

Review Paper:

A Review on Emergency Management of Pediatric Acute Ischemic Stroke



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ABSTRACT

Context: Based on current literature, there is no consensus regarding the proper emergency management of Pediatric Acute Ischemic Stroke (P-AIS). In other words, there are lots of considerable controversies in this regard. Therefore, the current review was conducted to provide a more comprehensive discussion on this topic.

Evidence Acquisition: The search was conducted using the terms “Pediatrics”, “Stroke”, and “Recombinant tissue plasminogen activator” in the PubMed database. English papers on the management of P-AIS published after 2000 were selected. An expert panel performed a critical appraisal to summarize the findings and make them applicable. Finally, the extracted data were categorized under proper subheadings, and the manuscript was prepared.

Results: The related papers provided limited evidence on this topic. All extracted findings were categorized as follows: etiology and the underlying diseases, clinical presentations, diagnosis, management (thrombolytic therapy and thrombectomy), and outcome.

Conclusions: Although thrombolytic therapy is recommended in P-AIS, most cases are diagnosed outside the therapeutic window, so P-AIS is practically impossible, and they are candidates for mechanical interventions. On the other hand, the proper device may not be available to fit the size of the younger children’s vasculature.

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1. Context

The World Health Organization (WHO) has defined stroke as “a sudden non-convulsive loss of neurological function due to an ischemic or hemorrhagic intracranial vascular event” (1, 2). Although the disease is well-defined in the adult population, there are considerable gaps in the topic of Pediatric Acute Ischemic Stroke (P-AIS) (3, 4). With the prevalence of 1.2 to 5.11 per 100000 children/year in developed countries, P-AIS is considered a rare health event (5, 6). The differences in the reported incidence of P-AIS in different studies might arise from the discrepancies in the age of the included populations, as the incidence of P-AIS amongst the neonates (birth to 28 days) is much higher than the incidence in children (29 days to 18 years) (6).

Cerebrovascular diseases have significant importance due to their high morbidity and mortality rates. Indeed, they have been reported amongst the top 10 leading causes of pediatric mortality in the United States (7). P-AIS patients can suffer long-term, sometimes even life-long complications, such as permanent cognitive and motor disabilities. These complications emphasize early diagnosis and management of P-AIS (8, 9). Based on current literature, there is no consensus regarding the proper emergency management of P-AIS. Also, there are lots of considerable controversies in this regard. Therefore, the current review was conducted to provide a more comprehensive discussion on this topic.

2. Evidence Acquisition

We searched the PubMed database using the terms “Pediatrics”, “Stroke”, and “Recombinant tissue plasminogen activator”. By reviewing the titles and abstracts, we selected all English language papers on P-AIS management published after 2000. Two investigators were assessed eligible articles in respect of relevance to the topic. Then the full-texts of selected papers were further studied.

Furthermore, an expert panel performed a critical appraisal to summarize the findings and make them applicable. Finally, the extracted data were categorized under proper subheadings, and the manuscript was prepared. Then, the complete manuscript was reviewed, revised, and approved by all of the authors.

3. Results

Etiology and the underlying diseases

Several classification systems have been reported regarding P-AIS, but none of them has been universally accepted. Three subtypes have been proposed by the International Pediatric Stroke Study (IPSS): Arteriopathy, cardioembolic, other or undetermined (10). The most common known etiologies of P-AIS that may even accompany with recurrence stroke are sickle cell disease, cardiac disease, antiphospholipid antibodies, metabolic and mitochondrial disorders, elevated lipoprotein A, protein C deficiency, and vasculopathy (7, 11-13). Risk factors for P-AIS are not well understood, but thrombophilia, sickle cell anemia, and infection are among the most studied ones (14).

Clinical presentation

P-AIS symptoms include headache, vomiting, vertigo, ataxia, altered level of consciousness, apnea, hypotonia, seizures, which in most cases are not typical for a stroke. Unlike adults, most children presenting with acute-onset focal neurological symptoms suffer from stroke mimics. Many conditions, including migraine, seizures, Todd's paralysis after focal seizures, conversion disorders, tumors, demyelinating diseases, can mimic stroke presentations in children; migraine is the most common one to simulate P-AIS clinical manifestations (15-18).

Diagnosis

Because of similar symptoms in both stroke and the previously mentioned diseases, making a definite P-AIS diagnosis is difficult. Considering early complications such as cerebral edema and “stroke mimics” are crucial to get better results (14). Some clues can help distinguishing stroke from such diseases, including children's well-being during the prior week to the clinical presentation of acute ischemic stroke, their inability to walk, and weakness in the face and arm (17, 19). There is a very limited time window for evaluating and diagnosing AIS in children, outlining the importance of a guideline in this regard. To the best of our knowledge, at present, there is no published consensus guideline on this subject. Non-enhanced Computed Tomography (CT) helps distinguishing hemorrhage from AIS, but it is not always helpful in the hyperacute state (20). Magnetic Resonance Imaging (MRI) is more sensitive and specific in diagnosis, but it is not available in all centers, especially in centers with no pediatric stroke protocols (21).

Management

In contrast to adult stroke, P-AIS management is mostly based on expert opinions, case reports, and a few non-randomized trials (1). Overall, management should focus on removing the clot in the vessels (primarily) and treating the underlying causes. As in adults, there are two management options for P-AIS: Thrombolytic therapy and mechanical thrombectomy.

Thrombolytic therapy

Excluding case reports and case series, there are two important studies regarding the use of recombinant tissue plasminogen activator (rt-PA) in P-AIS named as International Pediatric Stroke Study (IPSS) and Thrombolysis in Pediatric Stroke Study (TIPS).

IPSS is a prospective multi-center cohort study conducted from 2003 until 2007 in which 687 patients with P-AIS with a mean age of 8.9 years were enrolled. Fifteen patients were treated with rt-PA, either intravenously or intra-arterially. Their mean time to treatment was 3.3 hours in the intravenous group and 4.5 hours in the intra-arterial one. The patients were administered a total dose of 0.02–0.9 mg/kg. Out of 15 treated patients with rt-PA, 2 died. The causes of death in both were reported to be unrelated to rt-PA administration. Out of 13 survivors, 4 had brain hemorrhage yet remained asymptomatic, 9 had neurological deficits at the time of discharge, and neurological symptoms resolved in only 1 patient (22).

The TIPS trial assessed the safety and the optimal dosage of rt-PA. The rationale of the TIPS trial has argued that the use of rt-PA outside therapeutic windows defined for adults and the different fibrinolysis pathways in pediatrics have a considerable impact on the outcomes. For instance, higher levels of tissue plasminogen activator inhibitor-1 and lower endogenous plasminogen levels necessitate higher doses of rt-PA in pediatrics. Considering these factors, TIPS was started in 2012 but got terminated after 1 year due to poor enrollment. Out of 43 patients identified as P-AIS, only 1 met their designated criteria for rt-PA administration (23).

The Australian Childhood Stroke Advisory Committee guidelines provide a weak recommendation on the use of rt-PA in P-AIS patients of 2-17 years old, with pediatric stroke severity score between 4 and 24, lack of bleeding, and the ability to start the treatment in 4.5 hours of symptoms onset (level of evidence: III, IV). These guidelines advise strongly against the use of rt-PA after 4.5 hours from the onset of symptoms (Level of evidence: I-III) (24).

The “Canadian Best Practice Recommendations for Stroke Care” recommends that all patients should be evaluated for their eligibility for thrombolytic therapy if there is the possibility to initiate the treatment within 4.5 hours of symptom onset. The recommended door-to-needle time for intravenous alteplase is less than 60 minutes (Evidence level C) (25). Rajani et al. argued that making arterial occlusion a mandatory criterion for P-AIS would result in children being denied a potentially lifesaving treatment (26).

Thrombectomy

To our knowledge, no published clinical trials exist considering mechanical interventions in P-AIS. Case series on this subject may seem to have a bias since unsuccessful interventions are unlikely to get published. However, 2018 American guidelines for endovascular therapy recommend stent retrievers as a reasonable method for some children under 18 with large-vessel occlusion (27). They also recommend starting the treatment 6 hours from the onset of the symptoms. The limitations include the difference between vessel size in children and adults that make some clot retrieval devices out of use. Besides, stroke mechanisms differ in children from adults, mostly focal cerebral arteriopathy, sickle cell arteriopathy, and moyamoya, which are not amenable to thrombectomy (21, 28, 29).

Outcome

Recent evidence has suggested that the existence of multiple risk factors is associated with worse outcomes. Therefore, metabolic, hematologic, and angiographic studies should be carried out to evaluate further risk factors. Other risk factors include a history of head trauma, developmental delay, headaches, fever, family history of bleeding disorders, etc. Based on these findings, neuroimaging, echocardiography, and metabolic and hematologic studies may be indicated.

4. Conclusions

Although thrombolytic therapy is recommended in P-AIS, since most cases are diagnosed outside the therapeutic window, this treatment is practically impossible, so they are candidates for mechanical interventions. On the other hand, a proper device may not be available to fit the size of the younger children’s vasculature.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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