Childhood haemorrhagic stroke: a 7-year single-centre experience

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ABSTRACT

Background In recent years, there has been increasing research interest in improving diagnostic and management protocols in childhood arterial ischaemic stroke (AIS). However, childhood stroke comprises, in approximately equal parts, both arterial ischaemic and haemorrhagic stroke (HS).

Objective The aim of this study was to focus on the aetiology, clinical presentation, treatment and short-term outcome of children with spontaneous intracranial bleeding in a university hospital and elucidate differences to childhood AIS.

Design We performed a retrospective analysis of electronic medical records of children (28 days–18 years) diagnosed with HS between 2010 and 2016.

Results We included 25 children (male child, n=11) with a median age of 8 years 1 month. The most common clinical presentations were vomiting (48%), headache (40%) and altered level of consciousness (32%). In more than half of the patients, HS was caused by vascular malformations. Other risk factors were brain tumour, coagulopathy and miscellaneous severe underlying diseases. Aetiology remained unclear in one child. Therapy was neurosurgical in most children (68%). Two patients died, 5 patients needed further rehabilitation treatment and 18 children could be discharged home.

Conclusions HS differs from AIS in aetiology (vascular malformations as number one risk factor), number of risk factors (‘mono-risk’ disease), clinical presentation (vomiting, headache and altered level of consciousness) and (emergency) therapy.

INTRODUCTION

Childhood stroke occurs with an incidence of 1.3–8/100 000 children/year, approximately as often as brain tumours, and is among the top 10 of mortality in children.1–4 Primary strokes may be either arterial ischaemic strokes (AIS) that are caused by a blocked arterial supply or venous (=cerebral venous sinus thrombosis) or haemorrhagic, when they are defined as non-traumatic spontaneous intracranial bleeding. There has been increasing research activity in the field of childhood AIS in recent years. Understanding the underlying pathological mechanisms (eg, focal cerebral arteriopathy), acute treatment options (eg, intravenous thrombolysis and mechanical thrombectomy) and reducing the time gap between clinical onset and diagnosis by using appropriate imaging modalities are examples of ongoing research.5–11 There has been less research interest in and awareness of haemorrhagic stroke (HS), although it accounts for almost half of all childhood strokes. Therefore, we aimed to describe a paediatric cohort with HS with respect to clinical presentation, aetiology and short-term outcome and point out the differences to childhood AIS. These data could support paediatricians in their clinical assessment and diagnostic investigation of children presenting with possible HS.

METHOD

We performed a retrospective review of electronic medical records of children with HS in a tertiary university children’s hospital in Munich, Germany between January 2010 and December 2016. This university children’s hospital provides, together with another university hospital and two other children’s hospitals, acute medical advice for 231,510

Table 1  ICD-10 codes for case identification

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Description</th>
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<tbody>
<tr>
<td>I61.X (I61.0-I61.9)</td>
<td>Intracerebral haemorrhage</td>
</tr>
<tr>
<td>I60.X (I60.0-I60.9)</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td>I62.9</td>
<td>Intracranial haemorrhage (non-traumatic), unspecified</td>
</tr>
<tr>
<td>I64</td>
<td>Stroke, not specified as haemorrhage or infarction</td>
</tr>
<tr>
<td>I67.5</td>
<td>Moyamoya disease</td>
</tr>
<tr>
<td>I67.1</td>
<td>Cerebral aneurysm, non-ruptured</td>
</tr>
<tr>
<td>Q28.2</td>
<td>Arteriovenous malformation of cerebral vessels</td>
</tr>
<tr>
<td>Q28.3</td>
<td>Other malformations of cerebral vessels</td>
</tr>
<tr>
<td>D18.0</td>
<td>Haemangioma, intracranial</td>
</tr>
<tr>
<td>D43.X+RS8</td>
<td>Neoplasm of uncertain or unknown behaviour of brain and central nervous system+haemorrhage, not elsewhere classified</td>
</tr>
<tr>
<td>C71.X+RS8</td>
<td>Malignant neoplasm of brain+haemorrhage, not elsewhere classified</td>
</tr>
</tbody>
</table>

ICD-10, International Classification of Diseases, Tenth Revision.

Inclusion criterion was the diagnosis of an HS defined as spontaneous, non-traumatic intracranial bleeding (intraparenchymal, ventricular or subarachnoid) in children and adolescents (≥28 days of life ≤18 years). As it remains unclear whether children who bleed in a brain tumour are subsumed under the term ‘haemorrhagic stroke’, we decided only to include those patients with a brain tumour, who bled into the brain parenchyma, ventricles or subarachnoid space. Exclusion criteria were perinatal/neonatal haemorrhage (<28 days of life), primary subdural or epidural bleeding, traumatic intracranial bleeding, haemorrhagic transformation of AIS or secondary HS due to venous infarction.

Patients eligible for inclusion were identified via ICD-10 codes (International Classification of Diseases, Tenth Revision) given by the treating paediatrician. In order to ensure a complete data collection as possible, we used a broad spectrum of ICD-10 codes (see table 1).

In total, 290 children were identified applying the above-mentioned ICD-10 criteria and their electronic medical records were further reviewed to see whether they met the inclusion–exclusion criteria as shown in figure 1.

Collected information included demographic data, clinical presentation, aetiology, imaging modality, acute treatment and short-term outcome with respect to discharge from hospital.

RESULTS

Patients

The study group consisted of 25 patients. Sex ratio was m:f=0.8:1. Median age at the time of bleeding was 8 years 1 month (range 1 month–16 years 9 months).

Clinical presentation

The presenting features of the children are presented in tables 2 and 3.

Most children presented with vomiting (48%), headache (40%) and altered level of consciousness (32%), followed by seizures (28%), brainstem symptoms (16%) and acute hemiparesis (12%). One child, receiving extracorporeal membrane oxygenation on the intensive care unit, showed signs of increased intracranial pressure. All three infants (ie, <1 year of age) with...
intracranial bleeding presented with vomiting. One infant also had seizures.

Three children suffered a ‘silent’ stroke, meaning that the haemorrhage was an incidental finding in otherwise indicated neuroimaging. The reasons for neuroimaging were: (i) routine MRI screening in a child with known multiple cavernoma; (ii) MRI in a child with a suspected transient ischaemic attack (clinical symptoms were not explained by the diagnosed cavernoma: localisation of the cavernoma: right fronto lobe; clinical symptoms: speech disturbance and right-sided hemiparesis) and (iii) a CT scan in a child to exclude cerebral oedema after cardiopulmonary resuscitation.

Aetiology

Vascular malformations were the most common underlying aetiology (n=13), but did not occur as haemorrhage in children in the first year of life. We identified six children with haemorrhage due to arteriovenous malformations (AVM) and seven children with cavernoma, but no patient with bleeding from an intracranial aneurysm. Further characteristics of these patients with vascular malformation are provided in table 3.

Patients with a brain tumour who bled into parenchyma or ventricles represent the second largest group (n=5). Brain tumours were histopathologically classified as glioblastoma, medulloblastoma, diffuse astrocytoma (WHO II), primitive neuroectodermal tumour (PNET) and atypical teratoid/rhabdoid tumour (ATRT).

There were two patients with an underlying coagulopathy: one had idiopathic thrombocytopenic purpura (thrombocyte count 3000/μL) and the other had vitamin K deficiency due to malabsorption and hypoproteinemia. Another patient with unknown aetiology with multiorgan failure in the course of a septic shock (n=1) and haematopoietic malignancy (n=1). Chronic lung disease (idiopathic pulmonary fibrosis, n=1) and aplastic anemia (n=1) were the underlying causes of haemorrhage in two children.

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secondary to severe underlying disease, and 1 child had no known risk factor.

Treatment
Treatment decision was based on the initial presentation of the child and underlying aetiology. Seventeen patients underwent neurosurgical intervention, 1 patient endovascular (embolisation of an AVM) and 7 children conservative treatment.

Short-term outcome
In our cohort, two patients died. Both patients suffered from a severe underlying disease (severe chronic lung disease and infantile obstructive cholangiopathy) with intracranial bleeding as a result of an extremely complicated course of the primary disease. Most patients could be discharged home (n=18). Five children had further in-hospital treatments or were transferred to a rehabilitation clinic.

Neurological examination at the time of discharge was normal in 13 children. Neurological deficits in the other patients were hemiparesis±facial palsy (n=8), ataxia (n=1), speech disturbance (n=1) and impaired short-term memory (n=1). One patient had multiple severe neurological sequelae after a brainstem bleeding. One small infant showed no neurological deficit but had a poor prognosis due to a malignant brain tumour (ATRT) without response to chemotherapy. Our collected data do not provide any information about the long-term outcome.

DISCUSSION
Treatment of children with HS is not only the preserve of neurosurgeons and interventional neuroradiologists and should involve paediatricians/paediatric neurologists. It is the paediatrician’s responsibility as the first medical contact to know when to think about HS and what to do as the first diagnostic steps in uncovering the most likely underlying aetiologies.

In our cohort, most children presented with vomiting, headache and an altered level of consciousness. This result is similar to literature where the headache is one of the main presenting symptoms.13–23 Headache is very frequently reported in children and adolescents in the general population and is one of the most common reasons for patients seeking medical advice from paediatricians. Sometimes it may be difficult to decide which child with a headache needs more extensive investigations because they may have intracranial bleeding. However, as de Ribau Pierre et al suggest, every headache that is described as ‘worst’ and/or has a ‘sudden’ onset as well as every headache with concomitant focal neurological deficits should immediately lead to further investigations.17

In younger children in whom headache may/could not be the leading (communicated) symptom, the clinical presentation of HS may be more non-specific. Presenting symptoms may include vomiting, irritability, reduced level of consciousness or seizures. It also follows that well-known stroke recognition tools like the FAST test, featuring the leading symptoms in AIS (facial palsy, hemiparesis and speech disturbance), are not applicable in children with HS. To increase awareness for both ischemic and HS, the paediatric stroke working group of the Ludwig-Maximilians-University Munich developed a pocket card for paediatricians called MERCS (Munich early recognition of childhood stroke) highlighting leading symptoms for both stroke types on the front and back of the pocket card (see the online supplemental material).

In our cohort, a cranial CT as first imaging was performed in 64% of the children. CT remains the imaging modality of the first choice in a clinically unstable child with a reduced level of consciousness. CT is widely available, quick and usually does not require anaesthesia in children. It provides information about the type of bleeding (intraparenchymal vs ventricular vs subarachnoid), the size of the haemorrhage and the presence of mass effect and sometimes reveals information about aetiology—all of which is essential information to guide emergency neurosurgical treatment. Outside the emergency situation, an MRI/MRA is required as part of the diagnostic workup to identify or exclude a vascular malformation as an underlying cause and—with respect to the known insufficient diagnostic yield of non-invasive imaging—in some cases (especially in patients with unknown aetiology) a CCA is necessary.24 But even a complete imaging and laboratory diagnostic workup may fail to detect the underlying reason for the bleeding (in our cohort n=1). One reason could be that the vascular anomaly is obliterated by the haemorrhage and therefore ‘invisible’ in post hoc investigations. Diagnostic workup may also remain incomplete in patients with an unfavourable outcome.

With respect to the underlying risk factors, our study concurs with the published literature: vascular diseases are the predominant risk factor for intracranial bleeding in a paediatric population (52% in our study vs 70%–91% in the literature).13–23 In our cohort, vascular malformation was more common in elder children and was not present in the first year of life. This is relevant information with reference to the required diagnostic workup, as investigation for coagulation problems, infections and malignancies (including brain tumours) then become more important in the younger age group. Aneurysms, as one of the three main vascular risk factors besides AVM and cavernoma, were not described in our cohort, probably due to the small cohort size. In some children, intracranial haemorrhage is described as the initial symptom of a brain tumour.18 20 The definition of HS related to a brain tumour is imprecise and not consistent. We decided to exclude patients who bled into a brain tumour (n=8) and only described patients with a brain tumour who bled into the brain parenchyma, the ventricles or subarachnoid space (n=5). One study with high percentages of children with a brain tumour as an underlying aetiology included patients who had bled into a brain tumour.24 One other study did not provide clear information about whether haemorrhage was into or outside the brain tumour, merely describing it as being associated with a brain tumour.20 Nevertheless, the proportion of children with a brain tumour as an underlying disease (20%) in our cohort remains high compared with other studies (up to 15%).

As our university hospital is a centre for paediatric oncology and haematology, this may be the reason for the higher percentages compared with non-specialised clinics. With respect to the number of risk factors, HS differs from AIS: while childhood AIS is known to be a ‘multiple risk’ disease and requires extensive diagnostic workup, most children with HS show a single risk factor with exception of children with severe underlying multiorgan diseases and complex medical treatment prior the intracranial haemorrhage. Apart from that, the percentage of the so-called cryptogenic strokes seems lower in HS compared with AIS.

An intracranial haemorrhage is a possible but rare complication in patients with HSV encephalitis.25 Hypotheses regarding the underlying pathological mechanisms include the presence of a small vessel vasculitis, raised intracranial pressure or damaged brain tissue being more vulnerable to bleeding or a combination of both altered parenchyma and vessels. It is important to know, that the bleeding may occur even in children treated with antiviral agents and the treating paediatrician should have a bleeding complication in mind in every child who has a secondary neurological deterioration. The patient in our cohort with HSV was a 15-year-old boy with an acute clinical deterioration (worst
headache, nausea and sinus bradycardia) and large haemorrhage in the temporal lobe on day 4 after admission and the initiation of antiviral treatment with acyclovir.

This was not an epidemiological study and therefore the patient population studied will have been subject to selection biases that influenced their referral to our hospital. For example, Ludwig-Maximilians-University Hospital is a paediatric oncology centre and the relatively high incidence of malignancy as an underlying cause of HS probably reflects this selection bias. Other selection biases, like the referral of adolescents to adult stroke units or neurosurgery departments, may be applied, but we believe that the range of underlying aetiologies that we found reflect the true range even if the proportions may have been different in a population-based study.

Our retrospective study only provides data about the short-term outcome. At the end of the acute care phase, 52% of the patients had no neurological deficit and 72% could be discharged home. But without using a standardised neurological examination instrument like the Pediatric Stroke Outcome Measure and because of missing short-term or long-term follow-up data, these results are barely comparable to other studies. Beslow et al found an abnormal neurological examination after a median follow-up time of 3.5 months in 71% of children after HS.13 Recently, a rehabilitation centre-based retrospective study focused on the long-term outcome of 128 children after childhood AIS and HS. In general, they saw better motor neurological, functional and academic outcomes after HS (vs AIS) at time of discharge from the rehabilitation department.26 However, at time of discharge (median time since the stroke of 4.7 months), 59.3% of children with HS showed some degree of motor deficit and 35.8% required special education after a median follow-up period of 43 months. Further prospective studies or registry-based outcomes are needed to capture all children with childhood HS in order to describe accurately long-term outcomes and how these outcomes are influenced by underlying aetiology, acute treatment and rehabilitative treatment after discharge from the acute hospital setting.

CONCLUSION

HS constitutes approximately 40% of all childhood strokes and may lead to significant morbidity and mortality. The knowledge of the leading clinical symptoms, aetiology and necessary diagnostic steps are essential for quick emergency management and professional discussion in a multidisciplinary neurovascular team. As HS differs from AIS in most aspects, the training of caregivers should not be limited to the recognition of AIS and the development of paediatric stroke recognition tools should include basic information about the clinical presentation of children with intracranial bleeding. With respect to further research, a first important step for comparable cohort studies should be a clear definition of HS in the paediatric population and consistent use of ICD-10 coding.

Contributors LG and FJO: conceptualised and designed the study, FJO: supervised all aspects of the work. LG, KB and FJO: analysis and interpretation of the data. RW: performed statistical analysis. LG: drafted the initial manuscript. FH, AP, FD, MB and SB: interpretation of the data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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Patient consent for publication Not required.

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