Epidemiology and etiology of pediatric stroke

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Abstract. Stroke may be an underestimated disease in children and adolescents. Several studies report an annual incidence as high as for brain tumors: 2–13 children for arterial ischemic, 1–5 for hemorrhagic stroke and 0.67/100,000 children for cerebral venous thrombosis. Recurrence of stroke ranges from 10–20% and depends on the underlying risk factors. Genetic predisposition underlying diseases and risk factors can often not be separated very precisely. The most prominent risk factors are vasculopathies and congenital heart disease, sickle cell anemia, coagulopathies, metabolic disorders and infections. Disorders in lipometabolism and genetic predisposition are now known to play also a role in the pathogenesis of pediatric stroke. A distinct stroke etiology can be determined only in a minority of children. However, most of them (> 80%) have more than one risk factor. The purpose of this review is to describe the epidemiology, risk factors, and etiologies of pediatric stroke in order to give rationales for understanding clinical symptoms and treatment decisions.

Keywords: Stroke, epidemiology, etiology, pediatric

1. Introduction

Pediatric stroke is becoming increasingly recognized as an important cause of morbidity and disability in childhood. It is among the top 10 causes of child mortality, and the incidences reported in several studies are as high as those for brain tumors. Research in adults has expanded our knowledge of pathophysiology, clinical course and treatment of stroke. In the last 10 to 15 years several groups of pediatric neurologists published their results on various aspects of stroke in children [1–9]. It is now known that pediatric stroke differs in many ways from adult stroke, is caused by heterogeneous diseases and can be an arterial ischemic stroke (AIS), a hemorrhagic stroke or a cerebral venous thrombosis (CVT).

The purpose of this review is to describe the epidemiology, risk factors, and etiologies of pediatric stroke in order to give rationales for understanding clinical symptoms and treatment decisions.

2. Incidence and recurrence of strokes

2.1. AIS

AIS is characterized as a sudden-onset, focal neurologic deficit resulting from irreversible ischemic damage to the brain parenchyma in a known arterial vascular distribution occurring between 30 days and 18 years of age. Annual incidence of AIS ranges from 2–13/100,000 children for ischemic stroke in North America and Europe [1–4,8,10,11] with a peak in the first years of life [2,4]. Fullerton states that stroke occurs more often in children and adults living in the southeastern states of the USA ("stroke belt"), where the relative risk for death due to stroke was significantly elevated as compared to that of children living in other states [12]. The authors conclude that risk factors applicable for both age groups – children and adults – should...
be considered a common explanation for this disease, such as various incidences of genetic disease, a different genetically determined susceptibility for stroke [13] or various environmental influences.

Recurrence of stroke is a serious problem in children and depends on the underlying risk factors. Two large studies describe a 5-year cumulative recurrence rate of approximately 15% to 20% for stroke, and of 25% [14] to 40% [15] for any cerebrovascular event (stroke or transient ischemic attack) [14,15]. Most recurrences occur 6 to 9 months after the first event: children with abnormal vascular imaging had a greater risk: two-thirds of those had at least one-second stroke, whereas none of the children with a normal cerebrovascular bed had a recurrent stroke [14].

2.2. Hemorrhagic stroke

Intracerebral hemorrhage is diagnosed from clinical symptoms and examination findings on computed tomography or magnetic resonance imaging scans. As described previously, hemorrhagic stroke occurs less often than does AIS, the ratio being about 1:2. The incidence is reported to range from 1 to 5 cases per 100,000 children per year [1,4,7,8,10,11]. Only a minority of stroke studies in childhood and no recent review investigate or describe hemorrhagic stroke [16,17]. Consequently, data about this type of stroke are rare.

In children with a traumatic hemorrhage, the overall 5-year cumulative recurrence rate for spontaneous hemorrhage is 10% at a median of 3 months. Two-thirds of the recurrences were within the first 6 months. Children with structural and medical etiologies have a 5-year recurrence rate of 13%, while children with undetermined etiology have no recurrences. These data demonstrate the importance of complete diagnostic evaluation when counseling patients and parents, because normal vascular imaging is the major factor determining positive prognosis [8].

2.3. CVT

The estimated incidence is reported to be 0.67/100,000 children per year, but might be higher due to difficulties in diagnosing and the lack of published studies [9,18–21]. The spectrum of risk factors and clinical presentation again is wide and the outcome poorer than in adults [19,20]. Predisposing conditions range from trauma, surgery or central venous lines as well as infection, tumor, drugs (asparaginase, contraceptives, nicotine) to obesity and prolonged bed rest [18,20].

The recurrence rate for a second CVT is 3% [20]. Two-thirds will happen within 6 months after the initial stroke. A recurrent venous thrombosis independent of localization occurred mainly in patients who were older than 2 years of age at the first event, who had no anticoagulation therapy and who showed heterozygosity for G201210A mutation in factor II [20].

In general, recurrence rates for strokes, whether as AIS, hemorrhagic stroke or CVT, as cited in the above studies, are data provided by retrospective studies. Therefore, it is essential to point out that these data – recurrence rate of < 5% for CVT and up to 40% for AIS - do not reflect the natural history of the disease, but rather the clinical course despite adequate interventions and medical treatment.

3. Risk factors and etiology

Risk factors, underlying diseases and genetic predisposition cannot be viewed separately with any great accuracy, and most children with stroke will have more than one risk factor. In approximately half of stroke children, a presumed etiology can be determined. However, most children have more than one risk factor [1–5,10].

For AIS the predominant risk factors are congenital heart disease [1–4], vascular abnormality [5,22], prothrombotic [23–27] and metabolic disorders [28] and infections [6,29] (Table 1).

3.1. Vasculopathy/cerebrovascular disease

The largest prospective study investigating predictors for AIS included 667 children [22]. Of 525 children with known vascular imaging results, 53% had arteriopathy. The most common forms were focal arteriopathy (25%), moyamoya syndrome (22%) and arterial dissection (20%). The etiology of isolated large vessel stenosis often remains unknown; the lesions can be congenital, like localized vascular hypoplasia associated with congenital heart defects or acquired due to infections like varicella, where the risk for AIS is threefold increased in the first year after an infection [2,29,30].

Predictors of arteriopathy include early school age (5 to 9 years), recent upper respiratory infection and, not surprisingly, sickle cell disease. A congenital structural heart disease is associated with abnormalities of the cerebral arteries in one-third of these children, for
which reason cerebral vascular imaging continues to be indicated in these children after suffering a stroke [22].

Risk factors for hemorrhagic stroke (Table 2) are mainly structural lesions such as vascular malformations (aneurysm, arteriovenous and cavernous malformation) or tumor in around 50% and medical causes such as thrombocytopenia, hypertension, hemophilia, leukemia, drug abuse or sickle cell anemia in 10% of these children [4,6–8]. An undetermined etiology was diagnosed in 20% of hemorrhages [3,4,6–8]. However most of these children had no vascular imaging and were therefore of ‘idiopathic’ origin [8]. Trauma was a risk factor for hemorrhagic stroke in 25% of the children [8].

### 3.2. Genetics

Genetic abnormalities have important implications for stroke, its recurrence and therapeutic options. Certain chromosomal (Down syndrome) and single gene diseases (sickle cell disease, homocysteinuria) are risk factors for all kinds of stroke. Two single nucleotide polymorphisms on chromosome 12p13 in a genome-wide association study are linked to a higher susceptibility for stroke [13]. All groups of risk factors cited below (prothrombotic abnormalities, metabolic disease, lipid disorders) are also predominantly genetically based diseases.

### 4. Prothrombotic abnormalities

The best-investigated group of risk factors for pediatric stroke is prothrombotic abnormalities. In recent papers authors agree that genetic prothrombotic mutations are a prominent risk factor for all kinds of stroke in childhood age [16,17]. The most consistent associations have been described for factor V Leiden [25], Factor II [23,26], prothrombin mutations [24] and plasminogen activator inhibitor-1 genotype 4G/4G [23,31]. Activated protein C resistance, anticardiolipin antibodies, and protein S and C deficiency may also play a role [2,16,17]. Prothrombotic risk factors seem to be more common in CVT than in AIS: 60% [18,20] vs. 30% [2,23,32,33]. Testing for congenital thrombophilia should be systematic, even when there is a known cause for stroke, because almost all patients have more than one risk factor [20,16].

### 5. Disorders in lipometabolism

From adult studies, it is evident that cholesterol, low-density lipoproteins and lipoprotein (a) are the most
predominant overall risk factors for stroke [34]. Measurement of these variables in children will become more important in future as the prevalence of metabolic syndrome, obesity and diabetes mellitus type 1 increases.

A limited number of studies reported an odds ratio of > 7 for stroke and its recurrence in children with an elevated lipoprotein (a) level > 30 mg/dL [23, 24, 27]. The prevalence of pathological lipids in children may be greater than expected and greater than that of prothrombotic abnormalities [2, 23, 26]. A retrospective study describes in > 80% of children a least one pathological lipid measure and diagnoses a new lipid disease in four out of 22 children: hyperlipoproteinemia type II a Fredrickson in two, alpha-lipoproteinemia and pro-beta-lipoproteinemia in one child each [10]. These results underscore the importance of screening programs for high-density lipoproteins and triglycerides for all children, like that in Austria (Gesundheitspass für Jugendliche). Screening should be done no earlier than at age 2 years and no later than at age 10 years. If the screening outcome is within the age-related reference range, the patient should be retested in 3 to 5 years [34].

6. Metabolic disorders

Methylene tetrahydrofolate reductase mutation is associated with hyperhomocysteinemia. Some studies demonstrate no association [35], while others state that the risk for stroke is quadrupled if homocysteine exceeds the 95th age-related percentile [6, 26, 28]. The most recent study did not reveal any relationship between methylene tetrahydrofolate reductase genotype, hyperhomocysteinemia and childhood stroke [35], and the rationale for folic acid and vitamin B treatment remains unproven, because it is known that adult stroke patients did not benefit from homocysteine reduction [36].

Metabolic disease such as organic acidemia, mitochondrial disease, urea cycle or lysosomal disorders can manifest as stroke with imaging abnormalities in an atypical vascular distribution. They begin unspectacularly with stroke-like episodes accompanied by intermittent neurological signs and continue to a clinical state with persisting neurological deficits. Typical examples are MELAS or Fabry disease [21].

Arginine deficiency, perhaps genetically determined, depresses nitric oxide levels and results in failure of vasodilation, which may contribute to the pathogenesis of stroke [37].

Other diseases associated with an increased risk for stroke are iron deficiency [38], Ehlers-Danlos syndrome, hereditary telangiectasia, polycystic kidney disease and neurofibromatosis [21].

7. Conclusions

Several limitations on the incidence studies cited above have to be discussed; these studies are retrospective single-center studies, describe multiple risk factors, report mainly on AIS, and do often not include CVT, transient ischemic attack or stroke-like episodes. Some studies include trauma patients, despite the fact that these patients have a different pathophysiology, treatment and outcome.

Retrospective epidemiological studies are inaccurate [39] and may detect secondary effects and not etiological causes. Radiology-based searches increase the incidence of stroke when compared to an ICD-9 based search [11]. Re-evaluation of children with stroke has the great advantages of diagnosing new risk factors with therapeutic implications (e.g. lipid status) [19] and searching for new genetic polymorphisms that can explain, at least in part, the susceptibility for a stroke event [13].

Studies using data prospectively collected from a registry show an incidence of up to 13/100,000 for all kinds of stroke [2, 4, 22] and 1.5–8/100,000 for AIS [2, 4]. A distinct stroke etiology can be determined only in a minority of children. However, most of them (> 80%) have more than one risk factor. Recent clinical studies found parameters that had not been known to be risk factors, and genome-wide association studies will provide us with new knowledge on providing optimal care for these children. Whether all these factors will continue to be of clinical relevance in future will remain the subject of discussion.

References


