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Reminder of important clinical lesson

Paediatric acute basilar thrombosis successfully treated with intravenous alteplase

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Summary

Acute ischaemic stroke has significant attendant morbidity and is one of the top ten causes of childhood death. It requires prompt investigation and management, however little is known about the safety and efficacy of acute thrombolytic therapies in childhood arterial ischaemic stroke. The authors report a case of a 13-year-old girl with an acute basilar thrombosis, successfully treated with intravenous recombinant tissue plasminogen activator and discuss the management of paediatric arterial ischaemic stroke.

BACKGROUND

Paediatric stroke is defined as a stroke occurring in patients who are between 1 month and 18 years of age, is an under-recognised, potentially treatable cause of childhood neurologic disease with a misconception that it is a rare childhood disorder. Approximately 2–6/100 000 children are affected annually, and is one of the top ten causes of childhood death.[1–4] Limited awareness regarding paediatric stroke among paediatricians and in community is a major issue once that stroke symptoms are attributed frequently to stroke-mimickers such as migraine, encephalitis, tumours and postictal Todd paralysis, which can account for up to one fifth of cases presenting with stroke-like symptoms.[5 6]

The mechanism of vertebro-basilar ischaemia had not been adequately studied until a few years ago; its occlusion is usually a life-threatening disease leading to death or major disability and is very rare in paediatric age.[7–9] Although recanalisation with thrombolytic agent has substantially improved outcomes in adults, in children the role of thrombolysis remains to be determined.[10]

We report a case of a 13-year-old adolescent who suffered an acute ischaemic stroke (AIS), due to acute basilar artery thrombosis, successfully treated with intravenous recombinant tissue plasminogen activator (rt-PA).

CASE PRESENTATION

A 13-year-old female adolescent, right-handed presented to the emergency department with 21 h history of a diffuse onset of headache, nausea and vomitting and a 2 h of diplopia. Her history was unremarkable, with no history of trauma or neck manipulation, no history of taking oral contraceptives neither alcohol, smoking or illicit drug use. There was no family history of early stroke, haematologic, vascular or metabolic disorders.

Physical and neurologic examination showed mental confusion, right facial upper motor neuron weakness and mild left hemiparesis, followed by a rapid decreasing level of consciousness to a stuporous state and decorticate posturing. A clinical diagnosis of acute brainstem ischaemia was suspected. A CT scan was performed and showed a hyperdensity of the distal third part of basilar artery, with no opacification after contrast injection, features consistent with acute basilar thrombosis (figure 1A,B).

After discussion with the adult cerebrovascular intensive care unit and paediatric neurology, it was decided to recommend the administration of intravenous rt-PA to the patient. After obtaining informed consent from the parents, with a complete explanation of the benefits and risks, including death, and a discussion of the lack of evidence for this treatment for children, intravenous alteplase was given. Because no procedure for the administration of rt-PA to children exists at our institution, we followed the adult stroke protocol, which result in a intravenous infusion of 63 mg of rt-PA (0 9 mg/kg).

The patient was locked-in for about 24 h, after that her condition dramatically improved, with recovering of the hemiparesis and diplopia, however she remained with dysarthria.

Subsequent laboratory evaluation included a normal complete blood count and smears, electrolytes, urea, creatinine and serum lipids. The toxicology screen was negative for cocaine, amphetamines, ethanol, cyclic antidepressants, paracetamol and salicylates. Auto-immune and hypercoagulable screen including antinuclear, antiphospholipid antibodies, proteins C and S deficiency, factor V Leiden, antithrombin III deficiency and lupus anticoagulant were negative. Serum and urine amino acids and urine organic acids were normal. Frequent infectious agents such as parvovirus B19, Cytomegalovirus, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, enterovirus, HIV were discharged. A neck blood vessels echo-Doppler was normal and transesophageal echocardiography showed an atrial septal defect (ASD), ostium secundum type measuring 17 mm of diameter, with left-to-right systo-diastolic non-restrictive shunt; in the doubt of the ASD be regarded as an incidental finding, it was decided to initiate anticoagulation with warfarin until its closure. Molecular diagnosis of thrombophilia and warfarin pharmacogenetics showed homozygous angiotensin-converting enzyme delection/delection, and

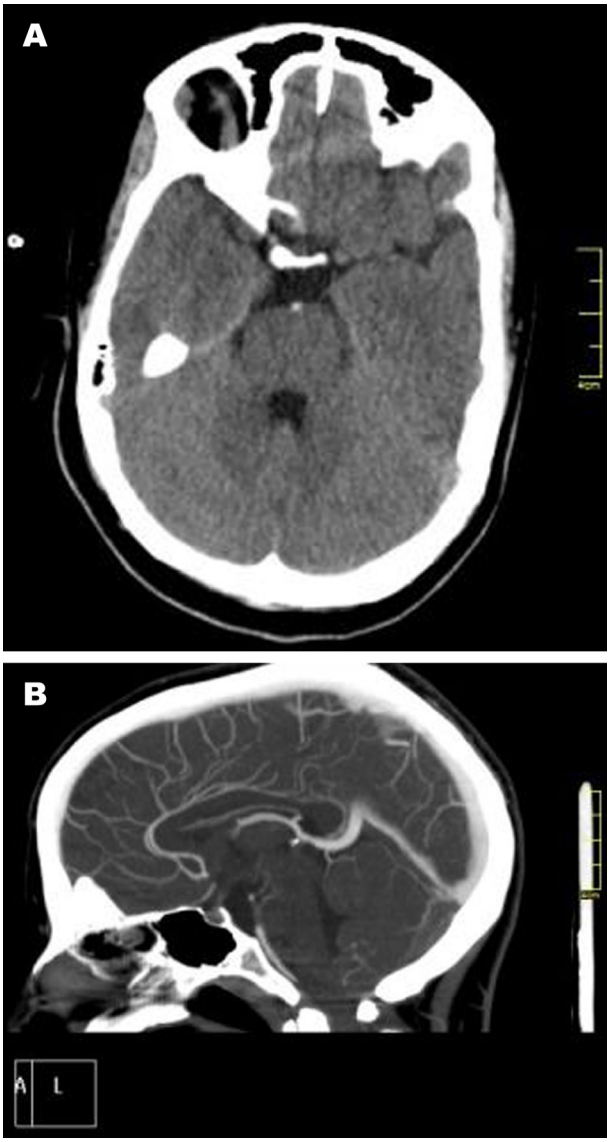

Figure 1 (A) Hyperdensity of the distal third part of basilar artery, with no opacification after contrast injection. (B) Hyperdensity of the distal third part of basilar artery, with no opacification after contrast injection.

heterozygous plasminogen activator inhibitor-1 genotype -844 A and -675 4G/5G genotype polymorphisms.

After a period of rehabilitation, the patient was discharged with resolution of dysarthria and normal neurological examination. The patient had an angio-MRI brain control 2 months after discharge which showed a total permeabilisation of the basilar artery and a small pons sequelae infarct (figures 2 and 3).

DISCUSSION

The incidence of ischaemic stroke in childhood is estimated to be 2–7.91/100 000 children/year, is an under-recognised, potentially treatable cause of childhood neurologic disease with a misconception that is a rare childhood disorder.[1–4]

Limited awareness regarding paediatric stroke among paediatricians and in community is a major issue once that stroke symptoms are attributed frequently to stroke-mimickers such as migraine, encephalitis, tumours and

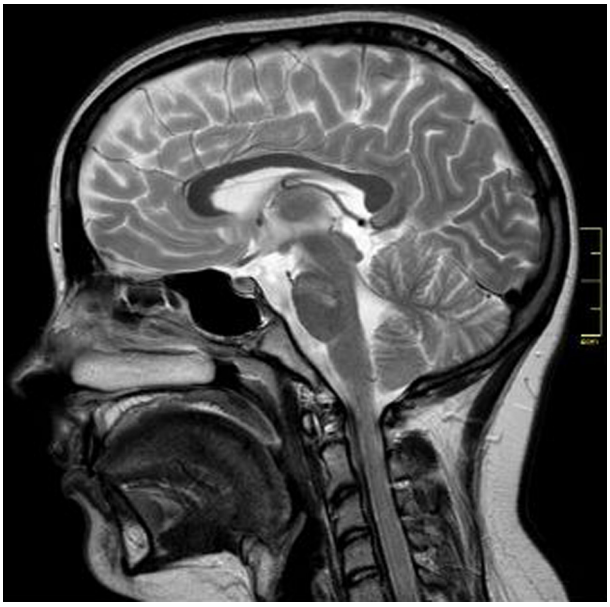

Figure 2 Brain MRI: small pons sequelae infarct.

postictal Todd paralysis, which can account for up to one fifth of cases presenting with stroke-like symptoms.[5 6]

Morbidity and mortality from paediatric stroke is substantial, being one of the top ten causes of childhood death. At least half of children will develop sensory or motor problems, seizure, development delay or cognitive disorders; 15% die and 35% are neurologically normal. The outcome and recurrence risk depend on the underlying cause. No risk factors will be identifiable in approximately 25% of children with stroke.[11–14]

Childhood stroke may be ischaemic or haemorrhagic, although ischaemic stroke is far more common.[15] The mechanism of vertebro-basilar ischaemia had not been adequately studied until a few years ago; its occlusion is usually a life-threatening disease leading to death or major disability and is very rare in paediatric age[7–8 10]

Acute management to restore cerebral blood flow improve prognosis and are nowadays a reality in the intervention of adult stroke.[16] Although that in adults, in children there are no guidelines based on clinical trials for acute management of childhood stroke, with exception of sickle cell disease so, the role of thrombolysis in children stroke remains to be determined, and adult guidelines cannot be extrapolated to children due to age-related differences in cerebrovascular, neurological and coagulation system, as well in causes and pathophysiology.[10]

The thrombolytic agent of choice in children may be alteplase, compared with other agents that include evidence of increased thrombolysis invitro, decreased immunogenicity, higher fibrin selectivity and better side effect profile.[17 18]

The Thrombolysis in Paediatric Stroke study is a clinical trial to asses the safety of intravenous t-PA and intra-arterial in children with AIS. Doses for intravenous t-PA will start at 0.6 mg/kg and escalate to 1.0 mg/kg depending on toxicity. The intra-arterial t-PA dose will range from 0.2 to 0.5 mg/kg. Inclusion criteria include 0–3 h from onset of stroke for treatment with intravenous t-PA and 3–6 h from stroke onset for intra-arterial t-PA; and significant neurological

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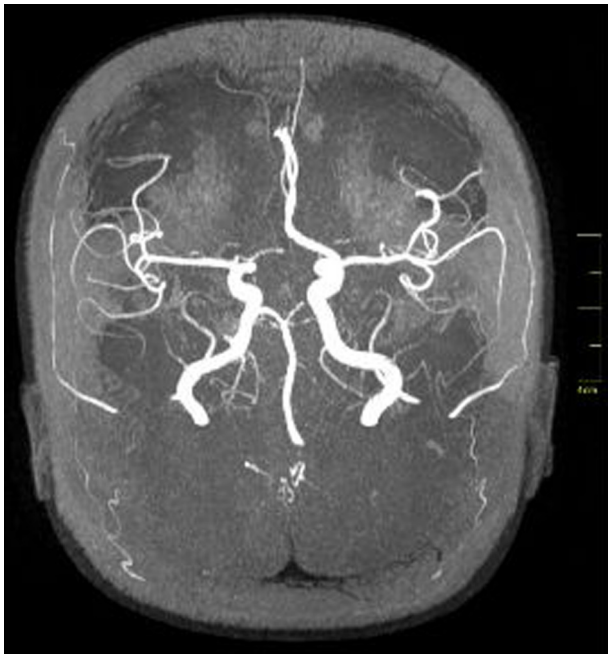

Figure 3 Angio-MRI: total permeabilisation of the basilar artery.

damage defined as ≥10 or ≤30 on the paediatric version of the National Institute of Health Stroke Scale that is not improving is required before t-PA administration.[19]

In our patient, treatment with intravenous rt-PA was considered, after parents' informed consent and unanimous agreement of the physicians involved, because the prognosis of basilar occlusion was so bad that the risks could be tolerated and ethically justified. Multiple cases of successful late interventions in arterial stroke have been documented, including good outcomes with interventions up to 80 h after symptoms onset, with better outcomes with intra-arterial thrombolysis.[20 21]

Pre-existing cardiac disease, particularly complex congenital malformations with right to left shunts, can account for up to one third of the AIS in children[1 22]

However, the contribution of a paradoxical embolus through an isolated patent foramen ovale (PFO) as a risk factor for AIS in children is not well established and remains contentious. PFO is essentially considered a normal variant being found in approximately 25% of the general population.[23]

Infarcts of cardiac disease are usually with typical peripheral involving the cortex and subcortical white matter of both the anterior and posterior circulation.[1]

In our case, the doubt of the ASD be regarded as an incidental finding, it was decided to initiate anticoagulation with warfarin until its closure.

In paediatric stroke it is important to clarify all of the risk factors and possible causes, for that it was considerable to perform a molecular study of thrombophilia and warfarin pharmacogenetics which result a homozygous angiotensin-converting enzyme delection/delection, and heterozygous plasminogen activator inhibitor-1 genotype -844 A and -675 4G/5G polymorphisms. In some studies those polymorphisms were shown to be a risk factor for cerebral infarction, however the impact of thrombophilia in childhood stroke still remains unclear.[24–26]

We were unable to identify an underlying cause for our patient's stroke, but all of the predisposing factors for arterial ischaemic stroke were evaluated.[10]

Our report focuses attention on the striking and successful treatment of an adolescent with acute thrombotic basilar stroke using intravenous alteplase.

Learning points

- Limited awareness regarding paediatric stroke among paediatricians and in are attributed frequently to stroke-mimickers such as migraine, encephalitis, tumours and postictal Todd paralysis.
- In paediatric stroke it is important to clarify all of the risk factors and possible causes.
- Despite the small number of cases reported on thrombolysis of paediatric stroke, the favourable outcome reinforces that thrombolytic therapy should not be withheld in case of life-threatening or potentially disabling paediatric stroke.

Competing interests None.

Patient consent Obtained.

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