic drugs (AEDs) has in the past been part of a standard protocol for patients undergoing neurosurgical procedures such as craniotomy. A survey conducted in 2002 by the American Association of Neurological Surgeons showed that 24% of neurosurgeons routinely prescribed AEDs for 3 months after SAH regardless of whether seizures occurred at presentation, in hospital, or not [16, 48, 49, 65]. In contrast, only 4% of German neurosurgeons routinely prescribe AEDs for patients with aneurysmal SAH [66]. More recently, however, routine use of AEDs for SAH patients has come under question [23] because of lower seizure rates associated with the minimal invasive technology to obliterate cerebral aneurysms [15, 67]. The Stroke Council of America guidelines recommend against routine perioperative use of AEDs in aneurysmal SAH because of the paucity of evidence of benefit [12]. However, the guidelines suggest that AED prophylaxis may be considered in the posthemorrhagic period and longer term for those with risk factors for seizure recurrence. These include a prior seizure, parenchymal infarction or hematoma formation, and middle cerebral artery aneurysm [12]. Marigold et al. attempted to evaluate the utility of AEDs in primary and secondary prevention using the Cochrane database [68]. They concluded that there is insufficient evidence to support routine use of AED for primary and secondary seizure prevention after SAH. No specific recommendation exists to stratify the risk of seizures or late epilepsy by the location of hemorrhage in the brain on the initial head CT. For example, patients with perimesencephalic hemorrhage are usually at the lowest risk of initial seizure or late epilepsy; whereas superficial cortical hemorrhage typically has a higher risk of associated seizures. The recommendations for the latter two groups usually follow any individual with aneurysmal SAH.

There are many AEDs available for seizure prophylaxis; though only a few have been studied in the context of SAH. One study found aneurysmal SAH patients treated with older AEDs (phenytoin, phenobarbital, carbamazepine) had more in-hospital complications including cerebral vasospasm and neurologic worsening

measured by Glasgow Outcome Scale (GOS) at 3 months when compared to those without AEDs (odds ratio 1.56; $P = 0.003$), even after controlling for admission neurological severity grade for hemorrhage [69]. Compared to phenytoin for seizure prophylaxis after SAH, levetiracetam showed a much improved side-effect profile. In a report of 176 patients initially treated with phenytoin, 70 of these (39.8 %) had adverse reaction to phenytoin and needed to change to levetiracetam [70]. After switching, all adverse effects resolved except for the gastrointestinal disturbance and worsening mental status in four patients [70]. In a study of 35 patients with initial seizures or high risk of seizures following SAH, there was no difference in the incidence of seizures between those treated with levetiracetam compared to valproate as a primary anticonvulsant [71].

Prognosis

The clinical implications of seizures in SAH are controversial. Electrographic seizures and particularly status epilepticus have been independently associated with poor outcome after brain injury [31, 72], including patients with aneurysmal SAH [73]. Early-onset seizure in SAH predicts poor outcomes [14, 16]. In 247 patients admitted to a neurological intensive care unit with SAH, the occurrence of inhospital seizures was an independent predictor of 1 year mortality (65 % with seizures vs. 23 % without seizures) [16]. Another study found that post-SAH epilepsy was more frequent in patients with severe residual neurological impairment with 28 % risk of developing epilepsy at 1 year, and 47 % at 4 years compared with patients who had mild or no neurological impairment (risk of 12 % at 1 year and 15 % at 4 years) [24]. Continuous EEG monitoring has been found to provide prognostic value, especially in those with poor-grade SAH (Hunt–Hess 3–5). Unfavorable EEG findings include periodic epileptiform discharges, electrographic status epilepticus, and the absence of sleep architecture [73].

Adverse reaction to AED may influence the neurological recovery after SAH [69, 74]. There is evidence from animal and human studies that indicate that administration of certain AEDs after brain injury (including stroke and SAH) might lower the chance of good functional recovery [74, 75].

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Chapter 5
Seizures in Subdural Hematoma

Bashir Shihabuddin, Archana Hinduja and Shadi Yaghi

Introduction

Subdural hemorrhage (SDH) or hematoma is a common neurological condition complicating about 35 % of traumatic brain injury (TBI) cases. It occurs as blood accumulates between the dura mater, which adheres to the skull, and the arachnoid mater, which covers the cortical surface. This hemorrhage is usually caused by tearing of bridging veins that drain blood from the surface of the brain to the dural sinuses. A less common cause of SDH is an arterial rupture occurring in 20–30 % of these cases [1, 2]. SDH may cause variable degrees of increased intracranial pressure with compression and structural damage to the brain tissue. Based on the time of occurrence, SDH is often divided into one of the three following groups: Acute, if the patient presents within 1–3 days following the injury (Fig. 5.1a); subacute, when the patient presents between 4 and 21 days following the injury (Fig. 5.1b); and chronic, when the patient presents between 3 weeks and 4 months following the injury (Fig. 5.1c).

SDH can result from either accumulation of blood around a cerebral contusion secondary to traumatic head injury or tearing of the surface bridging veins after cerebral acceleration–deceleration injury during violent head motion. Acute SDH is a neurological emergency that carries a high risk of mortality if not managed rapidly. Chronic SDH typically start acutely then induce an inflammatory response

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_5

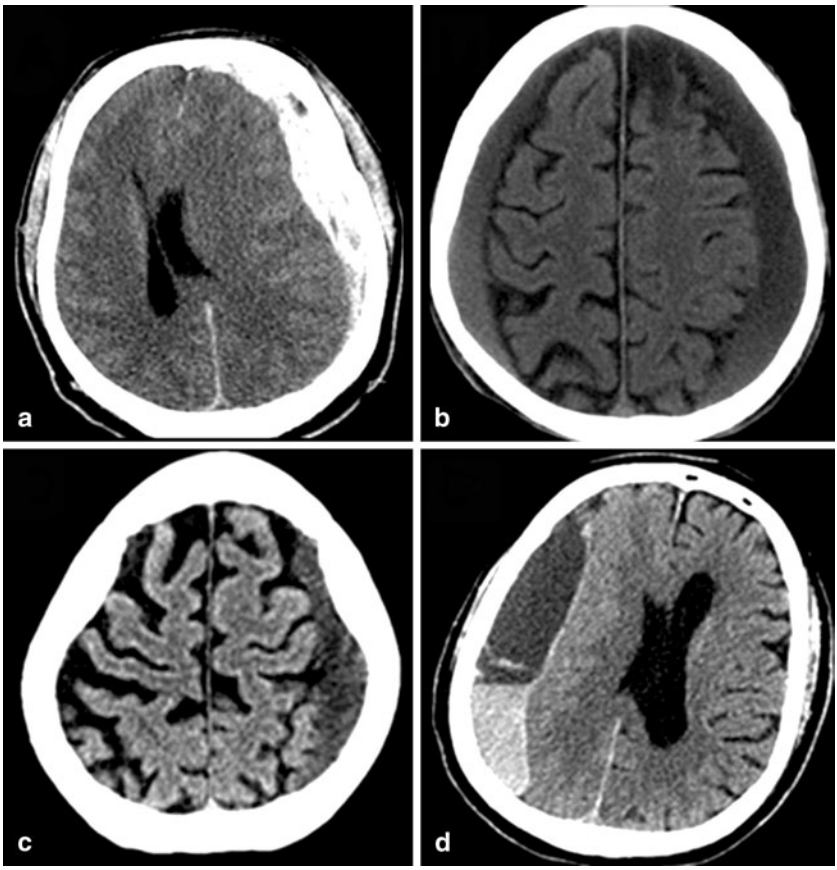

Fig. 5.1 Axial non-contrast head computed tomography (CT) scans demonstrating the classical appearance of the different types of subdural hematoma (SDH). **a** Acute SDH shows a crescent-shaped homogeneously hyperdense extra-axial collection that spreads diffusely over the left frontoparietal region. **b** Subacute SDH shows bilateral frontoparietal iso-dense fluid collection adjacent to the cortex. **c** Chronic SDH shows a left frontoparietal hypodense subdural collection. **d** Acute-on-chronic SDH shows a right hemispheric hypodense extra-axial collection with a posteriorly located hematocrit level

triggering dural collagen synthesis and the recruitment of fibroblasts. This results in the complete encapsulation of the hematoma by the formation of a thick outer membrane and a thin inner one. This is followed by neocapillary formation, fibrinolysis, and liquefaction of the blood clot within the encapsulated structure. Chronic SDH may expand either due to recurrent bleeding (Fig. 5.1d) or due to accumulation of water through osmosis within the SDH [3, 4]. Common risk factors for SDH formation include: cerebral atrophy which is often seen in older individuals and chronic alcohol users, closed head injury especially if associated with cortical contusion, and coagulopathies which can precipitate a SDH following a trivial head injury [3, 5, 6]. SDH can present with a variety of clinical signs and symptoms related to

compression of the cerebral structures and increased intracranial pressure. Common presenting complaints are headaches, confusion, focal neurological deficits, lethargy, and seizures. The focus of this chapter is on seizures associated with SDH.

Epidemiology of Seizures in Subdural Hematoma

TBI is defined as head trauma associated with loss of consciousness for more than 24 h, intracranial hemorrhage, or depressed skull fracture. Approximately 5–7% of all patients with TBI will experience early seizures that are defined as seizures occurring within 1 week following the trauma [7–9]. The incidence of early seizures in patients with acute traumatic SDH is 11–30% when prophylactic AEDs are not used [7, 9–11], with 60–70%of those occurring in the first 24 h following the insult [8, 9, 11]. Furthermore, acute SDH is present in about 60% of all patients with TBI experiencing early seizures, while 50% of these patients suffer from brain contusion and 10% from an epidural hematoma [7]. Patients with TBI and an acute SDH are approximately three times more likely to develop early seizures than TBI patients without an SDH [7]. In addition to being at an increased risk of developing early seizures, patients with acute SDH carry an increased risk of developing late posttraumatic seizures, defined as seizures occurring more than 1 week following the TBI. Patients with acute SDH that is large enough to require surgical intervention have a 44% risk of developing seizures within 2 years following the TBI. This risk decreases to approximately 20% in patients with an acute SDH that did not require surgical intervention [10]. The latter rate is similar to the one experienced by TBI without SDH. The risk of developing seizures in patients with chronic SDH ranges between 2.3 and 17% depending on the type and severity of the head injury [12–16]. Clinical and radiological risk factors for developing seizures associated with chronic SDH include brain atrophy, mixed-density SDH, prior stroke, and low Glasgow Coma Scale (GCS) at presentation [16–18]. In patients with chronic SDH who underwent surgical intervention, the incidence of seizures is between 5 and 22% in the acute postoperative period [17–21]. Predictors of seizures in this group include low GCS on admission, low postoperative GCS, acute-on-chronic SDH, and open craniotomy [17, 18]. The degree of midline brain shift and the volume of the SDH are reported not to predict the occurrence of seizures [17]. Seizures in this patient population had an impact on the short-term, postoperative outcome but did not impact the long-term outcome [17].

Imaging

SDH is commonly seen along the cerebral convexities, the falx cerebri, and the tentorium cerebelli. It undergoes a typical temporal evolution on both computed tomography (CT) and magnetic resonance (MR) imaging [22]. An acute SDH appears

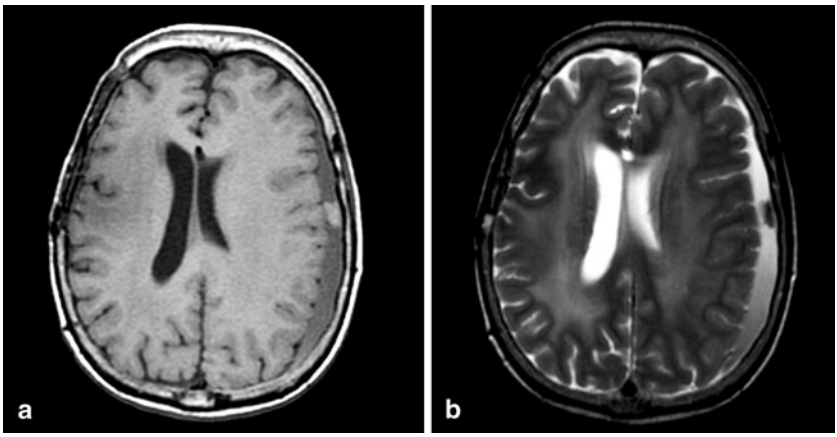

Fig. 5.2 Axial non-contrast brain MRI scan showing a left frontoparietal crescent-shaped hyperintensity on both T1- (**a**) and T2-weighted (**b**) images consistent with subacute subdural hematoma

as a hyperintense crescent-shaped collection on a head CT scan (Fig. 5.1a). On rare occasions, such as in patients with anemia, disseminated intravascular coagulopathy, or with tears in the arachnoid membrane causing dilution from the cerebrospinal fluid, an acute SDH may be isodense or hypodense on a head CT scan. Subacute SDH appears isodense to gray matter, making it challenging to recognize on a head CT scan, especially if there are bilateral SDHs (Fig. 5.1b). Chronic SDH appears homogenously hypodense on head CT scan (Fig. 5.1c). Acute-on-chronic SDH has a bilayered appearance on head CT with a hypodense layer in the less position-dependent portion and hyperdense component in the position-dependent portion (Fig. 5.1d). Magnetic resonance imaging (MRI) is more sensitive than CT imaging for the detection of a small SDH. Acute SDH is isointense on T1-weighted images (WI) and hypointense on T2-WI. Subacute SDH is hyperintense on T1-WI and T2-WI (Fig. 5.2). Over time, the hyperintensity diminishes, and chronic SDH appears as isointense or hypointense on T1-WI and hypointense on T2-WI.

Pathophysiology

SDH is formed through the extravasation of blood within the dura–arachnoid interface layer that splits the space while leaving a few tiers of dural border cells over the arachnoid. These cells that cover the internal surface of the hematoma may proliferate later to form a neo-membrane. The outer membrane may expand due to repeated hemorrhage and in conjunction with the inner membrane leading to a capsule formation (Fig. 5.3). Acute SDH is usually absorbed within a few weeks but might persist to become subacute SDH and evolve into chronic SDH.

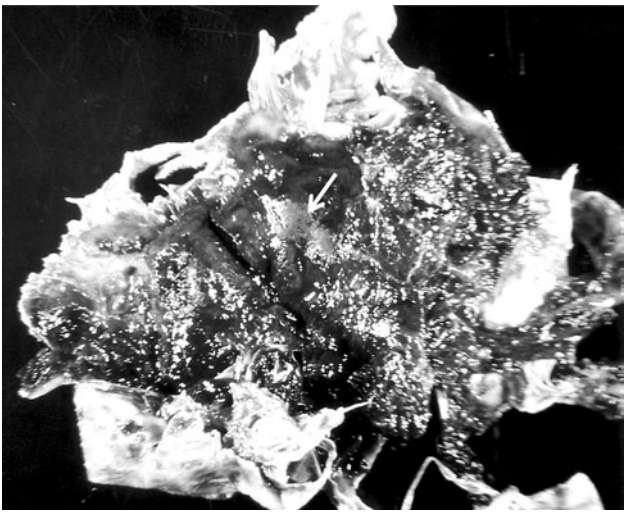

Fig. 5.3 Macroscopic appearance of a chronic subdural hematoma. The blood clot is tightly adhering to the inner surface of the dura mater. It is gradually being covered by granulation tissue, seen here as a light gray layer (*arrow*). (Courtesy of Dr. Murat Gokden)

There are several proposed mechanisms to explain the pathophysiology of seizures in patients with SDH. The traditional proposed mechanism for epileptogenicity in these patients is direct cortical irritation and hyperexcitability [23]. A mixed-density SDH on head CT scan is due to the presence of fresh erythrocytes. This may lead to increased fibrinogen degradation products in patients with acute on top of chronic SDH, which may influence the permeability of the SDH capsule membrane affecting the brain parenchyma and causing seizures [18]. Also, the volume of a mixed-density SDH tends to be larger than a low-density SDH, which may potentially generate more mass effect and pressure on the brain parenchyma resulting in seizures [24]. Another postulated mechanism is that the SDH may reduce the regional cerebral blood flow resulting in cortical ischemia and hyperexcitability [24]. The surgical techniques employed in the treatment of SDH might also be important in the pathogenesis of seizures. Although the SDH capsule is thought to be the source of epileptogenesis, the incidence of postoperative seizures in patients who underwent capsulotomy was higher than in those who underwent burr-hole drainage [13, 17, 20]. This suggests that cortical injury and gliosis due to either surgical intervention or the SDH itself can result in late seizures [17]. Another important factor is that SDH is often associated with other brain injuries such as cerebral contusions, subarachnoid hemorrhage, cerebral ischemia, and increased intracranial pressure with midline shift. All these coexisting brain injuries have been independently associated with seizures as well. Considering all the possible mechanisms by which seizures can develop in patients with SDH, health-care providers should have a very low threshold for considering seizure diagnosis in patients with SDH based on the clinical presentation and course.

Seizure Types and EEG Findings

There are limited data detailing the clinical seizure types encountered in patients with SDH. Considering the focal nature of the lesion, the commonly expected seizure types are various forms of partial-onset seizures with or without secondary generalization. However, the available literature regarding seizure types in patients with acute SDH indicates that about 60–80% of the seizures following subdural hematoma are generalized, while only 20–40% are focal seizures [16, 18]. These reports raise questions regarding the certainty in seizure classification between primary generalized and secondary generalized convulsive seizures based purely on the available clinical seizure semiology. In addition to single seizure, patients with SDH are at risk of convulsive and nonconvulsive status epilepticus. Although all forms of status epilepticus are not uncommonly encountered in neuro-intensive care units, specific medical literature addressing status epilepticus in patients with SDH is lacking. Status epilepticus (convulsive or nonconvulsive) is reported in 2–8% of patients with severe TBI [25–30]. However, the real incidence is likely higher, perhaps in the range of 20%, due to the fact that about 50% of seizures may be subtle and clinically undetectable [25]. This makes electroencephalography (EEG), particularly continuous EEG monitoring, essential for detecting and managing clinical and subclinical seizures in this population.

The EEG is a necessary tool in evaluating patients with SDH as it can provide both diagnostic and prognostic information. It often shows epileptiform and non-epileptiform findings, which can help in lateralizing and localizing the site of hemorrhage. The reported non-epileptiform EEG findings include generalized or focal slowing patterns, focal voltage attenuation and asymmetries, and intermittent rhythmic delta activity (IRDA). These findings are nonspecific and reflect the lateralization and localization of the SDH and its structural effects. The diagnostic role of EEG in SDH has diminished greatly with the advent of CT technology in the mid-1970s. However, it remains of utmost importance in the evaluation and management of clinical as well as subclinical seizures, and it can sometimes provide prognostic information in patients with SDH. Very few studies report the EEG findings in patients with SDH without confounding cerebral injuries. Rudzinski et al. [31] reported EEG findings in patients with acute SDH as an isolated lesion. Patients in this study underwent surgical evacuation of acute SDH and postoperatively either had clinical seizures or other neurological deterioration requiring an EEG recording. Epileptiform discharges were common, occurred in 87% of the cohort, but were not necessarily lateralizing to the side of SDH. Bilateral epileptiform discharges were noted in 66% of these patients [31]. In the absence of cerebral contusions or prior brain disease, epileptiform discharges contralateral to the SDH could be related to disturbed function of the contralateral hemisphere from mass effect imposed by the SDH [32]. Additionally, contralateral epileptiform discharges may also be markers of severe diffuse cerebral dysfunction in these patients (Fig. 5.4). The presence of midline epileptiform discharges on the EEG correlated significantly with the presence of midline shift on brain imaging studies. This was proposed to be secondary to vascular insufficiency involving the watershed regions of the medial cerebral hemisphere [31]. In addition to focal epileptiform discharges, 43% of these patients had periodic lateralized epileptiform discharges (PLEDs) on routine EEG (Fig. 5.5).

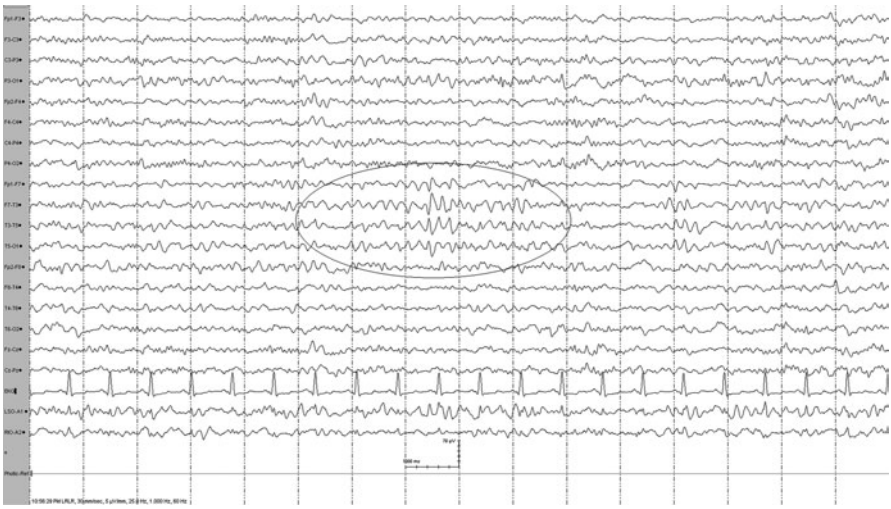

Fig. 5.4 Bipolar montage EEG of a 69-year-old woman who developed secondary generalized tonic–clonic seizures starting with language difficulties and followed by prolonged postictal aphasia following evacuation of a right hemispheric acute subdural hematoma with midline shift. The EEG shows left mid-temporal rhythmic sharply contoured waves (*oval*) in addition to diffuse slow waves and right hemispheric voltage attenuation as compared to the left

PLEDs tended to be much more localizing to the side of the SDH than focal epileptiform discharges and always correlated to an underlying hematoma. Patients with SDH and PLEDs on the EEG are also more likely to have a midline shift on brain imaging studies [33, 34]. Focal epileptiform discharges and PLEDs were more likely to be noted in patients with acute SDH as compared to patients with acute on top of chronic SDH. Focal or multifocal subclinical electrographic seizures were also noted in 12 % of these patients undergoing EEG postoperatively (Fig. 5.6) [31]. Bihemispheric diffuse slowing is the most common background abnormality present on the EEG of 92 % of patients with SDH. It is often asymmetrical and more prominent on the hemisphere that is ipsilateral to the hematoma. Focal slowing is most likely to be noted in the temporal regions and is thought to be secondary to mass effect compromising the regional cerebral blood flow [35]. Amplitude asymmetries are also a common finding on the EEGs of patients with SDH. Decreased amplitude is expected on the side ipsilateral to the SDH prior to evacuation, but it might persist for a prolonged period following evacuation (Fig. 5.4). This is postulated to be secondary to compression of the ipsilateral subcortical tracts [32]. Increased amplitude of the EEG activity ipsilateral to the SDH may be due to a breach rhythm which commonly occurs following surgical burr holes and craniotomies (Fig. 5.7). In addition to background slowing and amplitude asymmetries, frontal intermittent rhythmic delta activity (FIRDA) and bihemispheric frontally dominant triphasic slow waves might be observed on the EEG of patients with SDH. FIRDA and triphasic slow waves are more likely to be encountered in patients with acute on top of chronic SDH than in patients with acute SDH. Focal IRDAs are of special interest if encountered as they correlate with focal potential epileptogenicity (Fig. 5.8).

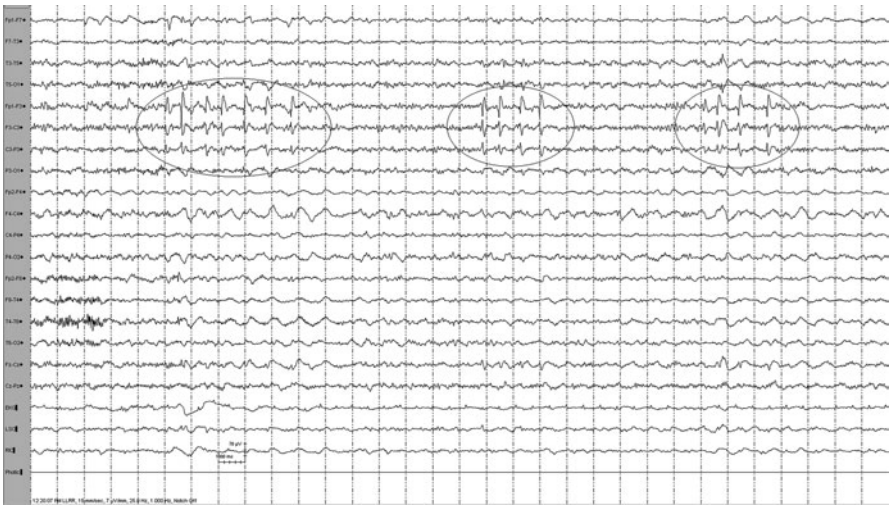

Fig. 5.5 Bipolar montage EEG of a 58-year-old man with acute left frontotemporal subdural hematoma showing intermittent left frontal periodic lateralized epileptiform discharges (PLEDs, *oval*)

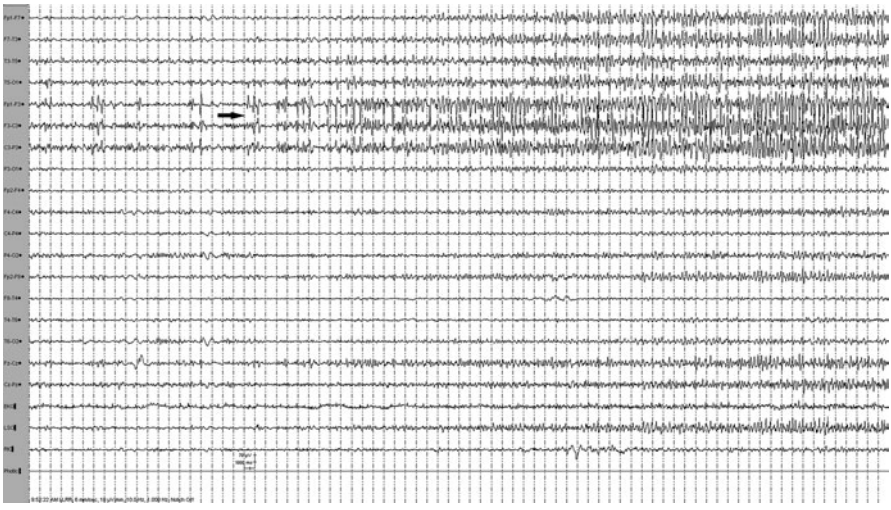

Fig. 5.6 Bipolar montage EEG of a 58-year-old man with acute left frontotemporal subdural hematoma showing an ictal discharge of left frontal onset (*arrow*) and subsequent spread in the left hemisphere

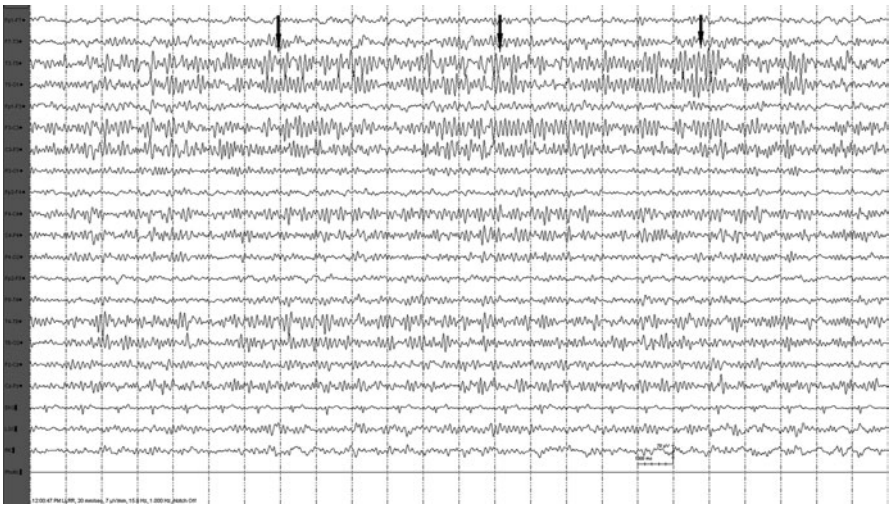

Fig. 5.7 Bipolar montage EEG of a 24-year-old woman after a left temporal craniotomy demonstrating the presence of breach rhythm in left posterior temporal area (*arrows*) secondary to underlying skull defect

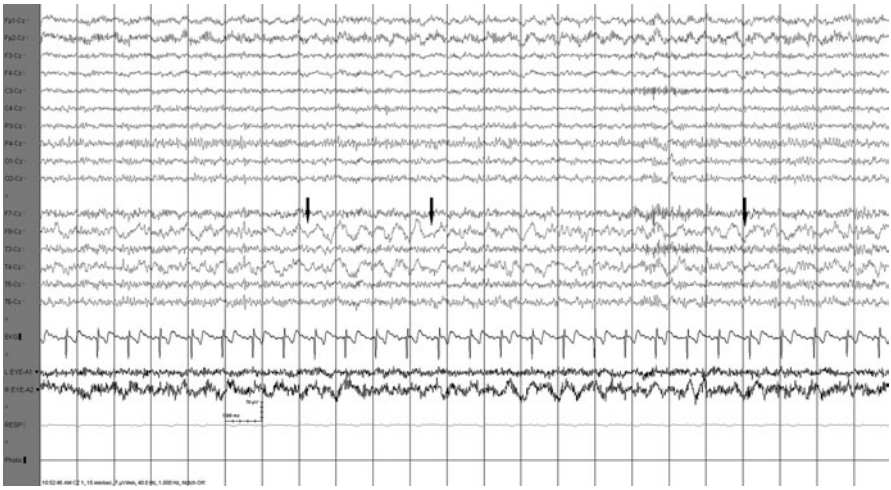

Fig. 5.8 Referential montage EEG of a 58-year-old man who experienced his first seizure 3 months following the evacuation of an acute left temporal SDH showing intermittent rhythmic delta activity (IRDA) in the left anterior temporal area (*arrows*)

Prognosis

The mortality rate of patients with acute SDH ranged from 40 to 60% [36] in the early 1990s and more recently decreased to about 20% [37]. The mortality rate of chronic SDH is between 3 and 10% [38, 39]. Predictors of increased risk of mortality include older age, low admission GCS, prolonged hospitalization, coagulopathy, mechanical ventilation, and multiple comorbidities. Acute SDH can recur in 14–22% of cases [40, 41]. This is more likely to happen if there is an active extravasation of contrast on head CT angiography (CTA) [42]. Chronic SDH may recur in 6–24% [38, 43]. Recurrence is more likely to happen in patients with preoperative hematoma volume greater than 115 mL and postoperative residual hematoma volume greater than 80 mL, postoperative midline shift greater than 5 mm, preoperative seizures, and in patients on anticoagulant therapy [38, 44–46]. In addition, patients with diabetes mellitus, multilocular hematoma, and massive postoperative subdural air are at an increased risk of SDH recurrence. In recent years, the in-hospital mortality from SDH has decreased nationwide, but there is a major increase in discharges to hospice and long-term care facilities leading to increased consumption of health-care resources [47].

Rudzinski et al. suggested a possible role for the EEG in predicting functional outcome of patients with acute SDH. Patients with bilateral, midline, and multifocal independent epileptiform discharges on EEG had poor functional outcome at the time of hospital discharge and at 6-months follow-up with Glasgow outcome scale (GOS) of 3 or less. However, 73% of patients who showed improvement on serial EEGs during the hospitalization in terms of less frequent epileptiform discharges or improved background activity had good functional outcome at the 6-months follow-up after hospitalization with GOS of more than 3 [19, 31]. These findings suggest that an early EEG recording and follow-up EEGs are valuable in patients with SDH especially if the patient's clinical condition does not progress as anticipated, deteriorates, or seizures occur. The EEG findings would be helpful in the immediate management of these patients as well as in predicting the potential functional outcome. Prolonged continuous video-EEG (VEEG) recording is currently available in numerous neuro-intensive care units and is even more helpful in these patients than routine EEGs. VEEG is much more likely to detect not only interictal epileptifrom discharges but also clinical and subclinical ictal epileptiform discharges (Fig. 5.7). Utilizing continuous VEEG will assist in tailoring medical treatment to suppress ictal discharges and potentially improve the outcome of these patients.

Treatment

Acute SDH is a neurological emergency often requiring rapid surgical intervention to prevent irreversible brain damage and death. Surgical interventionis indicated if an acute SDH is 10 mm in thickness or greater or is associated with greater than

5 mm midline shift as measured on head CT scan[36]. Intracranial pressure (ICP) monitoring is needed in all patients with GCS of less than 9. Surgical intervention is necessary if the ICP is greater than 20 mm Hg or if the GCS decreases by two or more points between the time of injury and hospital admission. Patients with GCS of less than 8 and bilateral pupillary dilatation have a high operative mortality and hence are poor surgical candidates [48]. In patients with GCS of 8 or more, if the midline shift is more than the acute SDH thickness and the ICP is more than 40 mm Hg, surgical intervention alone may not alter the outcome. This is because diffuse cerebral edema or diffuse axonal injury may be more important than the size of the hematoma. The recommended surgical procedure is craniotomy with or without bone flap removal and duraplasty [36, 49], and recent data have shown usefulness of decompressive craniectomy in the presence of a coexisting cerebral edema [50]. Surgical evacuation of chronic SDH is performed if there is evidence of moderate-to-severe cognitive impairment or progressive neurological decline attributable to the hematoma. Surgical treatment options include twist drill craniostomy, burr-hole craniotomy with or without subduro-peritoneal shunt [35]. Burr-hole craniotomy over the hematoma site is the most popular technique [36, 51]. The placement of a drain following a burr hole has been shown to reduce hematoma recurrence and 6 months mortality [52]. Recurrent SDH is managed with burr hole and placement of a drain, small craniotomy with membranectomy or subduro-peritoneal shunt placement, and instillation of tissue plasminogen activator [53, 54].

AEDs should be used if clinical seizures occur in the setting of SDH in combination with appropriate surgical intervention and other symptomatic treatment. There is a lack of consensus regarding the administration and duration of prophylactic AEDs in acute and chronic SDH due to the absence of large randomized trials addressing this issue. In the setting of TBI, prophylactic AEDs have reduced the risk of early posttraumatic seizures occurring within 7 days after injury. However, this group includes patients with multiple structural brain lesions and not SDH alone [55]. In a retrospective analysis of patients who underwent evacuation of acute or acute-on-chronic SDH and were not on prophylactic AED, 25% developed clinical or electrographic seizures postoperatively despite adequate evacuation, absence of hematoma recurrence, or ischemic changes [19]. Seizures and epileptiform discharges correlate positively with lower postoperative GCS scores and craniotomy [19]. This information greatly favors the use of prophylactic AEDs in acute SDH. Reduction of seizures from the prophylactic use of AEDs in chronic SDH is more controversial [12, 13, 15, 56, 57]. Although AEDs are not routinely used in this setting in the absence of a clinical suspicion of seizures, seizures should always be considered when the clinical progress is not as anticipated. An unexplained decrease in the level of consciousness or neurological changes should prompt a prolonged VEEG monitoring [52]. This will aid in detecting electrographic seizures and other EEG abnormalities such as PLEDs that require treatment. Surgical intervention resulted in resolution of PLEDs and seizures in patients who had altered mentation and PLEDs or seizures preoperatively [17, 58, 59]. This is possibly due to improvement in cerebral blood flow and removal of the hematoma capsule. Worsening seizure frequency or status epilepticus in patients with chronic subdural hematoma of

any size that has failed medical management with AEDs warrants surgical intervention. Most of the seizures related to SDH occur within 3 months following injury [13] making it reasonable to maintain prophylactic AEDs for at least 3 months following the SDH occurrence unless seizures occur. For patients who experience seizures several months following the SDH occurrence, the seizure management is similar to other forms of symptomatic epilepsy. Specific data regarding long-term seizure control and outcome of patients with SDH are lacking. The choice of AEDs depends on the clinical situation and the patient's characteristics; however, AEDs with intravenous formulations are used preferentially. These medications include fosphenytoin, valproic acid, levetiracetam, and lacosamide. For many years, phenytoin and then fosphenytoin were the initial AEDs used in patients with SDH, but in recent years levetiracetam has been used increasingly due to its favorable pharmacology and tolerability [60]. There are no controlled studies aimed specifically at addressing the role, duration of treatment, and type of AEDs used with SDH. To clarify these ambiguities and to establish clear treatment guidelines, controlled clinical studies in these areas are necessary.

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Chapter 6
Seizures in Cerebral Cavernous Malformations

Justin Lindquist and Mohamad Koubeissi

Introduction

Vascular malformations of the central nervous system (CNS) have been described since at least the seventeenth century, but it was not until the nineteenth century when cerebral cavernous malformations (CCMs) were described [1]. In 1854, the German anatomist Hubert von Luschka reported an asymptomatic left frontal CCM in a 40-year-old patient who committed suicide [2]. Nine years later, Rudolf Virchow described CCMs as a form of neoplasm. The first surgical resection was performed by Bremer and Carson in March 1890 when they removed a CCM with a spoon. Their patient, a 23-year-old male, presented with a 3-year history of increasingly frequent partial seizures involving the left side of the body, which resolved completely after surgery [3]. It was not, however, until 1928 that CCMs obtained their most commonly used name: cavernomas. Harvey Cushing suggested that cavernomas were a form of hemangioblastoma [4], and, while the ensuing years discredited this view, the misnaming survived. CCMs were later characterized microscopically as "large, sinusoidal vascular spaces forming compact masses, which are not separated by parenchyma" [1]. Though once thought to be rare, modern imaging modalities have changed this view [5]. As regards epilepsy, CCMs are the most common vascular malformation to cause a seizure [6].

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_6

Epidemiology

CCMs constitute up to 20% of all cerebral vascular malformations [7]. They occur equally in males and females [8] with a prevalence of 0.1–0.5% [9, 10] and a familial incidence of about 20% [11]. A recent population-based study in the UK found that the 5-year incidence of a first seizure due to a CCM was no more than 4% [12]. In one survey of more than 24,000 autopsies, only 131 had CCMs and, of those, only 3 caused seizures [13].

The majority of CCMs are solitary, but multiple CCMs are common with approximately one third of patients having more than one [10], likely representing patients with familial CCMs [14]. It is estimated that only about 20% of all CCMs become symptomatic, but this may not be accurate since most asymptomatic lesions are never evaluated. In one series of 24,535 autopsies, only 6 of 131 CCMs were symptomatic, with 3 of these 6 cases causing seizures [13]. When supratentorial CCMs are symptomatic, they most commonly present with seizures. They are, however, less likely to cause seizures than neoplasms, as 12–51% of patients with intractable epilepsy have tumors [15]. Symptomatic CCMs may present at any age, but commonly present around the age of 30 years [14].

Genetics

CCMs can be familial or sporadic. Familial CCMs are most common in individuals of Hispanic descent [14]. All of the three known mutations, CCMs 1, 2, and 3, are autosomal dominant [14, 16]. Cumulatively, these three mutations account for approximately 80% of all familial CCMs suggesting there is at least one additional unidentified mutation, which is believed to be on chromosome 3q [9, 11].

CCM1: (Krev Interaction Trapped 1; KRIT1)—7q21.2. Identified in 1999, this is the most common mutation [17]. It is expressed in both astrocytes and endothelial cells, and serves to inhibit angiogenesis and stabilize vascular endothelium. When expressed, CCM1 inhibits response to vascular endothelial growth factor (VEGF)-induced and fibroblast growth factor-2 (FGF-2)-induced vascular sprouting through delta-like ligand 4 (DLL4)–Notch signaling. The deletion of this gene leads to vascular proliferation in zebra fish and is fatal in mice [18]. More than 100 mutations of this gene have been identified, including nonsense, splice-site, frameshift, and false missense mutations.

CCM 2: (MGC4607)—7p15–p13. Identified in 2003 [17], this mutation encodes the malcavernin protein and binds with KRIT1 [14]. Interestingly, it is expressed in neuronal and glial cells, rather than vascular endothelial cells, suggesting that CCM development may be related to signaling between the vessels and parenchyma [19]. At least ten mutations within this gene are known to cause CCMs [17].

CCM 3: (programmed cell death 10)—3q25.2–q27. Identified in 2004 [20], the exact function of this gene is unknown, but it appears to play a role in protein syn-

thesis, migration, apoptosis, and cell proliferation. Mice lacking PDCD10 expression experience defective angiogenesis and die as embryos. Recently, expression of this gene was identified in T cells where it inhibits apoptosis [21]. Thus far, only intronic mutations have been identified [14].

Despite the fact that all cells possess an inherited mutation, there can be some heterogeneity between lesions. This may be explained by a "double-hit" phenomenon wherein either a second somatic mutation or an environmental insult ultimately leads to the CCM [22]. This may account for how existing CCMs can change and new ones can appear over time [23]. Of the three known genes, *PDCD10* is most likely to undergo de novo mutations [11]. All CCMs have the same anatomical and radiological appearance irrespective of etiology, but familial CCMs have been described outside the brain, such as in the retina, spinal cord, skin, and liver. Patients with CCM1 and CCM3 mutations appear more likely than those with CCM2 mutations to have cutaneous CCMs [11].

The pathogenesis of the more common, sporadic form of CCM is more elusive. Sporadic CCMs can be congenital, and they have been found in fetuses [7]. Some deemed sporadic may also be, in fact, genetic in etiology due to incomplete penetrance [19], which can vary according to mutation. The penetrance is 88% with CCM1, 100% with CCM2, and 63% with CCM3 [11]. The only known risk factor for developing CCMs is exposure to radiotherapy in childhood. Males are at a higher risk for CCMs than females, and patients who have received radiotherapy for medulloblastomas have higher risks than those treated for other cancers [24]. In one literature review of 76 cases, the mean latency between radiotherapy and detection of CCMs was 8.9 years, although CCMs may be diagnosed as early as 5 months after radiation. Radiotherapy-induced CCMs are rare in adults [24].

Morphology and Location

CCMs are focal tangles of blood vessels that appear similar to capillaries [16] with the absence of any elastic or muscle tissue [12], and of brain parenchyma [25] (Fig. 6.1a, b). Their tight junctions are rather leaky [26] and, thus, tend to result in many asymptomatic microhemorrhages over time. This leads to hemosiderin deposition surrounding the CCM with resultant gliosis in the surrounding brain parenchyma [25]. The size varies anywhere from a few millimeters to several centimeters [9], and large CCMs can exceed 6 cm in diameter [8].

As regards their location in the brain, a review of 690 CCMs in 680 patients reported that 80% of CCMs were supratentorial and 18% infratentorial [27]. There are fewer CCMs per unit volume in the frontal lobes, and no predilection towards either hemisphere [27].

CCMs may coexist with adjacent focal cortical dysplasia (FCD) [28]. A series of 18 patients with CCMs reported 13 cases with FCD [29]. FCDs seen with CCMs tend to be Palmini type I (ILAE type IIIc), and all patients in this series lacked cortical layer II. The etiology of the surrounding FCD, and whether it represents

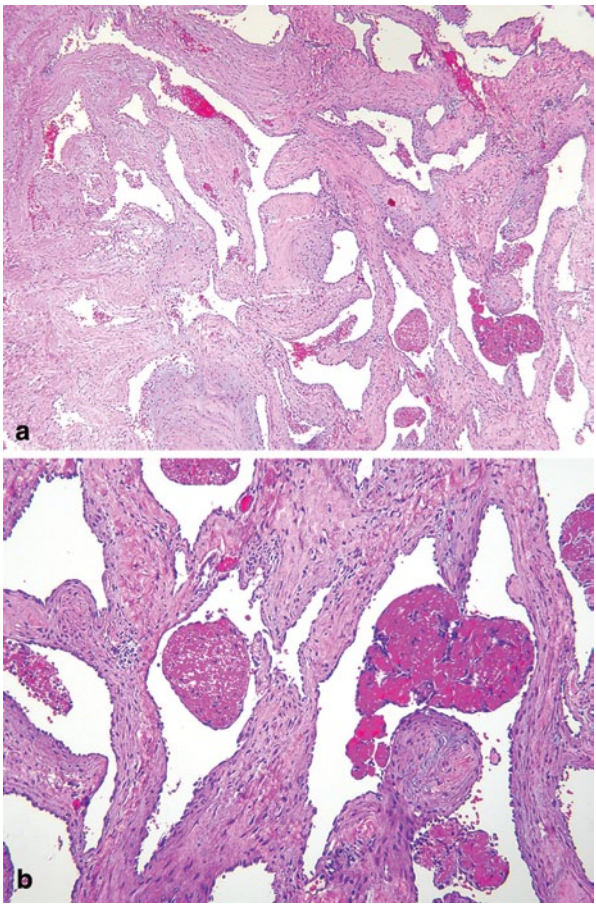

Fig. 6.1 Photomicrograph of a cerebral cavernous malformation (CCM) stained with hematoxylin and eosin at low **(a)** and high **(b)** magnifications. CCMs appear as clusters of dilated, thin-walled blood vessels with no brain tissue in between. Unlike AVMs, there is no arterial component

a reactive pattern to the CCM, is unknown. FCD may be underreported since pure lesionectomies do not remove adjacent parenchyma for pathology, and since low-grade FCD is often not seen on magnetic resonance imaging (MRI) [30] .

Imaging

The advent of MRI has increased the sensitivity of detecting CCMs. Standard T1 and T2 images are highly sensitive and specific for CCMs [5], with susceptibility-weighted imaging (SWI) being the most sensitive modality [31]. CCMs are known to have a characteristic “popcorn” appearance on MRI, owing to the deposition of blood products in varying states of decay in the adjacent brain parenchyma [6]. MRI appearance of CCMs can be [1] hyperintense on T1 and T2 images

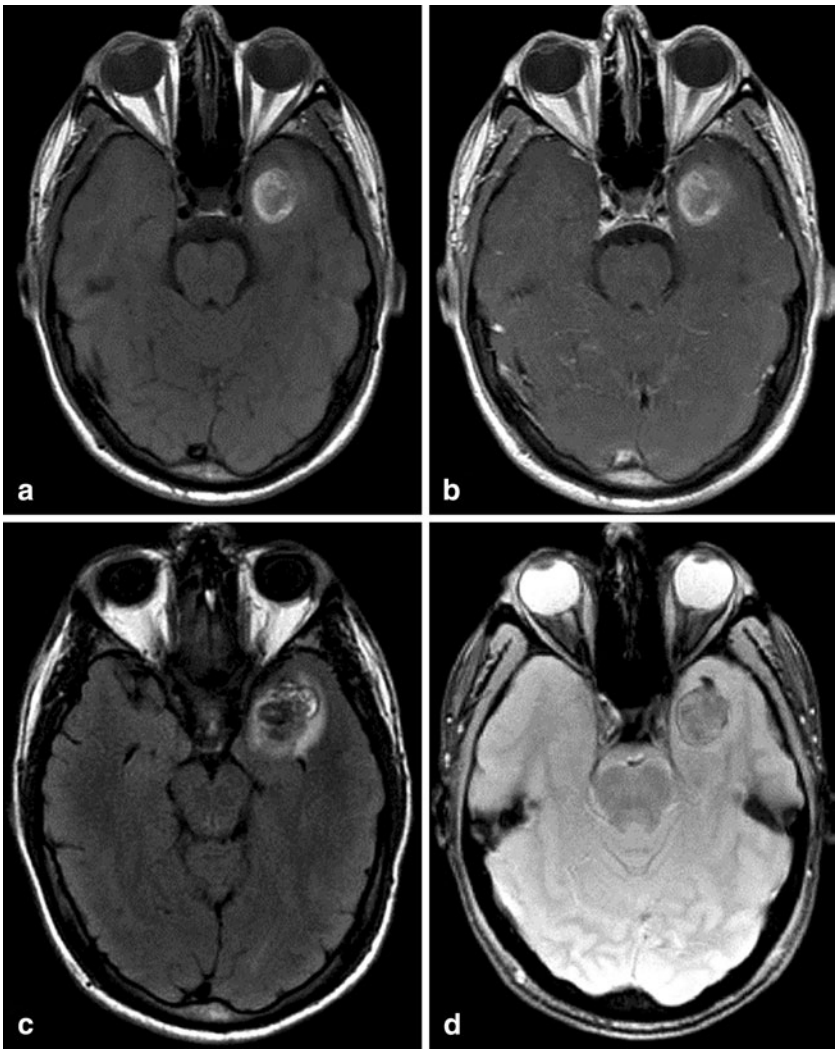

Fig. 6.2 MRI shows CCMs as characteristic "popcorn" ball of loculated, mixed hyperintensities, with minimal surrounding edema, and hemosiderin rim best seen on the gradient-echo sequence. **a** T1-weighted axial MRI, **b** T1-weighted axial gadolinium-enhanced MRI, **c** T2 FLAIR axial MRI, and **d** gradient-echo sequence axial MRI

without active enhancement with gadolinium, [2] central mixed-signal intensity on T1 and T2 surrounded by a hypointense ring on T2 images—these are the characteristic "popcorn" lesions (Fig. 6.2a–c), [3] central isointense to hypointense core on T1 and T2 with a hypointense ring on T2 images (Fig. 6.2d), or [4] punctate hypointense lesions on gradient echo (GRE) that may represent nascent familial

CCMs. Subacute hemorrhage or degraded blood product make it difficult to differentiate these lesions from tumors. Besides the lack of uptake with gadolinium T-1 MRI, fluoro-deoxy glucose positron emission tomography (FDG-PET) demonstrates a hypometabolic focus (Fig. 6.3). There are no radiological differences between familial and sporadic CCMs, except that familial CCMs tend to occur in groups, whereas sporadic CCMs are solitary and may occasionally occur adjacent to a developmental venous anomaly [32]. Additionally, there is no angiographic difference between familial or sporadic CCMs, both lacking afferent and efferent vessels [33]. Although contrast enhancement was thought to indicate the presence of other vascular malformations in the past, we now know that this is not always true. CCMs may enhance if time-delayed double doses of gadolinium are used. One retrospective review of 32 patients found that at least 20% of CCMs showed enhancement, which correlated neither with the size of the CCM nor with the presence of developmental venous anomalies. Therefore, radiographic diagnosis should be based primarily upon morphology and signal intensity rather than enhancement [34].

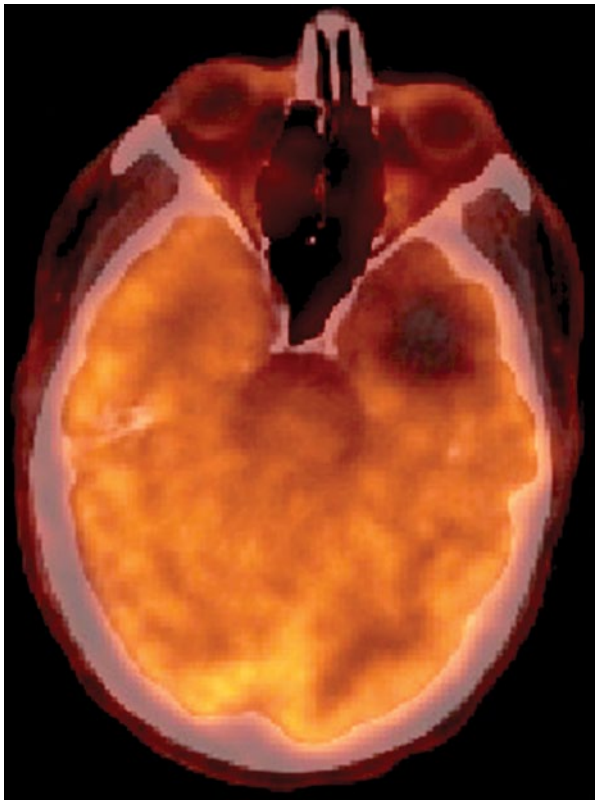

Fig. 6.3 FDG-PET scan showing a CCM as a hypometabolic focus in the left temporal lobe

CCMs and Epilepsy

There are no neurons within the CCM itself [25], and seizures caused by CCMs arise from the neighboring cortex. Over time, CCMs leak minute amounts of blood that degrade into hemosiderin, a toxic substance that leads to neuronal death and synaptic reorganization. In addition, extracellular iron appears to trigger reactive gliosis, likely via free radicals, and inhibit glutamate reabsorption. Collectively, these changes produce a hyperexcitable state. Unlike tumor-induced seizures, mass effect from the CCM does not appear to influence epileptogenesis [15].

Neurons adjacent to CCMs were extracted during surgery and proved to have normal membrane properties, including a normal resting potential [15]. However, more than half of those neurons emitted spontaneous depolarizing discharges that were likely synaptically driven. These neurons also generated large-amplitude postsynaptic potentials resembling paroxysmal depolarization shifts, although these potentials were graded rather than being all or none. These phenomena were more common in neurons sampled from the vicinity of CCMs than those adjacent to neoplasms. Another study compared the intraoperative electrocorticographic (ECoG) discharge patterns of CCMs with those of neurodevelopmental lesions, such as neoplasms and cortical dysplasias, in patients with pharmacoresistant epilepsy [7]. The authors found that coincident mesial temporal discharge bursts were more common in CCMs than in neurodevelopmental lesions. Continuous spiking was seen in both groups correlating with longer disease duration. Interestingly, the absence of coincident bursts in the CCM group was associated with increased density of microglia, with no relationship between the degree of iron deposition or gliosis and the frequency of ECoG epileptiform discharges.

Seizures are the most common symptomatic presentation of supratentorial CCMs [35], and CCMs located in the mesial temporal regions are more likely to result in seizures than in other brain regions. Temporal CCMs, however, respond better to surgery than extratemporal CCMs [36]. Seizure semiology in CCMs varies depending on the location of the CCM [27]. Of note, neither prior intracerebral hemorrhage (ICH) nor focal neurological deficits seem to increase the risk of seizures in patients with CCMs, which stands in contrast to arteriovenous malformations (AVMs) [12].

Incidentally identified CCMs rarely cause clinical symptoms. On the other hand, CCMs that cause a seizure will have a 94% chance of causing a second seizure [37], which is far more than the chances of having a second seizure due to AVMs (58%). This difference is believed to be due to the hemosiderin ring surrounding a CCM [12].

Treatment

As with other epilepsies, the first-line treatment for seizures caused by CCMs is pharmacotherapy. There are no preferred antiepileptic drugs (AEDs), although some avoid valproic acid as it may cause thrombocytopenia [4]. An AED should be considered after a first seizure as it reduces the time to 2-year seizure freedom when compared to placebo [37]. It is not clear if dual AED therapy offers any additional effect beyond monotherapy [25]. One emerging form of pharmacotherapy is the use of a multiple kinase inhibitor: sorafenib. Though developed for use in renal and hepatocellular carcinoma, it has been used with success to shrink a hepatic cavernous hemangioma, whose size decreased from 1492 to 665 mL after 78 days [38]. Another case report cited similar results with bevacizumab [39].

Medical intractability in epilepsy is defined as the failure of two AEDs to achieve full seizure control, and must necessitate a surgical evaluation [40]. With CCMs, a prompt surgical evaluation is even more highly recommended than with most other focal epilepsies since longer duration of seizures may be associated with decreased chances of seizure freedom after lesionectomy [25]. As with other focal epilepsies, the adverse effects of AEDs as well as the functional and occupational limitations imposed by uncontrolled seizures will further clarify the need of early surgical evaluation.

A thorough preoperative evaluation is certainly recommended. This should include at least a seizure-protocol brain MRI and continuous video-electroencephalograph (EEG) monitoring with ictal recordings. The intracarotid amobarbital procedure, neuropsychological testing, and other preoperative procedures may be recommended in individual cases. Sometimes, intracranial monitoring may be used in order to identify the epileptic margins of CCMs. Diffusion tensor imaging has been used to help identify white matter tracts passing through the surrounding hemosiderin ring [32]. Functional imaging such as single-photon emission computed tomography (SPECT) or functional magnetic resonance imaging (fMRI) remains a useful adjunct [35].

The extent of optimal surgical resection is unknown due to a lack of adequate data that compare lesionectomies with more extensive resections [35, 41]. Lesionectomies involve the removal of only the CCM itself, whereas tailored resections involve removal of all or part of the hemosiderin rim surrounding the CCM [25]. The borders of such resections can be further refined with ECoG monitoring [42]. Only around 60 % of patients whose lesionectomy is limited to the malformation itself will achieve Engel class I surgical outcome [43], likely due to limited or no resection of hemosiderin-laden tissue [25]. Importantly, sparing subcortical hemosiderin deposition to preserve white matter tracts does not appear to influence the outcome [35].

As with other lesional epilepsies, resection of CCMs from eloquent areas poses greater difficulties. Extraoperative intracranial monitoring or intraoperative awake mapping is often indicated in such situations. In one series of nine patients with dominant hemispheric CCMs of whom six had seizures, five patients attained sei-

zure freedom off AEDs [44]. Multiple CCMs do not contraindicate surgery, and one report mentions a patient who achieved seizure freedom after removal of ten malformations [41]. It is uncertain, however, if asymptomatic CCMs should be removed alongside epileptogenic ones [25].

Gamma Knife radiosurgery has also been used with CCMs since the mid-1980s [45]. The focally applied radiation leads to obliteration of the CCM lumen by virtue of endothelial proliferation. This process can take as long as 3 years to complete. The optimal dose of radiation has not been determined. Furthermore, the risk of bleeding persists until ablation is complete and only approximately half of all patients will achieve seizure freedom, which is less than what is seen with lesionectomy. Stereotactic radiosurgery may still be useful for patients with CCMs near the eloquent cortex [35]. In one study of 49 patients with pharmacoresistant epilepsy due to CCMs, radiosurgery achieved seizure freedom in 26 patients (53 %) [46]. Of note, medial temporal CCMs in that series were associated with a higher risk of failure.

Prognosis

Patients with mesial temporal CCMs are more likely to experience seizure freedom after lesionectomy than those with CCMs in other brain regions [36], but some authors suggest that this difference is short lived [47]. Otherwise, there is no correlation between the location of the CCM and seizure freedom [35]. Of note, neither the size of the lesion nor the presence of perioperative bleeding has an effect on long-term outcome. Also, age at the time of surgery does not seem to affect the outcome, although the data about this are inconsistent. Patients who experience secondary generalization or high seizure frequency (defined in one series of 60 patients as one or more seizures per month over 1 year) have less favorable outcomes after surgery [35].

In one survey, 70 % of 168 patients who underwent lesionectomies or more radical resections of CCMs achieved Engel I surgical outcome after 1 year of follow-up [47]. This rate declined to 65 % 3 years after surgery. Part of this decline in seizure freedom rates may be due to the loss of seizure-free patients to follow up. Only nine patients had Engel IV surgical outcome, of whom four had multifocal slowing and epileptic discharges preoperatively suggesting other seizure foci [47]. The rate of AED discontinuation after surgery is also unclear [25].

Surgical complications pertaining to surgery are rare. In the immediate postoperative period, 17 % of patients experience focal neurological deficits, but this falls to 2.6–8 % during follow-up. There are no reported deaths due to surgery [35]. This low complication rate correlates with patient satisfaction. In one survey, patients were asked if they would have surgery again and 90 % of respondents stated they would [42]. Given all of the above, surgery should be considered in those with supratentorial CCMs and epilepsy [47].

For those with familial CCMs, genetic testing is also recommended as a screening MRI may be negative due to disease latency. Furthermore, those with familial CCMs who have successfully undergone lesionectomy may still require periodic MRI screening as new lesions can form at the rate of 0.2–0.4 CCMs per patient year [11].

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Chapter 7
Seizures in Arteriovenous Malformations

Prachi Mehndiratta and Amer Alshekhlee

Introduction

Arteriovenous malformations (AVMs) are congenital lesions resulting from lack of a capillary bed between arteries and veins, thereby resulting in an abnormal conglomeration of vessels known as "nidus." Population studies have estimated an incidence of 1.34 per 100,000 person-years [1].Cerebral AVMs are commonly associated with seizures, hemorrhage, headaches, and ischemic stroke secondary to a steal phenomenon. They account for 1 % of all stroke symptoms in patients who present with acute ischemic stroke [2]. Cerebral AVMs are the common cause of intracerebral hemorrhage (ICH) in the young population [3]. The type of hemorrhage can be intraparenchymal, subarachnoid, or intraventricular. The risk of hemorrhage is approximately 2–3 % per year based on the available literature [4–6] with a mortality rate of 10–30 % after the first hemorrhage [4, 5]. Hemorrhage risk is higher in AVMs with the following characteristics: central venous drainage, intranidal aneurysm, periventricular or intraventricular location, arterial supply via perforators, basal ganglia location, single draining vein, and impaired venous drainage [7, 8]. The Spetzler–Martin grading scale is a widely used scale to classify AVMs and correlate their risk of rupture. It takes into account the size of AVM (<3 cm, 1 point; 3–6 cm, 2 points; and >6 cm, 3 points), pattern of venous drainage (superficial 0 point or deep 1 point), and eloquence of adjacent brain (0 or 1 point). Points are

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_7

allocated for each feature, and aneurysms are classified into grades to determine the risk for surgery. A grade 1 AVM is small, superficial, and located in noneloquent brain, and is low risk for surgery. Grade 4 or 5 AVMs are large, deep, and adjacent to eloquent brain and are considered moderate to high risk for surgery. Grade 6 AVMs are considered nonoperable [9].

Seizures are also a frequent clinical symptom in patients harboring cerebral AVMs, and their incidence, risk factors for seizures, treatment, and prognosis are further elucidated in this chapter.

Epidemiology

The true incidence ofcerebral AVMs isdifficult to ascertain from different studies. Between 0.1 and 0.8 % of the population may present with cerebral AVMs in a given year [10]. An autopsy study suggested 0.15 % incidence rate among all examined brain and 3 % rate among hemorrhaged brains [10]. Seizures have been reported in 24–40 % of patients with AVMs [11, 12]. Subclinical hemorrhage in patients presenting with seizures occurs and was demonstrated in 6.5 % of AVM patients presenting with seizures.

Mechanism of Seizure in AVM

There is paucity of data regarding the pathophysiology of seizures in AVMs. Previously ruptured AVMs may result in seizures secondary to gliosis or encephalomalacia; however, no clear explanation exists for seizures resulting from unruptured AVMs [13–15]. Arterial steal resulting from large nidus size has been believed to cause hypoxemia of the surrounding tissue, in turn resulting in gliosis and seizures [16, 17]. Another hypothesis is related to a disruption in venous outflow rather than inadequate arterial supply [18–20]. Recently, several angioarchitectural characteristics of the malformations have been studied and reported to confer a higher risk for seizures. Garcin et al. prospectively studied 155 consecutive patients with AVMs from a single center; of these, 29 % were found to have seizures on presentation. They demonstrated that the presence of superficial venous drainage, increasing AVM size, frontal lobe or arterial border-zone location, and male sex predispose to the occurrence of seizures [21]. Sturiale et al. retrospectively reviewed angioarchitectural characteristics of AVMs in 168 patients and established similar results. Seizures occurred in 29 % of patients; AVMs greater than 4 cm, fed by dilated arterial feeders, cortical location, and AVMs fed by middle and posterior cerebral arteries were associated with a higher risk for seizures [22]. Shankar et al. further studied the aforementioned risk factors (Table 7.1) and their presumed pathophysiologic mechanisms [23]. These features are elucidated below:

Table 7.1 AVM angioarchitectural characteristics and their association with seizure presentation [23]

Angioarchitectural characteristics	Univariate OR (95% CI)	Multivariate OR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Nidus size >3 cm	3.79 (1.47–10.86)	–	61 (42–79)	71 (58–82)
Frontal, parietal, temporal	5.0 (1.50–19.07)	4.52 (0.95–21.47)	91 (82–100)	33 (20–47)
Arterial dilatation	NA	–	100	22 (11–36)
Perinidal angiogenesis	3.71 (1.47–12.05)	–	70 (53–83)	61 (48–75)
Fistulous component	4.11 (1.45–13.20)	–	75 (59–91)	58 (44–71)
Pial long draining vein	14.86 (5.67–66.09)	5.71 (1.32–24.65)	79 (64.91)	80 (69–91)
Pseudophlebitic changes	3.08 (1.21–9.25)	–	61 (46–76)	67 (53–80)
Venous outflow stenosis	6.50 (2.22–32.49)	6.71 (1.99–22.56)	50 (34–69)	87 (76–96)
Venous ectasia	3.00 (1.05–13.75)	–	82 (70–94)	40 (27–56)

AVM arteriovenous malformation, *CI* confidence interval, *NA* not applicable, *OR* Odds Ratio

a) Size: Large AVM nidus size greater than 4 cm was significantly correlated with seizure occurrence. Seizures may be related to sheer size, the likelihood of affecting a potentially epileptogenic zone, and widespread hypoxemia.
b) Location: Frontal, temporal, and parietal location of AVMs is associated with increased risk for seizures due to cortical involvement. The vascular supply of these territories is predominantly from the middle cerebral artery (MCA), and, hence, MCA arterial feeders have also been associated with seizures [24–26].
c) Dilatation of arterial feeder: High flow states resulting from dilatation of the arterial supply of the AVMs can result in a "steal phenomena" drawing blood away from the surrounding brain tissue. This can result in chronic hypoxemia that may trigger epileptogenesis [19].
d) Venous congestion: Arterialization of venous outflow due to a high-flow state may result in impaired venous drainage that may result in seizures [27, 28].

A scoring system to predict the risk for seizures was established [23] taking into account the three strongest predictors—restriction of venous drainage, location of AVM, and a long pial-draining vein. Each risk factor was given 1 point, thus establishing a scoring system of 0–3 points. A score of 0 had 97 % sensitivity and 93 % negative predictive value whereas a score of 3 had 98 % specificity and 80 % positive predictive value for seizure development. Although radiographic risk factors have been well established, there are limited data available on seizure types and the risk of development of epilepsy in patients with AVMs. Osipov et al. described 92 of 328 patients with AVMs that presented with seizures. Complex partial seizures were identified in 22 %, focal seizures with secondary generalization in 12 %, and generalized tonic-clonic seizures in 65 % of patients [29]. Recently, a prospective population study by Josephson et al. found that patients who did not have a history of seizures and experienced a first unprovoked seizure at presentation or during the follow-up had a 58 % chance of developing epilepsy over 60 person-years of follow-up. Sixty-five percent of patients with AVMs were started on antiepileptic drugs (AEDs) following the incident seizure [3]. There is a paucity of data to suggest any change in risk of rupture of AVM after the occurrence of seizures and the relationship of a high-flow state with seizure occurrence. Salman et al. performed a population-based study to determine the risk for a first-ever seizure in patients with AVMs. They found that the 5-year risk for seizure development was higher (23 %, 95 % CI 9–37 %) in patients presenting with an intracranial hemorrhage secondary to the malformation and a focal neurological deficit as compared to those with incidentally discovered AVMs (8 %, 95 % CI 0–20 %). The increased incidence after intracranial hemorrhage is often attributable to the size and location of the hemorrhage [30].

Imaging

The diagnosis of AVMs is usually based on clinical grounds and supported by imaging studies. Noninvasive head imaging may confirm the presence of large and conspicuous AVMs. CT scan of the head may initially be normal if no evidence of dilated veins or calcification appears (Fig. 7.1). Imaging modalities such as specialized brain MRI, MR angiography, and MR venography are often employed to identify the underlying arteriovenous communication. Besides the location, MR studies assist in evaluating the cytoarchitectural changes associated with large AVMs such as gliosis and involution of adjacent parenchymal tissue (Fig. 7.2). High venous pressure and venous distension and distortion may lead to a mass effect on important structures such as the brain stem. Invasive vascular studies such as catheter angiography reveal more detailed information and provide pathway to the management [31–33]. The angioarchitectural analysis includes the study of various components of the AVMs (arteries, nidus, and veins). It also includes the vascular response to chronic arteriovenous shunting (arterial stenosis, associated aneurysms, venous stenosis, and ectasias) (Fig. 7.3).

The diagnosis of AVMs-associated seizures entails using sophisticated imaging techniques as well as electrophysiology to identify the epileptogenic zone. Routine EEG usually does not suffice due to its short duration and prolonged monitoring, or video EEG may be necessary to capture clinical as well as subclinical spells.

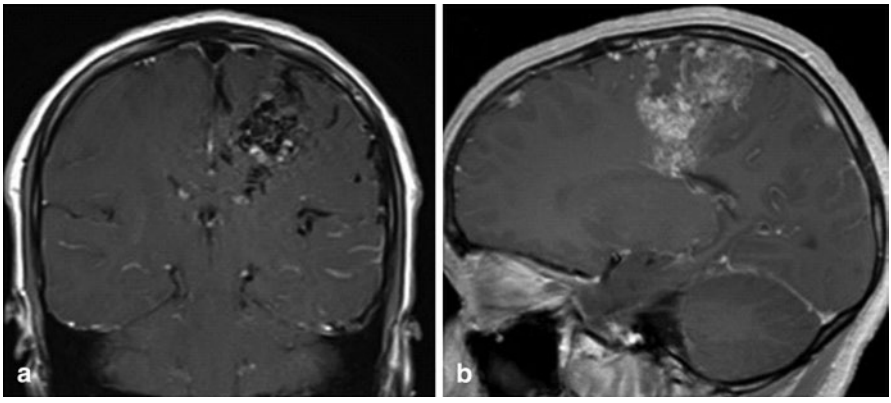

Fig. 7.1 CT scan of the head (**a**) showing dark flow voids in the left sylvian fissure in a young woman presented with headache and focal seizures affecting the language function. Cerebral angiography (**b**) shows a tangle of abnormal vessels supplied by arterial feeders and often drained by large dilated veins. (Case abstracted from: Neuroimaging in Neurology by Dr. David C. Preston, with permission)

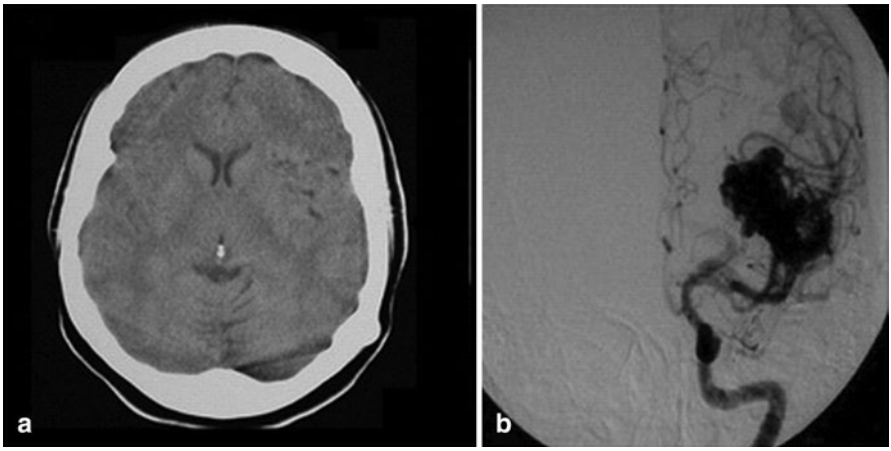

Fig. 7.2 T2-weighted coronal MRI (**a**) demonstrating a tangle of blood vessels in the left frontal lobe, consistent with an arteriovenous malformation. Sagittal post-gadolinium-enhanced MRI (**b**) demonstrating an enhancing nidus of blood vessels in the left frontal lobe

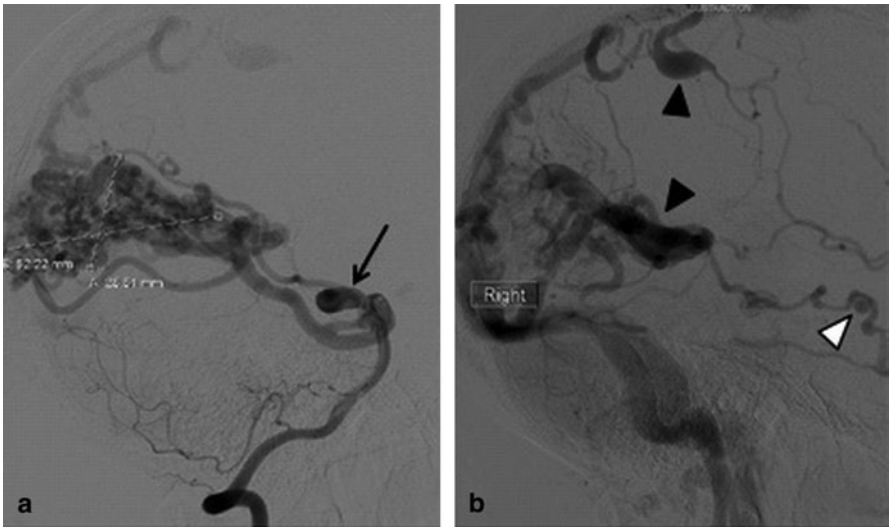

Fig. 7.3 Catheter angiography of the right vertebral artery (arterial phase) (**a**) showing a large posterior AVM with multiple arterial feeders and dysplastic basilar-tip aneurysm measuring 11 mm (*black arrow*). The venous phase of the same angiogram (**b**) shows large and dysplastic veins (*black arrow head*) and dysplastic venous aneurysm (*white arrow head*)

Treatment

Medical management of seizures secondary to AVMs involves utilizing one or more AED. Currently, there exist no treatment guidelines or recommendations for utilization of antiepileptic medications for seizures in AVMs. Medical intractability in epilepsy is defined as the failure of two antiepileptic drugs to achieve full seizure control and must necessitate a surgical evaluation [34]. The Spetzler–Martin grading system as highlighted previously has been used widely to classify AVMs into grades based on size, eloquence of adjacent brain, and pattern of venous drainage [9]; a higher grade confers greater surgical risk. Different treatment approaches have been utilized to target an AVM lesion. Most instances, multiple approaches are required to obliterate a lesion. Endovascular treatment includes embolization technology usually coupled with either surgical resection or radiosurgery. Data regarding seizure freedom following either of these treatment approaches are conflicting:

A) Surgical resection and seizure outcomes
   Piepgras et al. followed 110 of 280 patients with preoperative seizures secondary to AVMs for 2 years. The follow-up study revealed that 7% of patients died, and of the survivors, 83% were seizure-free while 17% had intermittent seizures [35]. In another study by Yeh et al., 54 patients with a supratentorial unruptured AVM were followed postoperatively [36, 37]. Heros et al. evaluated 153 patients that underwent complete surgical excision of acerebral AVM and were followed longitudinally for a mean period of 3.8 years. About 33% of these patients had a seizure at presentation, 8.2% of patients that did not have a seizure prior to surgery developed a postoperative seizure, and 7.1% developed late seizures that were medically managed. About 50% of those with history of preoperative seizures either improved or were seizure-free at follow-up [38]. In contrast, Murphy and colleagues found no difference in seizure frequency in patients that underwent surgical treatment of AVMs as compared to those who were managed medically [39].
B) Endovascular treatment and seizure outcomes
   Several endovascular approaches to AVM treatment have been established, but few studies addressed seizure outcomes following embolization. Lv et al. treated 109 patients with cerebral AVMs endovascularly. Complete embolization was achieved in four patients. Thirty of 109 patients (27.5%) experienced seizures before treatment. Seizure types were classified as generalized tonic-clonic seizures (56.7%), simple partial (20%), complex partial (3.3%) seizures, or partial seizures with secondary generalization (20%). Following endovascular treatment, seizure control over an unclear follow-up period was described as excellent in 21, good in 4, fair in 2, and poor in 3 patients. Eighteen patients required one embolization to achieve seizure freedom whereas others required multiple attempts at embolization [40].
C) Stereotactic radiosurgery and seizure outcomes
   Stereotactic radiosurgery holds promise for AVM treatment, and results pertaining to seizure outcomes have been uplifting as compared to other treatment techniques. Schauble and colleagues followed 65 patients with single or multiple

Table 7.2 Risk of seizure following medical (conservative) or surgical treatment

Treatment type	Monotherapy at follow-up	Polytherapy at follow-up	Therapy withdrawn	Two-year seizure-free	Five-year risk of first seizure following therapy
Medical ($n=21$)	57%	19%	19%	57%(95% CI 35–79)	26% (95% CI 2–50)
Surgical ($n=39$)[a]	56%	18%	18%	52% (95% CI 32–68)	35% (95% CI 25–45)

[a] Surgery including resection, embolization, radiosurgery, or combination
Seizure freedom in patients with incident seizure

seizures who underwent AVM radiosurgery for more than a year after surgery. Median follow-up period was 48 months. Fifty one percent of patients were observed to be seizure- and aura-free at 3 years. Factors associated with seizure freedom were a low (<4) Engel Seizure frequency score and small size of AVM [41]. However, studies have reported a delayed increase in seizure frequency in patients undergoing radiosurgery [42].

D) Multimodal approach and seizure outcome
Recently Josephson et al. [43] conducted the Scottish Intracranial Vascular Malformation Study (SIVMS) to prospectively evaluate and compare patients withcerebral AVMs that underwent conservative management or AVM treatment (surgery, endovascular, stereotactic, or multimodality). Of the 229 patients enrolled in the study, 44 (19%) presented with epileptic seizures at onset, 68% underwent AVM treatment, whereas 32% were managed conservatively. There was no difference demonstrated in the 5-year risk of first or recurrent seizures between the two groups, and seizure at onset did not confer any additional risk for the development of seizures in these patients. Table 7.2 summarizes the risk of seizure recurrence and seizure-free intervals for various treatment modalities employed in their study. The limitations of the above study included possible confounding factors due to nonrandomization of patients. Results of the Randomized Trial of Unruptured Brain Arteriovenous (ARUBA) Malformations are eagerly awaited to confirm the impact of AVM treatment on seizures and other outcomes [44, 45].

Prognosis

As highlighted earlier in this review, several clinical and imaging characteristics predispose patients with AVM to develop seizures. These include male sex, younger age, temporal location of nidus, nidus size >3 cm, and arterial feeders arising from the MCA to name a few [46]. Multiple or recurrent seizures can be a cause of significant morbidity in these patients. Only a handful of studies have attempted to quantify the risk for seizures and epilepsy in patients with AVMs. A population-based study in Scotland determined that the risk for a first ever seizure with an incidental AVM diagnoses was 8% (95% CI 0–20%) [30]. However, if patients

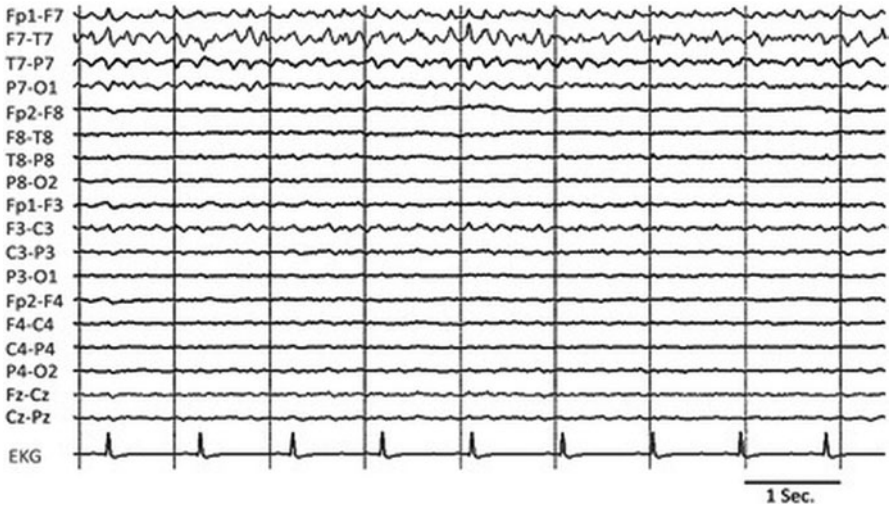

Fig. 7.4 Left temporal ictal discharges in a patient with focal epilepsy. Discharges are indistinguishable in temporal lobe AVM from other focal pathologies

present with a focal neurological deficit or intracranial hemorrhage, this risk increase to 23 % (95 % CI 9–37 %). In the absence of a focal neurological deficit and intracranial hemorrhage, the 5-year risk of epilepsy following a first seizure was 58 % (95 % CI 40–76 %). Adults that developed epilepsy secondary to AVM in the absence of structural hemorrhage or a clinical neurological deficit had a 45 % (95 % CI 20–70 %) chance of achieving 2-year seizure freedom on medical management. The study was however limited by small sample size, observer bias, and lack of randomization. Further research in the form of randomized controlled trials such as ARUBA is necessary to improve the precision of these estimates (Fig. 7.4).

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Chapter 8
Seizures in Cerebral Venous Sinus Thrombosis

Prachi Mehndiratta and Mohamad Koubeissi

Introduction

Cerebral venous sinus thrombosis (CVT) comprises 0.5–1 % of all stroke types [1]. It is a common cause of stroke in young adults and results from multiple predisposing causes. The International Study on Cerebral Venous and Dural Sinus Thrombosis (ISCVT) included the largest cohort of patients with CVT to date, and found that 78 % of patients were younger than 50 years of age [2, 3]. There is a paucity of population studies and stroke registries that include cases with CVT, making its true incidence difficult to ascertain.

Risk factors for CVT (Table 8.1) are categorized as genetic or acquired. Ferro et al. studied various risk factors of CVT in 624 patients [4]. They found that thrombophilia accounted for 34.1 % cases, malignancy 7.4 %, hematologic disorders 12 %, pregnancy 6.3 %, and puerperium 13.8 %. In 12.5 % of cases, no definite cause could be identified. Of these risk factors, pregnancy and puerperium result in transient pro-thrombotic states that can cause stroke [5]. About 2 % of strokes associated with pregnancy are secondary to CVT [6, 7]. Pregnancy induces several changes in hormones and blood-coagulant and anticoagulant factors resulting in an overall pro-thrombotic state. Following delivery, the procoagulant state may even worsen due to trauma, surgical risks following cesarean section, dehydration, and infections.

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_8

Table 8.1 Common risk factors for CVT

Genetic risk factors	Acquired risk factors
Factor V Leiden mutation and resistance to activated protein C	Puerperium
Antiphospholipid, anticardiolipin antibodies	Pregnancy
Antithrombin III gene mutation	Hematological conditions (anemia, polycythemia)
Protein C and protein S deficiency	Infection (central nervous system, ear, nose, throat)
Prothrombin gene mutation	Drugs (oral contraceptives, hormone replacement, steroids)
Hyperhomocystinemia	Malignancy (CNS, extra CNS solid tumors)
Other inherited thrombophilias	Miscellaneous: antiphospholipid antibody, nephrotic syndrome

CVT cerebral venous sinus thrombosis, *CNS* central nervous system

Clinical Presentation

Clinical manifestations of CVT result from impaired venous drainage and focal brain injury secondary to venous infarction. These factors obviously overlap, and clinical findings are often attributable to both. Headache is the most common symptom of increased intracranial pressure and occurs in up to 90 % of patients. It may present as a progressive dull pain or as a thunderclap headache [8–11]. Concomitant findings in up to 25 % of the patients include papilledema or other signs of increased intracranial pressure, such as a sixth nerve palsy [12]. A high index of suspicion for CVT is needed in patients with known risk factors, but insufficient clinical findings.

Focal neurological findings vary according to the location of CVT. Superior sagittal sinus thrombosis is the most common, and often presents with headache and papilledema. Bilateral cortical venous infarctions may cause visual field defects, weakness, and speech disturbances [13, 14]. Thalamic or basal ganglionic infarcts may occur with involvement of the deep cerebral veins such as the internal cerebral vein or the vein of Galen in about 16 % of patients (Fig. 8.1a–c). These patients classically present with depressed levels of consciousness and difficulty with upward gaze [13, 15]. In patients with involvement of the lateral sinuses such as the transverse and sigmoid, ear pain and headache are the most common presenting features.

Seizures occur in about 40 % of patients with CVT [4]. These may or may not secondarily generalize, and may occur early or later in the disease process. Seizures are most commonly seen in patients with superior sagittal sinus thrombosis or cortical vein thrombosis due to involvement of cortical gray matter [4, 29]. The incidence, risk factors, and treatment of epilepsy in CVT are discussed in detail later.

Certain clinical findings differentiate CVT from other cerebrovascular diseases. First, the occurrence of seizures in CVT is frequent. Second, CVT often results in bilateral hemispheric damage and bilateral motor signs. Third, CVT can present with slowly progressive symptoms that may account for delays in diagnosis.

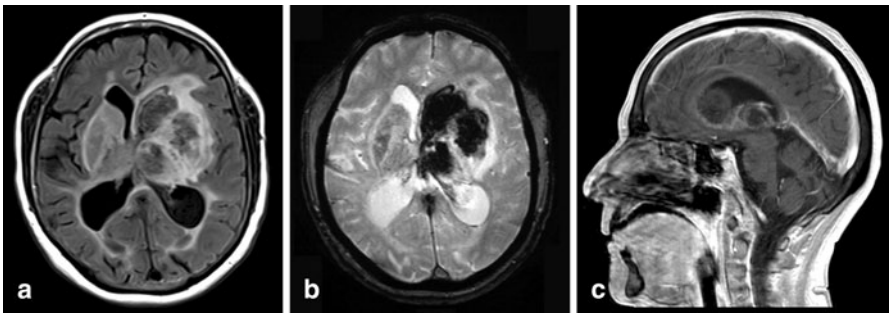

Fig. 8.1a–c This is a brain MRI of a 69-year-old woman who presented with a 2-day history of right-sided weakness and headaches. Initially, her brain CT did not demonstrate any abnormalities, but the patient's condition deteriorated rapidly over a few hours, with the development of altered mental status and worsening of right-sided weakness necessitating this MRI. **a** Axial FLAIR cut demonstrating bilateral deep thalamic venous hemorrhagic infarction with surrounding edema, **b** gradient echo showing hemorrhages within the left thalamic venous infarct, **c** sagittal cut after gadolinium injection demonstrating absent filling of inferior sagittal sinus and straight sinus consistent with venous sinus thrombosis

Diagnosis

The American Heart Association/American Stroke Association (AHA/ASA) published a Scientific Statement in 2011 to help streamline diagnosis and management of CVT [16]. Their recommendations regarding clinical and laboratory workup were as follows:

1. A thorough and complete metabolic workup must be performed in patients with suspected CVT. This includes complete blood count, basic metabolic panel, and coagulation studies.
2. Clinical history of prior thromboembolic events should be obtained. The use of oral contraceptives and underlying inflammatory conditions should be screened at initial presentation.
3. A normal D-dimer level should not prevent further evaluation in patients, where CVT is highly suspected [17, 18].
4. If initial imaging such as a non-contrast computed tomography (CT) of the brain demonstrates lobar intracerebral hemorrhage or hemorrhagic infarction not corresponding to a typical arterial territory, further imaging must be undertaken to visualize the cerebral venous system [19].
5. In patients with suspected idiopathic intracranial hypertension and in those with headache and atypical features, imaging of the venous system must be performed to exclude CVT [20].

Brain CT is a quick and easy neuroimaging test employed to screen patients with new-onset neurological signs and symptoms. However, brain CT without contrast is abnormal only in 30 % of patients with CVT [21]. Acute CVT may be identified on

a non-contrast CT as a hyperdense cortical vein or dural sinus [22]. A "delta sign" has been described on CT scans in patients with clot at the torcula or confluence of the venous sinuses [23, 24].

Magnetic resonance imaging (MRI) is superior to CT in identifying patients with CVT [25]. MRI assists not only in the diagnosis but also in staging the thrombus based on varying T1- and T2-weighted signals that result from evolution of the paramagnetic blood products within the thrombus. While diffusion-weighted and gradient-echo sequences of MRI assist in the diagnosis of hemorrhagic infarcts, the two-dimensional time-of-flight venogram or the contrast-enhanced venogram can directly visualize the site and extent of thrombosis. MR venogram is preferable to a CT venogram due to the lack of radiation exposure and risk of allergy to iodinated contrast [26, 27].

Cerebral Venous Sinus Thrombosis and Epilepsy

Seizures occur either before or soon after the diagnosis of CVT in 35–40 % of patients [28, 29]. In prospectively conducted population studies of all ages, seizures have been reported in 37 % adults, 48 % children, and 71 % newborns with CVT [30]. The ISCVT reported that 245 of 624 (39.3 %) patients experienced seizures, including 43 (6.9 %) early seizures within 2 weeks of diagnosis [31]. Of these subjects, 9.3 % had focal seizures without generalization, 19.7 % had generalized seizures from onset, and the remaining 10.3 % had both types.

Masuhr et al. reported seizures in 86 of 194 patients during hospitalization with CVT [32]: Twenty-one (24.4 %) presented with focal seizures without generalization and 65 (75.5 %) with secondary generalization. Seizures that occurred early (44.3 %) in the course of the disease (<2 weeks) were further studied. Multivariate logistic regression analyses identified intracranial hemorrhage, cortical vein thrombosis, and motor deficits as independent predictors of early seizures [32]. As expected, 12.8 % patients who developed status epilepticus required prolonged intensive care unit (ICU) stays and had greater mortality and morbidity compared to those who had fewer than 3 seizures.

In the Cerebral Venous Thrombosis Portuguese (VENOPORT) Collaborative Study Group [29], 91 patients with CVT were prospectively studied for the development of seizures. Of these, 31 (34 %) had early symptomatic seizures: 29 (31.9 %) as a presenting feature and two (2.1 %) after admission. Early symptomatic seizures were associated with sensory and motor deficits as well as an identifiable parenchymal lesion on CT or MRI. Late seizures occurred in patients with early symptomatic seizures and in those with hemorrhage or hemorrhagic infarcts on CT/MRI. Patients presenting with early seizures had a greater incidence of seizure recurrence within 2 weeks.

Pooled analyses of the VENOPORT [29], ISCVT [4], and other studies [32] confirm that focal motor deficits, cortical venous thrombosis, and supratentorial parenchymal lesions are associated with an increased risk of early seizures.

Treatment and/or prophylaxis are hence important clinical decisions that may require risk stratification of patients based on available literature.

Pregnancy and puerperal CVT have been associated with a very high percentage of seizures in some studies, but not others [7, 33]. Data regarding seizures associated with CVT in the pregnant or postpartum state are scarce. Possible confounders are young age and concurrence of preeclampsia. Thus, further studies are needed to determine the prevalence of seizures and CVT in this select population.

Treatment

Diagnosis and treatment of seizures in patients with CVT is in line with standard practice. Seizures necessitate brain imaging (CT or MRI) to rule out parenchymal hemorrhage if initial imaging is negative or has not been performed. Electroencephalography (EEG) is helpful in patients with altered mental status to rule out nonconvulsive seizures.

There are no studies regarding antiepileptic drug (AED) choices, dosage, or duration of therapy in patients with CVT. Existing studies such as the ISCVT [4] stratified patients according to two major risk factors that included seizures at onset (SAO) and the presence of a supratentorial lesion (STL). Patients were classified as those who received AEDs and those who did not. The risk of early seizures was found to be extremely low in those without STL and SAO, regardless of the use of AED prophylaxis. Contrary to the above finding, AED prophylaxis significantly decreased the risk of early seizures in those with STL and SAO. Based on existing data, AHA/ASA [16] recommended adopting the following strategies:

1. In patients with CVT and a single seizure with parenchymal lesion, early initiation of AEDs for a defined duration is recommended to prevent further seizures.
2. In patients with CVT and a single seizure without parenchymal lesion, early initiation of AEDs for a defined duration is probably recommended to prevent further seizures.
3. In the absence of seizures, the routine use of AEDs in patients with CVT is not recommended.

Prognosis

Seizures in CVT can result in systemic morbidity and death, although they have not been shown to be an independent predictor of death or disability [34, 35]. Data from prior case series have determined that 5–32 % of patients with CVT develop seizures within the first year of follow-up [36]. In the ISCVT cohort, 11 % patients developed late seizures, and 5 % developed post-CVT epilepsy, defined as the occurrence of > 1 late seizure. Late seizures were seen in patients who presented with

a hemorrhagic lesion on imaging, early seizures, and motor deficits. Treatment of seizures and prophylaxis hence need to be individualized according to clinical presentation and imaging data. Those with seizures at presentation, supratentorial parenchymal lesions, cortical vein thrombosis, and focal motor deficits must be treated promptly and prophylactically to prevent further morbidity. There is a need for further studies to determine AED type, duration of therapy, and long-term outcomes of patients with seizures in CVT.

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Chapter 9
Pediatric Stroke and Seizures

Ryan J. Felling, Alison Dloce and Adam L. Hartman

Introduction

The relationship between cerebrovascular disease and seizures is well known, dating back to 1864 when John Hughlings Jackson first reported on this observation [1]. Despite this recognized association, there is a paucity of data about seizure occurrence and outcomes in childhood stroke. Difficult questions are often posed to physicians caring for these children. *Will my child have epilepsy? How bad will it be? What treatment options are there?* This chapter aims to provide insights based on current literature on childhood stroke and seizures, focusing primarily on arterial ischemic stroke (AIS) in full-term neonates and children. By providing a comprehensive understanding, we hope to contribute to more rapid diagnosis, better management, and improved outcomes.

Overview of Pediatric Cerebrovascular Disease

The etiologic factors for pediatric stroke differ from those that result in adult ischemic stroke such as atherosclerosis, hypertension, and diabetes. Perinatal stroke is multifactorial, with both maternal and fetal factors contributing to the risk of

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_9

infarction. Childhood AIS can be associated with numerous conditions, some intrinsic to the cerebrovascular system as well as other cardiac and systemic disorders as summarized in Table 9.1. Hemorrhagic stroke in children is usually the result of structural vascular abnormalities such as arteriovenous malformations, cavernous malformations, and aneurysms, but can occasionally be associated with other conditions such as coagulopathies and cancer [7].

Cerebrovascular disease in children can result in significant neurologic morbidity. Nearly 20 % of children with AIS after the perinatal period can have a recurrent stroke within 5 years [8]. In a prospectively collected data set, > 70 % of survivors of AIS had neurologic deficits at the time of discharge, and more than half of the patients were treated with antiseizure medications during the acute hospitalization, emphasizing the important contribution of seizures in childhood stroke [9]. Data for outcomes at 1 year or longer also demonstrate that residual disabilities including both cognitive impairment and sensorimotor deficits persist in a majority of pediatric stroke patients [10–18]. A recent analysis of pediatric stroke survivors at very long follow-up also showed that a majority still exhibited neurologic deficits in adulthood, and while most were independent in their activities an important fraction of at least 20 % had moderate-to-severe deficits resulting in dependence on others in some aspect of their daily life [19].

Table 9.1 Selected conditions commonly associated with pediatric arterial ischemic stroke

Congenital heart disease
Vasculopathies
Moyamoya disease/syndrome
Traumatic arterial dissection
Connective tissue disorders
Radiation-induced vasculopathy
Hypercoagulable states
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Activated protein C resistance with or without factor V Leiden mutation
Prothrombin gene mutation G20210A
MTHFR mutations
Anticardiolipin antibodies and lupus anticoagulant
Sickle cell disease
Infection
Meningitis
Vasculitis
Intracranial tumors and hematologic malignancies
Genetic and metabolic disorders
Mitochondrial disease
Trisomy 21
Neurofibromatosis type 1

Seizures Associated with Pediatric Stroke

Seizures commonly occur in the context of pediatric stroke. Cerebrovascular disease is more commonly associated with seizures in infants and children than in adults. In fact, seizures are often the presenting symptom of stroke in this population, but they can occur later after stroke as well. The current knowledge of seizures in the acute setting of stroke in infants and children is discussed here.

Incidence of Seizures in Perinatal Stroke

One of the earliest reports of seizures associated with perinatal stroke identified cerebral infarction on autopsy in 29 preterm or term infants and found that convulsions were described in the records of five of these patients [20]. In the early 1980s, widespread use of diagnostic neuroimaging allowed for the antemortem diagnosis of perinatal stroke, and a number of case reports and small series quickly revealed a strong association between early-life seizures and perinatal cerebral infarction [21–23]. Clancy and colleagues drew attention to the fact that seizures may in fact be a heralding sign for ischemic stroke, as 8 of 11 neonates in their series exhibited seizures as the only localizing sign [24].

In a more recently published series of seven neonates with stroke, all presented with focal clonic seizures within the first 3 days of life with a mean presentation of 26 h [25]. Sreenan et al. described 46 term neonates with stroke, of whom 91 % exhibited clinical behaviors concerning for seizures [26]. These manifested as primarily apnea in 36 % and focal clonic movements in 38 %. Less frequent presentations were seizures described as generalized tonic–clonic and focal tonic seizures. The diagnosis of seizure in this population relied solely on clinical observations (i.e., the lack of continuous electroencephalography (EEG) recording means that many seizures may have been missed, and thus the burden of seizures likely was underestimated). Only 11 patients demonstrated epileptiform activity on EEG, and 16 demonstrated burst suppression. Low-voltage background was the most evident abnormality in 12 patients, and 7 had normal EEG recordings emphasizing the limitations of intermittent EEG recordings in these patients.

The data discussed above clearly indicate that seizures during the neonatal period should raise suspicion for stroke, but a subset of patients with perinatal stroke do not present with early seizures. In such cases, hemiparesis often does not become evident until several months of age as motor systems mature, and it has been estimated that up to 30 % of perinatal strokes may present in this delayed fashion and are then referred to as “presumed perinatal stroke” [27]. One study of an Estonian population of children formally assessed differences in the presentation of these two distinct groups [28]. They found that while seizures were commonly a presenting sign in children diagnosed with perinatal stroke, children who were retrospectively diagnosed later in life came to medical attention for hemiparesis far more often than for seizures. One possibility for this difference in presentation may be that there is

a specific and relatively narrow time window in which the neonatal brain is at risk for seizures due to acute focal infarction, a point that warrants further investigation as it may prove important in guiding treatment of these infants.

Early seizures in the acute setting of perinatal stroke are a well-defined occurrence, but late seizures and chronic epilepsy after perinatal stroke are less well understood. Variable rates of late seizures or chronic epilepsy have been reported, but many of these are provided by small case series and are difficult to reconcile because of small populations and variable periods of follow-up. An Australian registry with more than a decade of follow-up data for some patients found a cumulative incidence of epilepsy of 55% by 10 years of age, although only 15% had active epilepsy (defined as a seizure within the past year) after 10 years of follow-up [29]. Another study retrospectively reviewed the charts of 61 infants with perinatal stroke and at least 6 months of follow-up [30]. In this population, 67% were classified as having epilepsy at some point after discharge, but a majority of these patients were seizure free at the time of last follow-up raising questions about how chronic their epilepsy truly was. In their population, 9% of patients did not have any neonatal seizures but did develop later seizures. Specifically looking at patients with a delayed presentation of perinatal stroke, 38% still were diagnosed with epilepsy at some point during a median follow-up of 49 months [31]. This study contrasts to some extent with a more recent prospective study of perinatal stroke that estimated a seizure-freedom rate of 73% at 3 years [32].

Incidence of Seizures in Childhood Stroke

As in perinatal stroke, seizures are commonly associated with stroke during childhood. One population-based study found that children were 18 times more likely than adults to have a seizure within the first 24 h after stroke [33]. The larger studies of childhood stroke in the USA identified seizures in up to 50% of patients, most of which occurred within a day after presentation [34, 35]. In a Taiwanese cohort of childhood ischemic stroke, about 41% exhibited at least one seizure, and of these three quarters developed their seizures within 7 days after stroke [36].

Two groups have analyzed different prospectively collected US childhood stroke cohorts specifically for seizures as the presenting sign of stroke, each finding that more than 20% of patients actually presented with seizures [37, 38]. A Chinese study found that 52% of their childhood stroke patients presented with seizures, but this study was retrospective utilizing discharge diagnostic coding which may not be as accurate as prospectively collected samples [39]. Further analysis in one of these studies found that all patients presenting with seizures ultimately developed a hemiparesis, but seizures were the heralding sign and preceded any other symptoms [37].

Compared to the acute setting of stroke, there are few studies describing long-term epilepsy outcomes in children with stroke. Yang et al. found that 21 of their 73 children with stroke experienced recurrent seizures, but noted that 12 of these patients had only a few seizures. Of the remaining nine patients with chronic epilepsy,

five were well controlled on antiseizure medication, while four patients suffered from treatment-refractory epilepsy [35]. A more recent study similarly found about 29% of childhood stroke patients with poststroke epilepsy [40]. While this study included both perinatal stroke and childhood-onset stroke, there was no difference in the prevalence of epilepsy between the two different groups.

Risk Factors for Seizures in Pediatric Stroke

One could reasonably surmise that particular patient characteristics or stroke features may confer an increased risk for seizures, and this has to some extent been borne out in the pediatric literature. Although seizures are more common in pediatric stroke than adult stroke, the relationship of age within the pediatric population is less clear. Studies have found variable conclusions related to age, with one of the more significant studies identifying an age less than 3 years as significantly associated with seizure [37]. Some studies have variably seen increased incidence of seizures in patients less than 1 year of age [41] or greater than 1 year of age [42], and yet others have failed to identify any significant difference between age groups.

Most studies of pediatric stroke have not identified any difference in the occurrence of seizures in different subtypes of stroke (i.e., ischemic vs. hemorrhagic). Cortical involvement, however, is significantly associated with the occurrence of at least one seizure regardless of timing of onset (early or late) and also with recurrent seizures and epilepsy [35, 40]. Location, in terms of either supratentorial versus infratentorial or anterior versus posterior, was not associated with seizures being the presenting sign of stroke [37].

Use of these epidemiologic studies to define risk factors for seizures has significant limitations with the primary one being a lack of statistical power to identify differences. The conclusions of such studies must be analyzed with this in mind. Identifying risk factors for seizures should certainly be a priority, as it may impact the way we treat children with cerebrovascular disease [6]. For example, identifying specific characteristics of stroke patients who present with seizures may help us determine which patients presenting with seizures should be evaluated for stroke. Similarly, identifying patient or stroke characteristics that are predictive of recurrent seizures and epilepsy may help to better select patients that will require maintenance antiseizure medications. Achievement of these goals, however, will require assessment of larger multicenter populations using consistent criteria for the identification of such risk factors.

Seizure Semiology in Pediatric Stroke

Findings in children post stroke illustrate that stroke should be considered in any child presenting with new-onset seizures in conjunction with focal neurological deficits [37]. The type of seizure after stroke may depend on whether seizures occur

early versus late (defined previously). Gupta et al. reported that early poststroke seizures were more likely to be focal (57%) with generalized seizures (65%) more commonly seen in the late poststroke seizure group [43]. Contrarily, Horner and colleagues reported that early poststroke seizures were more likely to be generalized [44]. Others have found no significant difference in seizure type based on early versus late [36].

Generally, the semiology of seizures with lateralizing signs has been shown to be concordant with the infarcted hemisphere [31, 37]. In an evaluation of epilepsy in hemiplegic cerebral palsy due to perinatal AIS, the authors found that these children may have seizure characteristics similar to children with non-symptomatic epilepsies (e.g., benign myoclonic epilepsy of infancy, benign childhood epilepsy with centrotemporal spikes, benign childhood occipital epilepsy) [29]. Given the similar electrophysiological and clinical features of such self-limited epilepsies of childhood, a more conservative approach towards management could be employed with regard to drug choice and length of therapy and less urgency for surgical consideration.

Pathophysiology of Seizures in Pediatric Stroke

In discussing the epidemiology of seizures in pediatric stroke, a point has been made to distinguish between seizures occurring early after stroke and those occurring later because of a presumed difference in the underlying pathophysiology. The International League Against Epilepsy (ILAE) defines acute symptomatic seizures after a cerebrovascular accident as that which occurs within 7 days of stroke [45]. But studies have variably defined them as occurring within either 1 or 2 weeks after stroke. Nevertheless, the pediatric literature shares the hypothesis of the adult literature that early and late seizures represent distinct pathophysiologic mechanisms [35, 46, 47]. Acute or early seizures are thought to be secondary to metabolic derangements related to the stroke, while late seizures are more likely to be the sequelae of structural changes that have resulted in established epileptogenic foci. In several studies, the timing of initial seizure onset was related to the ultimate development of recurrent seizures or epilepsy [35, 40]. Here, we discuss the unique nature of the immature brain with respect to commonly proposed mechanisms for both acute seizures and later epileptogenesis.

Various factors contribute to the common occurrence of seizures in perinatal and childhood stroke (Fig. 9.1). It is important to remember that the brain already has a reduced seizure threshold early in life. This is in part due to the developmental regulation of neurotransmitter systems. γ-Aminobutyric acid (GABA)ergic transmission, the primary inhibitory system in the adult brain, is poorly developed early in life and can even be excitatory in the first days after birth [48, 49]. Coupled with the fact that glutamatergic receptors exhibit distinct subunit compositions that promote facilitated and sustained activation [50], the balance between excitation and inhibition in the immature brain is shifted strongly in favor of excitation. Furthermore, the

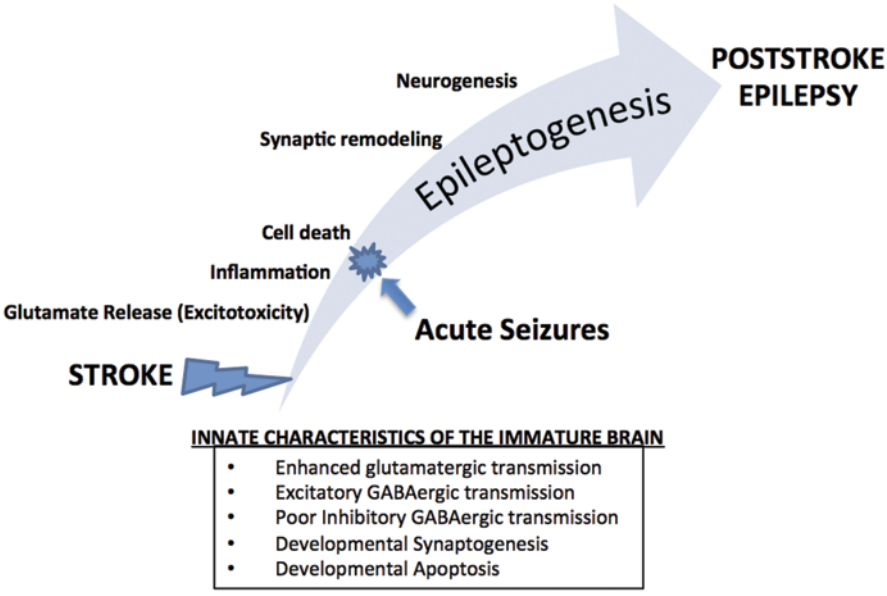

Fig. 9.1 The immature brain has an already low seizure threshold due to multiple factors of development. Pathological changes occurring after ischemic injury interact with these inherent characteristics to cause acute seizures and contribute to the process of epileptogenesis

synaptic pruning occurs during postnatal brain development, and children's brains may therefore have an overabundance of synapses [51]. This likely compounds the effects of the excitotoxic cascade that is initiated by ischemic injury, promoting both neuronal injury and seizures.

Glutamate is increased in the extracellular milieu after acute ischemia, and excitotoxicity has been associated with secondary neuronal injury and a permanent epileptiform phenotype in an in vitro model of stroke-induced epilepsy [52–54]. In an ischemic rat model, high extracellular potassium leading to neuronal depolarization was postulated to mediate postischemic seizures [55].

Simply having a lower seizure threshold may help to explain the frequency with which acute seizures occur after childhood stroke, but epileptogenesis (i.e., the predisposition to having recurrent, unprovoked seizures) following stroke is much more complicated. This process has been intensely investigated over the years, yet we still have no effective treatments to prevent the establishment of epileptic foci following stroke or other types of brain injury. A number of processes have been postulated to underlie epileptogenesis, many of which exhibit important differences between the immature and mature brain as reviewed by Rakhade and Jensen [56]. The most important consideration is that pediatric stroke occurs during a critical time period when neuronal networks are being established, and disruption of this process can result in aberrant networks that promote epileptogenesis.

"Plasticity" is a common term utilized when discussing recovery from stroke or other brain injury. This concept is invoked at many different levels and can re-

fer to molecular changes such as alterations of neurotransmitter and signaling systems, proliferation and differentiation of progenitor cells, or adaptation of surviving neural networks. It is widely accepted that the capacity for plasticity in the brain varies over the life span [57]. Immediate early genes expressed following stroke include Activity-regulated cytoskeleton-associated protein (Arc), brain-derived neurotrophic factor (*BDNF*), and others that have been implicated in synaptic reorganization and epileptogenesis [58–60]. Ischemic injury to the immature brain also can lead to increased neurogenesis and gliogenesis [61]. While these processes are normal components of brain development and may represent reparative strategies following injury, they also may contribute to the maladaptive consequence of aberrant structural changes that result in epileptogenesis.

Pediatric stroke is a unique entity that deserves its own study separate from adult stroke. The young or immature brain is markedly different from the aged brain in which adult stroke typically occurs. Children demonstrate different patterns of injury and, importantly, different patterns of recovery. The establishment of epileptic foci following injury is likely to be influenced by these factors; therefore, a better understanding of these processes may be helpful in understanding the differences in seizure occurrence following stroke in children and adults. Unfortunately, there is a paucity of data describing specific differences between stroke recovery in adults and children.

Electroclinical Manifestations in Pediatric Stroke

Role of Electroencephalography in Diagnosis

Neuroimaging is the most widely used modality in the early evaluation of stroke; however, EEG is an ancillary tool in the early evaluation of poorly defined poststroke focal neurologic symptoms, and both clinical and basic science data suggest that it may help with predicting neurologic recovery [62, 63]. In combination with MRI, an EEG also may be useful in distinguishing between a focal, structural, or vascular disturbance and a postictal paralysis in a patient presenting with a hemiparesis (i.e., a normal MRI combined with an EEG showing focal epileptiform discharges suggests the latter). Similar to other aspects of childhood stroke, there is a paucity of strong evidence to guide the use of EEG in the evaluation of these patients.

Generalized slowing, focal epileptiform discharges, and electrographic seizures on EEG are more likely to be seen in children with stroke who had a clinical seizure. Focal cortical dysfunction on interictal EEG has been associated with late poststroke seizures in children and a higher rate of poststroke epilepsy; however, this finding is not consistently seen in all studies [38]. Much of the adult literature reveals focal or diffuse slowing of background activity in those patients with seizure at the onset of stroke with approximately 16–23 % having interictal epileptiform discharges [64, 65]. Importantly, infrequent recurrence of seizures is reported. Adults with EEG detecting status epilepticus (SE) were often found to have fragments of periodic lateralized epileptiform discharges (PLEDs) interrupted by seizure activity.

This might suggest that antiseizure drugs are not necessary in stroke patients with single seizures; however, they may be appropriate in those with SE or PLEDs [65]. Detailed characterization of interictal EEG findings in pediatric stroke is lacking.

Seizure propagation in both the infarct core and the penumbra after stroke as well as epileptiform discharges such as PLEDs generated in the penumbra have been demonstrated in animal models [55]. PLEDs have been identified in adults with acute cortical lesions; however, subcortical lesions may also trigger this electrographic pattern [55, 66]. In a rat model, there was a significant association between the occurrence of PLEDs before nonconvulsive status (NCS) and prolonged NCS [55]. PLEDs detected in the early phase of stroke may be prognostic, as they typically are associated with a poor outcome and increased risk of seizures and status epilepticus [67]. Rat models have also demonstrated intermittent rhythmic delta activity (IRDA) in the setting of ischemic insult [55]. In the adult population, patients with frontal intermittent rhythmic delta activity (FIRDA) and diffuse slowing on the poststroke EEG had a higher risk of developing late poststroke seizures [68].

Continuous EEG monitoring is a tool often utilized in the adult population to analyze stroke evolution and predict clinical course. However, investigations on acute pediatric stroke and its associated electroclinical manifestations are scant. While EEG in the setting of acute pediatric AIS may have limited utility in predicting future epilepsy, for those patients with stroke who have altered mental status, it may be particularly helpful in evaluating for nonconvulsive status epilepticus (NCSE) [38]. NCSE in children has a known association with stroke [69]. Abend et al. found that 23% of children with clinically evident seizures after ischemic stroke also had nonconvulsive seizures detected on EEG. Importantly, however, only four of their 13 patients underwent continuous EEG monitoring. Of those that did, 75% demonstrated electrographic seizures without any clinical correlate [37]. Given that acute structural brain lesions such as infarction and nontraumatic hemorrhage are reported to be the most common etiologies of NCSE in children, continuous EEG monitoring may be of paramount importance in this population [69, 70]. Studies suggest that NCSE is typically detectable immediately or within 24 h of monitoring [38]. Unfortunately, we still lack data that definitively indicate that treating early seizures or NCSE results in better outcomes.

Role of EEG in Prognostication

Quantitative EEG (QEEG) as a marker for brain dysfunction post stroke in children has also not been studied. In a comprehensive review of the adult literature by Finnigan and Putten, it was determined that QEEG has "substantial value" in ischemic stroke. Reductions in delta power, delta/alpha power ratio (DAR), (delta + theta)/(alpha + beta) power ratio (DTABR), or brain symmetry index (BSI) during the acute ischemic stroke interval were generally associated with better functional outcomes. Notably, these QEEG changes were found to have higher predictive value than concurrent neurological scales and assessments, and they were detected even before changes in patients' neurological symptoms or upon repeat imaging [71].

QEEG parameters such as the alpha-to-delta ratio (ADR) have been evaluated in a rat model of ischemic stroke and found to be closely correlated with functional recovery suggesting this type of monitoring may be useful in predicting outcome [63].

EEG monitoring is a relatively inexpensive bedside diagnostic study that can detect specific patterns and QEEG changes in electrical brain activity after cerebral injury such as stroke. Although it can help identify specific patterns such as PLEDs, it is still unclear what these pathologic EEG rhythms and changes might portend, especially in children who have different neuronal maturity. With further investigation into the specific electroclinical manifestations in children post stroke, EEG monitoring may substantially aid in therapeutic decisions.

Treatment of Seizures in Pediatric Stroke

Given limited data on poststroke seizures and epilepsy in children, current management is broadly extrapolated from the larger volume of adult literature that incompletely addresses many questions related to pediatric therapy. Physicians are faced with making difficult therapeutic decisions, such as whether to treat an isolated seizure and what antiseizure medications to use. Moreover, the potential neuroprotective role of antiseizure medications versus their potential negative impact on stroke recovery must be considered.

Acute Seizure Management

There is evidence to suggest that acute brain injury and seizures work synergistically to worsen outcome by contributing to metabolic stress and exacerbating injury in affected neurons [72]. Experimental studies in laboratory animals advance this concept demonstrating that recurrent seizure-like activity in the setting of cerebral ischemia considerably increases infarct size and can preclude functional recovery. Treatment with certain antiseizure drugs, also considered neuroprotective, tempered these effects [73, 74]. In studies of both humans and rats, increased cerebral metabolism following seizures has been associated with an enhanced mismatch between an already compromised energy supply and demand ultimately leading to mitochondrial damage and possible irreversible cognitive and neurological deficits [72].

Although there is such experimental evidence promoting treatment with antiseizure therapy, determining which patients would benefit from prophylactic treatment is difficult. Even in the adult literature, there is insufficient evidence to reliably predict those who will have development of poststroke epilepsy. Data from Abend et al. suggest that children without seizure on presentation with AIS may not require prophylactic antiseizure therapy [37]. Given that early poststroke seizures, although common, tend to not recur, therapy with antiseizure medication could possibly be avoided. Conversely, late poststroke seizures may be a risk factor for poststroke epilepsy; therefore, these patients may warrant additional prophylactic therapy [64].

These concepts are bolstered by data suggesting that treatment of early seizures in the setting of traumatic brain injury does not impact the development of late seizures or epilepsy in that setting [75].

Given the known association of NCSE in children with acute structural brain lesions such as infarction and nontraumatic hemorrhage, antiseizure drug treatment should be considered in any child with altered mental status after stroke. Although these patients have electrographic seizures without overt motor manifestations, the possibility of long-term neurologic consequences should be kept in mind. In an in vivo rat model of focal brain ischemia-induced NCSE, there was a higher mortality rate within the 24-h recovery period in the presence of NCSE, and this was effectively reduced by 73 % with effective blockade of epileptic activity [72].

Similarly, studies have demonstrated that PLEDs contribute to local increases in metabolism for several days after termination of SE; therefore, they have potentially harmful implications [76]. Stroke subtype (i.e., ischemic vs. hemorrhagic) should potentially be considered when making therapeutic decisions. Although not statistically significant, in an animal study, brain hemorrhage was found to have a 3.5-fold increase in the number of NCS events and a 2.3-fold higher mortality rate (consistent with clinical findings of increased seizures in patients with intracranial hemorrhage when compared to ischemic stroke) [72]. Interestingly, high doses (twice the reported effective dose 50, ED50) of ethosuximide and gabapentin effectively attenuated the NCS activity and provided neuroprotective effects, compared to commonly used drugs for status, fosphenytoin and valproate.

Considering medication effect on neurological recovery is important. Animal studies have shown that certain antiseizure medications (benzodiazepine, phenytoin, and phenobarbital) may hinder recovery after stroke or other forms of focal brain injury [77–79]. There are few relevant human studies, and they are mostly in adults; however, results were consistent with laboratory studies suggesting that use of benzodiazepines, phenytoin, and phenobarbital should possibly be avoided during the poststroke recovery period. Although detrimental effects have been associated with the abovementioned drugs, other studies have denoted them as neuroprotectants [80–82]. There are no clinical data confirming these results; therefore, clear guidelines on treatment after stroke are still lacking.

Epilepsy Treatment

The limited studies in children post stroke suggest that refractory epilepsy occurs in approximately 5–7 % of patients [35, 83]. Although children tend to have better recovery of language and volitional movement after stroke presumably due to their brain plasticity [84], long-term neurological and cognitive sequelae remain a significant burden. It has been suggested that refractory epilepsy after stroke is the major predicting factor for poor functional outcome [85]. In a study by Scavarda et al., complete seizure control after periinsular hemispherotomy was obtained in 87.5 % of children who suffered an ischemic stroke [83]. Despite the remarkable epilepsy outcome, there was no noted improvement in cognitive outcome. The authors

postulate that this could be secondary to the long duration of refractory seizures (40 months) and a delay between seizure onset and surgery (63 months), although this finding is similar to other studies of hemispherectomy for other indications [86]. Given the ongoing brain development in childhood, early alternative and potentially aggressive therapies such as surgery should be considered to improve long-term outcome which includes not only seizure control but also cognitive and neuropsychological performance.

Prognosis

The American Academy of Neurology has published a practice recommendation that "emergent neuroimaging should be performed in a child of any age who exhibits a postictal focal deficit not resolving quickly" [87]. A more rapid diagnosis of stroke can hopefully be realized with the knowledge that many children with acute stroke present with seizures accompanied by focal deficits. Seizure at presentation has been a factor considered to predict a poor prognosis [88]. In young patients with a long life expectancy, the unpredictability of seizures and their potential negative effects on stroke recovery might have a profound influence on quality of life and disability.

There are reports that correlate seizures at presentation (or within the first 24 h of stroke onset) and a worse neurological outcome and mortality (including epilepsy) [39, 89]. Some of these investigations included multiple stroke subtypes and differentiating them is likely critically important. For example, children with cerebral infarction have been reported to have better survival; however, they experienced more residual disability than children with cerebral hemorrhage [90]. On the contrary, late poststroke (ischemic) seizures have been associated with a higher risk of poststroke epilepsy; however, they have not necessarily been reported to affect mortality [91].

There are data suggesting that children with epilepsy associated with stroke demonstrate more neurological problems than children without seizures [92]. Chronic neurological morbidity including sensorimotor, cognitive, and behavioral problems are expected in up to three quarters of children after stroke [9]. Although motor deficits are the most apparent disabilities, seizures, neurocognitive disabilities, and behavior problems play a crucial role in long-term outcome [93].

Conclusions

The limited data available on pediatric stroke in association with acute symptomatic seizures and poststroke epilepsy leave many physicians treating on the basis of personal discretion or via conclusions drawn from the adult literature. Despite more extensive studies in the adult population, conclusions are equivocal often providing

varying results depending on small sample sizes, multifarious designs, inconsistent definitions, different periods of follow-up, and discrepancies in seizure identification and classification. Future investigation in children addressing these variables is clearly needed. Improved characterization of risk factors for the development of poststroke epilepsy could help identify those children who could benefit from treatment to suppress epileptogenesis. With additional studies, guidelines on diagnosis (e.g., role of continuous EEG monitoring), and optimal management (e.g., prophylactic antiseizure medication and duration of treatment) will hopefully be formulated. Ongoing research into ancillary tests (e.g., topographic EEG mapping and quantitative EEG) may provide novel insights into pathophysiology thereby uniquely informing clinical management and perhaps predicting outcomes. A more multifaceted knowledge base should leave treating physicians better equipped to discuss childhood stroke and seizures, rational therapeutic options, and long-term outcomes.

Recommendations

- Children presenting with a seizure who have a new postictal focal neurologic deficit warrant evaluation for stroke including MRI with diffusion-weighted imaging, as CT can frequently miss early ischemic changes.
- Early poststroke seizure that does not recur may not warrant ongoing antiseizure medication; conversely, prophylactic therapy should be considered in those children with late poststroke seizures.
- Antiseizure drug therapy should be considered in any child with altered mental status after stroke, given known association with NCSE.
- Early alternative and aggressive therapies such as surgery should be considered to improve long-term outcome.

Priorities for Future Research

- Further definition of ways to identify individuals at risk for late seizures or chronic epilepsy using a combination of patient characteristics, stroke characteristics, and electroclinical findings
- Better understanding of how the basic mechanisms underlying plasticity in the immature brain are impacted by stroke
- Identification of therapeutic targets within the cascade of events following stroke that may inhibit the process of epileptogenesis

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Chapter 10
Medical Management of Seizures in Cerebrovascular Disorders

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Comorbidity of Epilepsy and Stroke

Cerebrovascular disorders are one of the most common identifiable causes of epilepsy, especially in the elderly [1]. Seizures after a stroke can occur early, within 7–14 days [2–6], or late, after 14 days [7–10]. Early seizures do not necessarily progress to epilepsy, but may result in increased morbidity and mortality. Reports vary considerably regarding the incidence of single seizures and epilepsy after a stroke. In adults younger than 50 years of age, 12.7% with ischemic strokes and 25.6% with intracranial hemorrhage developed epilepsy. This study used the more recent definition of epilepsy, which is the occurrence of a single seizure associated with an enduring condition associated with epilepsy. Another large study reported the occurrence of seizures in 168 (8.9%) of 1897 persons following an ischemic stroke and 28 (10.6%) of 265 after a hemorrhagic stroke [4]. Most seizures occurred within 2 years of the stroke.

A critical question addressing the issue of treatment is the occurrence of a second seizure after a single seizure. Unfortunately, this is a difficult question to answer from the literature. Many physicians initiate treatment with antiepileptic drugs (AEDs) following a single seizure because of the perception that there is a high risk of additional seizures in the context of stroke and seizure. Thus, reports of recurrent seizures are confounded with treatment, and it is difficult to establish the risk of epilepsy as defined by two or more unprovoked seizures. In one study by Arntz, 75% of persons with an ischemic stroke and 80% with a hemorrhagic stroke were

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_10

prescribed AEDs. Nevertheless, nine with ischemic and four with hemorrhagic had additional seizures during AED treatment.

There is a paucity of data regarding morbidity and mortality resulting from seizures after a stroke; however, at least one study, the Canadian Registry, has shown a higher mortality rate at 30 days (36.2%) and 1 year (48.6%). The presence of seizures may also lead to longer hospital stay and disability [11].

Management

Clear evidence to support the role of prophylactic seizure medications in patients with ischemic and hemorrhagic stroke is lacking. The Cochrane review published in 2010 (covering a period of almost 60 years) did not find any randomized controlled trials evaluating the role of AEDs in either primary or secondary prevention of seizures post stroke and highlighted that there was not enough evidence for the use of AEDs in either primary or secondary prevention of seizures post stroke [12]. A more recent Cochrane review for primary or secondary prevention of seizures after subarachnoid hemorrhage (SAH) did not show any evidence to support or oppose the use of these as prophylaxis [13].

Based on currently available evidence, most neurologists support not initiating an AED for prevention of poststroke seizures. However, if a seizure occurs in the setting of a stroke, an AED is often started due to high risk of recurrence due to the underlying structural lesion. The duration of treatment depends on many variables. The risk–benefit ratio must be evaluated carefully, particularly in the elderly patients. A careful review of all the other medications that may interact with the AED chosen (including lowering of seizure threshold) has to be done to avoid poor outcomes. In most cases, a single AED is sufficient to control poststroke seizures when treatment was required [8].

The choice of an AED depends on many variables as well. No randomized clinical trials have explored the evaluation of older versus newer AEDs in stroke-related epilepsy. However, the newer agents offer the advantage of fewer side effects, which makes them appropriate to use particularly in the elderly [14, 15, 35]. A few studies have shown gabapentin and lamotrigine to be effective in the treatment of late-onset poststroke seizures [16, 17].

Several studies have tried to review early versus late onset of seizures and the role of AEDs. In poststroke seizures, there has been no evidence that AEDs affect the course of recurrent seizures after treatment is discontinued. Some studies suggest that AED treatment can be discontinued in early seizures after a month if there are no further seizures noted [18, 19].

The effects of poststroke seizures on the outcome of stroke are unclear, with conflicting reports from different studies [20]. However, the factor with the most impact on stroke outcome is the underlying cause of stroke itself.

Choosing the Right AED

Stroke incidence rises with every age decade, and the bulk of stroke patients are over 60 years of age. Age-related physiologic changes directly impact the blood levels of AEDs by influencing protein binding and reduction in liver volume and blood flow. Because of the complexity of confounding variables and the lack of correlation between simple measures of liver function and drug metabolism, the effect of age on hepatic drug metabolism remains largely unknown [21]. Interestingly, genetic determinants of hepatic isoenzymes may be more important than age in determining a person's clearance [22].

Renal clearance is the major route of elimination for a number of newer AEDs. It is well known that an elderly person's renal capacity decreases by approximately 10% per decade [23]. However, there exists a substantial amount of individual variability because clearance is also highly dependent upon the patient's general state of health [24]. Thus, purely age-based dose recommendations may not be appropriate. Measurements of serum creatinine and estimations of creatinine clearance may be more helpful in determining the dose. Measurement of the actual AED concentration at steady state is the most accurate means to determine that the dose is appropriate. Despite the known effects of age-related physiologic changes on drug disposition and the widespread use of AEDs in the elderly, few studies on AED pharmacokinetics in the elderly have been published.

Variability of AED Levels over Time

Studies have shown that in compliant patients, the variability of AED concentrations over time is relatively small. Compliant clinic patients experienced variability of approximately 20–25% [25, 26]. Approximately 5–10% of this variability may be due to inter-laboratory variability in measurement of drug concentrations, although laboratories not following rigid quality control standards may experience even larger amounts of variability. The remainder of noted variability arises from day-to-day alterations in absorption, metabolism, or differences in AED manufacturing processes between brand and generic drugs. In nursing homes, however, some patients experienced a difference in concentration of two- to threefold from the lowest to the highest level [27].

Clinical Trials of AEDs in the Elderly

All major AEDs have a Food and Drug Administration (FDA) indication for use for the seizure types most likely to be encountered in the elderly. However, there are little data relating specifically to these drugs in the elderly, and those that are available have been limited to the community-dwelling elderly. One post hoc Veterans Administration (VA) cooperative study of carbamazepine and valproate found that elderly patients often had seizure control associated with lower AED levels than

those seen in younger subjects. Notably, these elderly patients also experienced side effects at lower levels compared with those seen in younger subjects [28].

A multicenter, double-blind, randomized comparison between lamotrigine and carbamazepine in newly diagnosed epileptic elderly patients (mean = 77 years of age) in the UK showed that the main difference between the two groups was the rate of drop out due to adverse events, with lamotrigine incurring an 18 % dropout rate compared to that of carbamazepine which incurred a 42 % dropout rate [29]. The VA Cooperative Study #428, an 18-center, parallel, double-blind trial on the use of gabapentin, lamotrigine, and carbamazepine in patients ≥ 60 years of age found that drug efficacy did not differ, but the main finding favoring the two newer AEDs was better tolerability than carbamazepine [30].

Choosing AEDs for the Elderly

At the present time, there are little data regarding the clinical use of AEDs in the elderly. The paucity of information makes it very difficult to recommend specific AEDs with any confidence that outcomes will be optimal. A drug that is optimal for the elderly healthy with only epilepsy may not be appropriate for elderly with multiple medical problems or the frail elderly.

Phenytoin

Phenytoin is effective for localization-related epilepsies, and thus has an efficacy profile appropriate for the elderly. Evidence for this can be gathered from a VA cooperative study that included elderly patients that found phenytoin to be as effective as carbamazepine, phenobarbital, and primidone, but that phenytoin and carbamazepine were better tolerated [31]. Phenytoin has a narrow therapeutic range, is approximately 90 % bound to serum albumin, and undergoes saturable metabolism, which has the effect of producing nonlinear changes in serum concentrations when the dose is changed or absorption is altered. Clinical studies in elderly patients have shown decrease in phenytoin binding to albumin and increase in free fraction. A recent study suggested that metabolism does not decrease greatly with age in healthy elderly. Using stable-labeled (nonradioactive) phenytoin to very precisely measure the phenytoin clearance, one study found that advancing age was not as much of a factor as had been previously reported [32]. A range of 5–15 mg/L total may be more appropriate as a therapeutic range for the elderly due to abnormal protein binding [33].

Phenytoin has many drug–drug interactions and should be used cautiously in elderly patients receiving other medications. There is also some indication that selective serotonin reuptake inhibitor (SSRI) antidepressants may inhibit the cytochrome 2C family of P450 enzymes responsible for metabolizing phenytoin. Fluoxetine and norfluoxetine are more potent inhibitors of this enzyme, followed by sertraline and paroxetine. The latter two SSRI antidepressants may prove to be a safer choice in

the elderly. Coumadin also has a very complicated interaction with phenytoin, and often doses of both need to be manipulated.

Phenytoin is also known to be a mild blocker of cardiac conduction, and should be used cautiously in persons with conduction defects, especially heart blocks. Phenytoin is the least expensive major AED, but because of its issues that may lead to complications, its global cost may be greater than the cost of newer AEDs.

Carbamazepine

Carbamazepine is effective for localization-related epilepsies, and thus has an efficacy profile appropriate for the elderly. Evidence from two large VA cooperative studies showed it to be as effective as phenytoin, phenobarbital, primidone, and valproate, but better tolerated than the latter three [31, 34]. Two studies of new-onset epilepsy in the community-dwelling elderly found it to be as effective as lamotrigine, but noted that it had a higher incidence of side effects [29, 30].

The apparent clearance of carbamazepine has been reported to be 20–40 % lower in the elderly as compared to adults [26, 35, 36]. Carbamazepine has some significant drug–drug interactions with medications that inhibit the cytochrome P450 enzyme, CYP3A4. Among the inhibitors are erythromycin, fluoxetine, ketoconazole, propoxyphene (Darvon), and cimetidine (Tagamet). At least one food (grapefruit juice) has been identified to interact with carbamazepine, causing increase in its serum concentrations. Elderly healthy patients will need to be cautioned about these interactions, and should be instructed to inform the physician whenever they are beginning a new medication, including any over-the-counter medications. A major concern with carbamazepine is its effect on sodium levels. The hyponatremia associated with carbamazepine is more pronounced as a person becomes older [37]. This may become more problematic if a person is on a salt restriction diet or a diuretic. Carbamazepine is also known to affect cardiac rhythms, and should be used cautiously, if at all, in persons with rhythm disturbances.

Phenobarbital

Although phenobarbital is the least expensive of all AEDs, its side-effect profile, which includes worsening of cognition and depression, makes it an undesirable drug for the elderly, especially in the nursing home setting where declines in cognition are already present.

Valproic Acid

Only a few studies have compared the pharmacokinetics of valproic acid in young and old patients [38, 39]. Total valproic acid clearances are similar in young and elderly individuals; however, unbound clearance is higher in the elderly [40].

Much like phenytoin, valproic acid is associated with reduced protein binding and unbound clearance in the elderly. Because of its effects on mood stabilization, it may be especially appropriate for elderly patients with a need for this effect.

Gabapentin

Gabapentin is effective for localization-related epilepsies, and has an efficacy profile appropriate for the elderly. Gabapentin is not metabolized by the liver, but rather renally excreted; therefore, there are no drug–drug interactions [41].There is, however, a reduction of renal function that correlates with advancing age, so doses may need to be adjusted. Because gabapentin is effective in treating neuralgic pain, it may be additionally beneficial for someone suffering from both epilepsy and pain. The VA Cooperative Study #428 compared carbamazepine with gabapentin and lamotrigine. Efficacies were similar but withdrawal related to side effects was highest for carbamazepine [30].

Lamotrigine

Lamotrigine is effective for localization-related epilepsies, and has an efficacy profile appropriate for the elderly. However, very few studies regarding lamotrigine and its effects on the elderly have been published. Lamotrigine is primarily metabolized by the liver using the glucuronidation pathway, which, unlike the P450 system, is thought to be less affected by age [42]. Data from a population pharmacokinetic study of 163 epilepsy patients, which only included 30 subjects greater than 65 years of age, 10 subjects between 70 and 76 years of age and no subjects from the *old-old* age group, showed that age did not affect lamotrigine apparent clearance [43]. Based on a study of 150 elderly subjects, the dropout rate due to adverse events was lower with lamotrigine (18 %) than with carbamazepine (42 %). The difference was attributable to the finding that lamotrigine subjects had fewer rashes (lamotrigine 3 %, carbamazepine 19 %) and fewer complaints of somnolence (lamotrigine 12 %, carbamazepine 29 %) [29]. Elderly community-dwelling epilepsy patients aged 59–92 years from the VA Cooperative Study #428 showed that lamotrigine apparent clearance can be effected by blood urea nitrogen and serum creatinine ratio, weight, and phenytoin use [44].

Levetiracetam

Levetiracetam has been approved as an adjunctive therapy for partial-onset seizures in adults. Levetiracetam is extremely water soluble, which allows for rapid and complete absorption after oral administration. Levetiracetam is not metabolized by the liver, and thus is free of nonlinear elimination kinetics, auto-induction kinetics, and drug–drug interactions. Lack of protein binding (< 10 %) also avoids the

problems of displacing highly protein-bound drugs and the monitoring of unbound concentrations. Also, lack of drug interactions would make it useful for treating elderly epilepsy patients, particularly those patients who have other illnesses and are taking other medications [45]. Notably, the manufacturer reports a decrease of 38% in total body clearance and an increased half-life up to 2.5 h longer in elderly subjects (age 61–88 years) who exhibited creatinine clearances ranging from 30 to 74 mL/min. However, doses do need to be adjusted depending on the renal function of the patient as measured by serum creatinine and levetiracetam concentrations [46].

One prospective phase 4 study indicates a favorable efficacy profile in the elderly [47]. Levetiracetam also appears to have a favorable safety profile. It was initially studied as a potential agent for treating cognitive disorders in the elderly, and thus a considerable amount of data regarding its tolerability in this age group is available. Analysis of 3252 elderly persons involved in studies of levetiracetam for epilepsy and other conditions demonstrated that levetiracetam was well tolerated by the elderly [48] .

Oxcarbazepine

Oxcarbazepine appears to have a more powerful effect on sodium balance than carbamazepine, and this effect has been shown to increase with age resulting in more pronounced hyponatremia in this age group [37]. This effect may make it a particularly problematic AED in the elderly who may likely be on antihypertensive agents and other drugs that can alter sodium balance.

Pregabalin

Pregabalin is related to gabapentin but is more potent, with doses of only one fifth those of gabapentin needed for therapeutic effect. Its absorption also appears to be more predictable because of the lower amounts transported across the intestinal system. Although it may prove to be a favorable AED for the elderly, its cost and lack of experimental and clinical data may limit its use.

Topiramate

Topiramate is effective for localization-related epilepsies, and thus has an efficacy profile appropriate for the elderly. Topiramate is approximately 20% bound to serum proteins and is both metabolized by the liver and excreted unchanged in the urine. The enzymes involved in topiramate's metabolism have not been identified; however, the cytochrome P450 system may be involved. Topiramate clearance may decrease with age, causing higher than expected serum concentrations with doses that are used in younger adults. Topiramate does have effects on cognitive

functioning, especially at higher levels. However, it is not known if the elderly will be more sensitive to this problem.

Zonisamide

Zonisamide is effective for localization-related epilepsies [49]. Protein binding is approximately 40 % and its major elimination pathway is hepatic as a substrate of CYP3A4. It may thus have interactions with other drugs using this pathway. In addition to the usual side effects of AEDs of somnolence and dizziness, zonisamide may be associated with weight loss. It has an association with the development of renal calculi in approximately 1–2 % of persons during chronic use [50].

Drug Interactions with Non-AEDs

Co-medications are frequently used by elderly patients. Many concomitant medications taken by elderly patients can alter the absorption, distribution, and metabolism of AEDs, thereby increasing the risk of toxicity or therapeutic failure.

Calcium-containing antacids and sucralfate reduce the absorption of phenytoin [51, 52].The absorption of phenytoin, carbamazepine, and valproate may be reduced significantly by oral antineoplastic drugs that damage gastrointestinal cells [53, 54]. In addition, phenytoin concentrations may be lowered by intravenously administered antineoplastic agents [53, 54]. The use of folic acid for treatment of megaloblastic anemia may decrease serum concentrations of phenytoin and enteral feedings can also lower serum concentrations in patients receiving orally administered phenytoin [55].

Many drugs displace AEDs from plasma proteins, an effect that is especially serious when the interacting drug also inhibits the metabolism of the displaced drug; this occurs when valproate interacts with phenytoin. Several drugs used on a short-term basis (including propoxyphene and erythromycin) or as a maintenance therapy (such as cimetidine, diltiazem, fluoxetine, and verapamil) significantly inhibit the metabolism of one or more AEDs that are metabolized by the P450 system. Certain agents can induce the P450 system or other enzymes, causing an increase in drug metabolism. The most commonly prescribed inducers of drug metabolism are phenytoin, phenobarbital, carbamazepine, and primidone. Ethanol, when used chronically, also induces drug metabolism [56].

The interaction between antipsychotic drugs and AEDs is complex. Hepatic metabolism of certain antipsychotics such as haloperidol can be increased by carbamazepine, resulting in diminished psychotropic response. Antipsychotic medications, especially chlorpromazine, promazine, trifluoperazine, and perphenazine, can reduce the threshold for seizures, and the risk of seizure is directly proportional to the total number of psychotropic medications being taken, their doses, any abrupt increases in doses, and the presence of organized brain pathology [57]. The epileptic patient taking antipsychotic drugs may need a higher dose of antiepileptic

medication to control seizures. In contrast, central nervous system depressants are likely to lower the maximum dose of AEDs that can be administered before toxic symptoms occur [58–60].

Compliance

Adherence to a prescribed regimen (compliance) is a challenge in the elderly due to multiple medications, memory problems, and visual issues. In general, twice-daily dosing is preferable. In long-term care facilities, drug adherence may be less of an issue than with community-dwelling elderly patients; however, reductions in staff and time spent on the multiple administration of medicines may help to reduce errors and cost [61–69].

Summary

Seizures after a stroke are not uncommon, and early recognition and appropriate management can lead to reduction in morbidity and mortality as well as contribute to reducing functional restrictions. This is particularly important in the elderly, who may have other comorbidities which result in delayed diagnosis, especially if nonconvulsive status epilepticus is present. Although there is no role of primary prevention of seizures after stroke, AED is often introduced after a seizure. The duration and choice of agent have to be carefully determined according to patient profile. As the care of both stroke and seizures continues to improve, better guidelines may emerge in the future to evaluate, manage, and prevent further morbidity and mortality in those patients with poststroke seizures. At the present time, management of seizures in the elderly is more an art than a science, and more studies are needed.

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Index

M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9