Ischemic stroke in paediatrics - narrative review of the literature and two cases

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Stroke is a rare condition in childhood with an estimated incidence of between 1.3-13/100.000 patients. Clinical manifestation and risk factors for paediatric stroke are different from those of adults. The uncommon incidence, age-associated difference and plethora of clinical symptoms make the diagnosis of such strokes extremely difficult and often delayed. The history and clinical examination should point to diseases or predisposing factors. Neuroimaging (DWI MR) is the golden standard for diagnosis of paediatric stroke and other investigations can be considered according to the clinical condition. Despite advances in paediatric stroke research and clinical care, questions remain unanswered regarding acute treatment, secondary prevention and rehabilitation. The treatment recommendations are mainly extrapolated from studies on adult populations. In the review authors summarized the clinical characteristics and diagnostic steps for stroke in children/adolescents based on the most recent international guidelines and practical directions for recognising and managing the child/adolescent with stroke in paediatric emergency. In the two case reports, we describe the clinical course in both stroke patients.

Key words: stroke, childhood/adolescence, diagnosis, therapy, outcome

Received: July 12, 2016; Accepted with revision: October 11, 2016; Available online: November 10, 2016
https://doi.org/10.5507/bp.2016.053

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INTRODUCTION

Stroke is defined as a sudden loss of brain function caused by a decreased cerebral blood flow in affected areas. It can occur at all age groups. However, the clinical presentation, pathophysiology and other clinical perspectives are variable depending on the patient's age. Stroke in paediatric populations is associated with significant morbidity. The reported incidence of stroke varies between 1.3 to 13 per 100 000 (ref.[1-5]), which is significantly lower than for the adult population where the reported occurrence is between 175-200/100 000 (ref.[6]). There is a higher incidence in neonatal age (25-40/100 000), with the maximum occurrence in premature neonates and infants (100/100 000) (ref.[7]).

Paediatric stroke includes 3 different subtypes: acute ischemic stroke (AIS), haemorrhagic stroke (HS) and cerebral venous sinus thrombosis (CVST) (ref.[8,9]). Rapid, precise diagnosis is vital as the therapeutic approach differs according to the type of stroke. Although the majority of clinicians report that the incidence of haemorrhagic stroke is 50% of stroke cases in paediatrics[10-12], some describe a higher incidence (67-85%) of ischemic/thrombotic etiology of stroke[13,14]. The etiology of AIS is multifactorial[15,16] with congenital heart disease considered the major risk factor responsible for nearly 30% of paediatric strokes[16]. Other known risk factors are vascular disorders, thrombotic states, sepsis and sickle cell disease[10,17,18]. The classic symptomatology of stroke in adulthood includes: hemiparesis, aphasia, ataxia or hemianopia[7] and the loss of consciousness. However, children may have a different, incomplete and variable presentation of clinical symptoms, which could depend on the patient's age[19] and makes the diagnosis of paediatric stroke difficult. There is often a considerable delay between onset of clinical presentation and the definitive radiological diagnosis. The reported median time delay is 25 h and even then only 30% of patients are definitely diagnosed in the 6-hours "therapeutic window" (ref.[19,20,21]). Moreover, in hospitalized children the reported delay from onset to the diagnosis has been around 12.7 h[22,23]. Beside the classical clinical neurologic signs (hemiparesis, aphasia, ataxia, hemianopia) (ref.[7]), 30% children present with headache[24]. Also seizures are present in 20-48% paediatric patients with stroke[25]. Younger children present with more atypical signs, while older ones have more neurologic-specific signs, similar to adults. Because of non-specific signs and variability according to patient's age, all cases of acute onset of neurologic deficit should be considered as a potential stroke until definitive diagnosis has been made[26]. After clinical investigation and neurologic examination the neuroimaging study should be performed. The imaging methods of choice are: Magnetic Resonance imaging (MRI) or Computer Tomography (CT), followed by CT

angiography or DSA (ref.[19]). Initial CT during the first 12 h may be free of pathology[27,28] and therefore the MRI with DWI (diffusion weighted imaging) due to higher specificity and sensitivity, is considered to be a "golden standard" for imaging in paediatric patient with suspected AIS (ref.[19,28,29]). If MRI is not available, then CT with CT angiography of brain and neck can be performed[7]. The therapeutic options in the management of patients with stroke are: antithrombotic therapy with aspirin, thrombolysis (intravenous, intraarterial) and mechanical thrombectomy. For patients with cardioembolic etiology or patients with proven arterial dissection, anticoagulation therapy with unfractioned heparin (UFH) or low molecular-weight heparin (LMWH) is recommended[19]. According to the Canadian Best Practice Guidelines (CBP, 2010) (ref.[30]), American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (CHEST, 2012) (ref.[31]) thrombolytic therapy and/or mechanical thrombectomy are not recommended as a part of standard therapy[32] due to the lack of evidence based data (EBM). Despite this recommendation, the recombinant tissue plasminogen activator (rt-PA) has been used in selected cases[33,34]. Recent data show that only between 0.7% - 2% paediatric patients with stroke have been treated with rt-PA (ref.[35-37]) with inconclusive results. Intravenous rt-PA therapy can be administered in a 4.5 h interval from the onset of clinical symptoms, according to the data extrapolated from adult clinical practice. Intra-arterial thrombolysis and endovascular mechanical thrombectomy can be performed in a 6 h interval after onset of first clinical symptoms in selected cases. However, safety guidelines, based on the EBM data, are missing[19]. Additional supportive therapy is essential and should be aimed at maintaining normoglycaemia, euvolemia with normal blood pressure levels, sufficient oxygenation and normothermia. Hyperthermia is presumed to be a strong factor of low success rate in patients with stroke. Following the acute therapeutic period, conceptual long lasting rehabilitation should be considered. This is a very important factor affecting the high M/M rate in 6 months follow up[19,38-40]. The overall mortality is lower than that in adult patients (3-6%), although the morbidity is significant and around 70% of patients have lifelong disability[41,42].

Delivery of such care requires purposeful institutional planning and organization in paediatric acute care centers. Primary stroke centers established for adults provide an example of the multidisciplinary approach that can be applied to the evaluation and treatment of children who present with acute stroke. The organizational infrastructure of these centers can be employed and adapted for treatment of children with acute stroke. It is very likely that the superior care for children with acute stroke can be delivered by regional pediatric primary stroke centers dedicated to the care of children with pediatric stroke.

CASE 1

15-year old girl with recently diagnosed Alport syndrome and obesity (90 kg), presented with acute onset right-sided hemiparesis, aphasia, vomiting and urine incontinence. She was transported by the ground emergency unit to the local hospital, where the CT of brain revealed acute occlusion of the middle left cerebral artery (Fig. 1.).

The rt-PA (recombinant tissue plasminogen activator) (85 mg, 10% bolus, 90% in 60 min) was administered. Due to neurological progression to the soporous state, the patient was intubated and mechanically ventilated. After consultation with the neurologist in the primary stroke center and the progression of neurologic state despite rt-PA administration the patient was indicated for mechanical thrombectomy treatment and transferred to the nearest stroke center by air, without any delay (within 90 min after onset of clinical symptoms, mechanical thrombectomy was started). However, despite an experienced interventional radiology team and maximum effort, mechanical thrombectomy under general anesthesia was unsuccessful.

The patient was admitted to the intensive care unit (ICU) for conservative supportive neurocritical care. She was sedated and mechanically ventilated. Antioedematous therapy with mannitol in accordance with local treatment protocol was initiated. The next day, CT of the head showed acute ischemia in the left middle brain artery drainage area with the thrombus at M1/M2 level -dens artery sign. Another planned next-day CT showed progression of ischemia with signs of oedema.

The patient was considered as a high-risk for potential oedema progression and eventual cerebral herniation. After consultation with the on-call neurosurgeon, an intraparenchymal intracranial pressure monitoring transducer was introduced. The initial intracranial pressure values were within the acceptable range of under 20 millimeters of mercury (mmHg). After 48 h, the conservative neurocritical care was maximised (including hypothermia therapy with the target temperature 35 °C) with the aim of maintaining the intracranial pressure under 20 mmHg and cerebral perfusion pressure in the range of 60-70 mmHg. The neurocritical conservative therapy was depleted and it was impossible to keep intracranial pressure (ICP) within the acceptable range (under 20 mmHg). The decision for urgent decompressive craniectomy was made. The surgery was uneventful and ICP values after surgery returned to under 20 mmHg (Fig. 2.).

The condition was further complicated by nosocomial pneumonia (*Staphylococcus aureus*) - cured after prolonged antibiotic treatment. Due to long-lasting mechanical ventilation anticipation surgical tracheostomy was performed. Transoesophageal echocardiography was carried out without pathological findings. After nine days in ICU, the patient was conscious and cooperative with right-sided hemiplegia. On the 14th day after AIS, she was transferred to the high dependency unit (HDU) in the Children's medical centre. After 4.5 months the bone was replanted.

The patient is now aware and cooperative with a Glasgow coma scale (GCS) of 15, she walks with only one French crutch and she returned to normal school life. Her right-sided hemiplegia resolved with only mild hemiparesis.

Fig. 1. CT angiography with left temporal-middle cerebral artery occlusion.

Fig. 2. CT scan of the brain after decompressive craniectomy with hemorrhagic transformation of the ischemia in the drainage area of the left middlĕ cerebral artery, brain tissue exceeds the border of craniectomy.

CASE 2

A 17-year old girl with the Klippel-Trenaunay syndrome, congenital angiodysplasia of lower limb with chronic thrombosis on warfarin therapy was admitted (by the emergency medical unit) to the emergency department 45 min after consciousness disorder onset, aphasia and right-sided hemiparesis and anisocoria. Clinical and neurology examination was performed with a high suspicion of stroke. The patient underwent CT of the head, where despite motion artefact the dens-artery sign was recognized. A CT angiography was requested. However, the patient had anamnesis of severe anaphylactic shock after contrast medium application. For this reason, she was intubated, mechanically ventilated and transferred to the nearby MRI unit for MRI imaging of the brain.

In the meantime, the laboratory results came back with International normalized ratio (INR) in therapeutic range of 2.7. Due to the INR value the decision not to administer rt-PA was made with regard to potential risk of haemorrhage. The on-call neurologist in the primary stroke centre was contacted with the request to consider mechanical thrombectomy. The MRI results showed complete occlusion of left middle cerebral artery with thrombus progression to the left anterior cerebral artery and even to the left internal carotid artery (Fig. 3). Mechanical thrombectomy was indicated and the patient was transferred to the primary stroke centre in the university hospital. For the transport, the right a. radialis for invasive blood pressure monitoring and the right external jugular vein for norepinephrine infusion was cannulated The mean arterial pressure over 80 mmHg for effective cerebral perfusion was maintained. Mechanical thrombectomy started in 3 h after onset of clinical symptoms and was successful with complete recanalisation of the left middle anterior cerebral artery and left carotid artery.

The patient was transferred to the neurology ICU, she was sedated and mechanically ventilated. The next-day, the CT showed no signs of ischemia or haemorrhage. The patient was weaned and extubated on the same (2^{nd}) day. She was aware, cooperative with aphasia and mild right-sided hemiparesis. However, on the 5^{th} postoperative day, seizures with consciousness disorder emerged and the patient was intubated and mechanically ventilated. The urgent CT of the head showed new ischemia in the left middle cerebral artery drainage area with progression of oedema.

After correction of coagulopathy, intracranial pressure monitoring was introduced, but after a short period the conservative therapy was exhausted and urgent decompressive craniectomy was performed on the same day. The postoperative CT of the head, revealed extensive ischemia in the drainage area of left anterior, middle and posterior cerebral artery with intracerebral haemorrhage in the basal ganglia and haemocephalus.

The postoperative ICP values were within acceptable range under 20 mmHg. The progression of ICP values beyond acceptable range was detected on the 7^{th} ICU day, without any reaction to conservative therapy (mannitol, hypertonic saline, sedation, paralysis, sitting po-

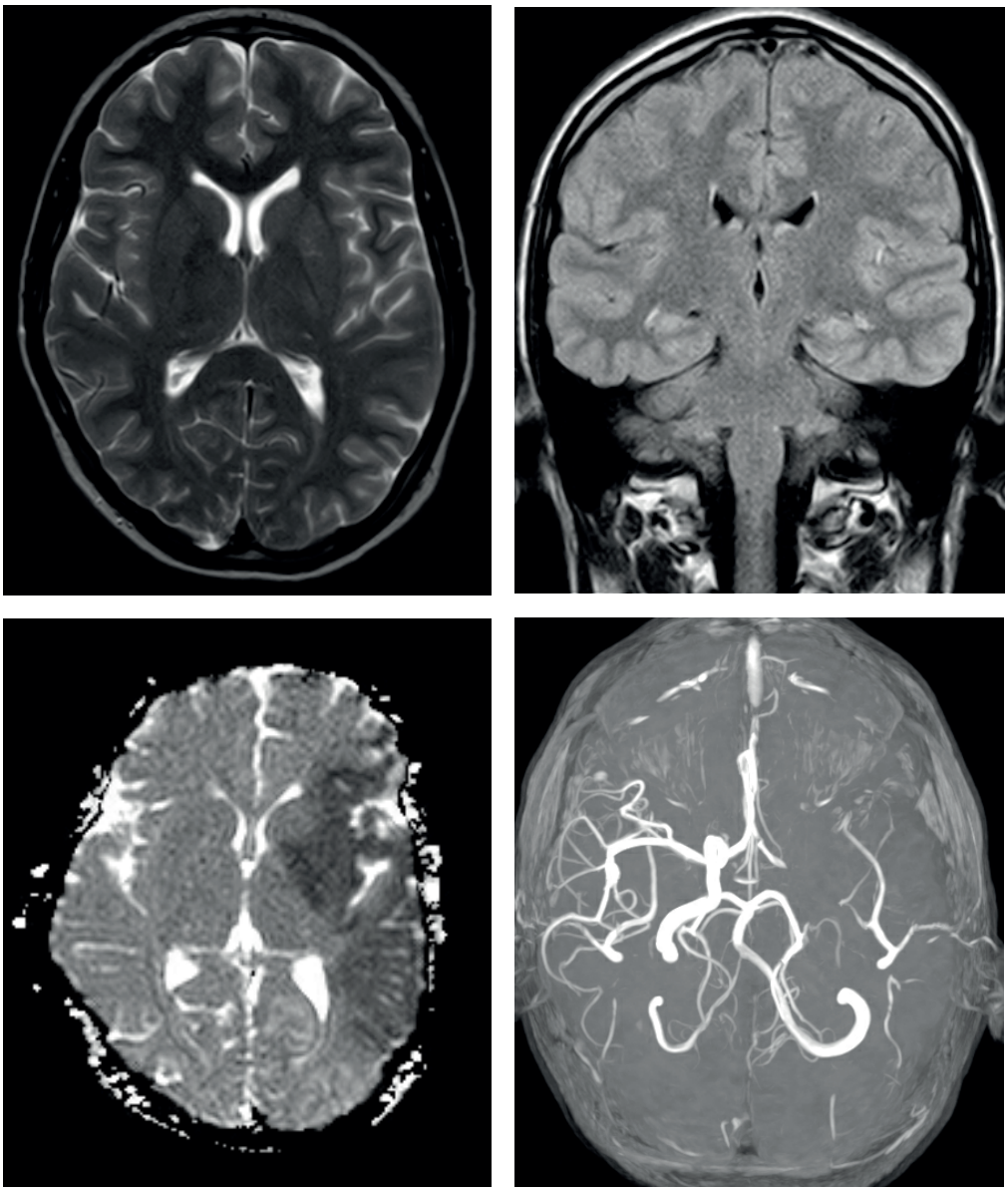

Fig. 3. Initial Magnetic resonance imaging of the brain, occlusion of the left internal carotid artery and left middle cerebral artery, extensive area of restricted diffusion refers to acute ischemic changes.

sition, thiopental, normoventilation on the lower level of $PaCO_2$, targeting cerebral perfusion pressure between 60-70 mmHg). The neurosurgery consultant maintained that no other surgery intervention was indicated at the moment. Mild hypothermia with a targeted temperature at 35 °C was induced and improvement in the ICP was detected. Nosocomial pneumonia (Stenotrophomonas maltophilia) was detected and treated with antibiotics. On the 16th day, the operative tracheostomy was performed. On the 18th day, the sedation was reduced and the patient was in contact, cooperative, mechanically ventilated on pressure support with right-sided hemiplegia. She was transferred to the Children 's medical centre at the university hospital for supportive therapy and weaning, where she was successfully weaned from mechanical ventilation in 5 days. The stay was complicated by thoracic empyema, probably due to the prolonged course of nosocomial pneumonia, with the need for thoracotomy revision. The surgery was uneventful. On the 46th day, the tracheostomy was cancelled and on 50th day of hospitalization the patient was discharged to home care with severe right-sided hemiparesis. The replantation of the skull bone was planned in one month but needed to be postponed due to persisting oedema of the left hemisphere (Fig. 4.).

The right-sided hemiparesis is very slowly improving.

DISCUSSION

We presented two different cases of AIS in two adolescents.

In the first case, the condition was very quickly diagnosed and the therapeutic process was derived from

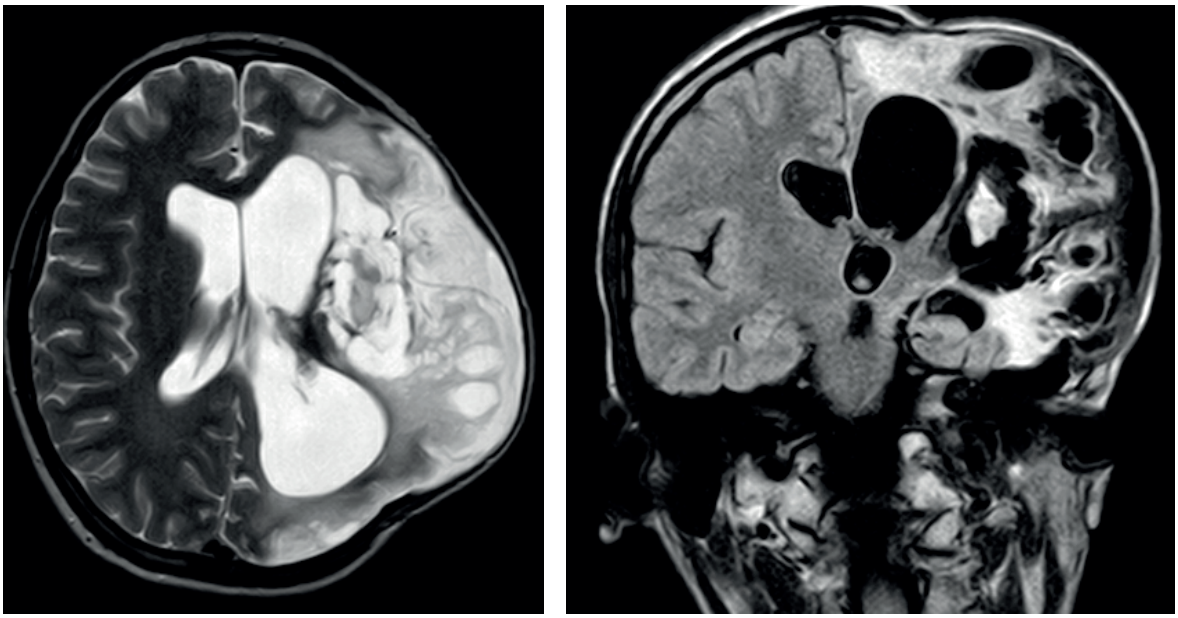

Fig. 4. Magnetic resonace imaging of the brain with extensive postischemic and postmalatic changes.

the adult-based guidelines. Urgently administered rt-PA did not improve the clinical status and regrettably the mechanical thrombectomy was unsuccessful. We assume that the fast indication of intracranial pressure monitoring in this high risk patient led to the early detection of oedema progression and the decompressive (life-saving) craniectomy was performed without delay. Despite unsuccessful intravenous thrombolysis and mechanical thrombectomy, the outcome of this patient is good with only mild neurological deficit.

In the second case, AIS occurred despite warfarin and INR in the therapeutic range. Due to INR 2.7, the rt-PA was not administered and the mechanical thrombectomy was successful with the complete recanalization. However, on the 5th day loss of consciousness with seizures pointed on the new ischemia of the whole left hemisphere. Shortly after ICP monitoring induction, the ischemia was expansive without any reaction to conservative therapy and urgent decompressive craniectomy was performed. Despite the ischemia of the whole hemisphere with oedema, hemocephalus and intracranial bleeding in the basal ganglia, the patient was weaned from mechanical ventilation, in contact and cooperative.

Although rt-PA and mechanical thrombectomy are not currently recommended for the therapeutic management of stroke in children, there are several published cases and case series describing it's use in this situation. Studies comparing the efficacy of intravenous thrombolysis in young adults (16-49 years old) showed that younger patients benefit from rt-PA application and the risk of intracranial haemorrhage was lower compared to older adults[43,44]. In the study by Deena M. Nasr et al. the rt-PA was given to 99 paediatric patients. Intravenous thrombolysis was indicated for the most severe cases of stroke according to mechanical ventilation and cerebral angiography rates. The incidence of intracranial haemorrhage (IC) was higher in the rt-PA group (4.9% vs. 1.6%, P=0.01), however none of them were fatal. In-hospital mortality in the rt-PA group was 0% vs 4.8% in the no-rt-PA group[33]. The authors reported no increase in mortality in the rt-PA group consistent with previously published data[36,45]. Although the guidelines are still missing, some stroke centres are planning to define the safety guidelines for rt-PA administration in children with AIS (ref.[46]). The interval for rt-PA administration (4.5 h from onset of clinical symptoms) and the dosage (0.9 mg/kg, 10% as a bolus) are derived from the adult studies and are nowadays considered appropriate[7].

The role of mechanical thrombectomy in the therapeutic management of children with AIS needs to be defined. Currently, it is not recommended as a standard therapeutic option, although it has been used in several cases including our case 1 and case 2. Potential candidates for this therapeutic option may be older patients with severe neurologic presentation (paediatric NIH Stroke Scale 10-30) and with large cerebral artery occlusion[19,32,57]. It appears that mechanical thrombectomy is an effective therapeutic option for selected paediatric patients with AIS[48], but the data only derive from case reports and case series. Well-designed randomized controlled trials (RCT) are still missing.

CONCLUSION

Although current guidelines for management of stroke, especially AIS do not recommend intravenous thrombolysis and mechanical thrombectomy as a standard therapeutic option for children with AIS, the proportion of patients treated with rt-PA and endovascular intervention is increasing. There is an urgent need for well-designed RCT to define the efficacy and safety of these methods that could lead to guideline formation.

Search strategy and selection criteria

We searched https://scholar.google.com, http://www.ncbi.nlm.nih.gov/pubmed/, Medline (OVID SP), and Dynamed for the keywords "stroke", "paediatric", "childhood", "children". Articles and reports from 1995 to May 2016 meeting search criteria and related to the topic - stroke in paediatric population, were included in the review.

Acknowledgment: The article was published with the non-financial support from Masaryk University and University Hospital Brno, Czech Republic.

Author contributions: All authors contributed equally to preparing the manuscript.

Conflict of interest statement: The authors declare there are no conflicts of interest regarding the publication of this article.

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