TITLE

Brain Attacks and Stroke in Children

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Abstract

Emergency physicians are often the first point of contact in children presenting with acute neurological disorders. Differentiating serious disorders such as stroke, from benign disorders such as migraine can be challenging. Clinical assessment influences decision making, in particular the need for emergent neuroimaging to confirm diagnosis. This review describes the spectrum of disorders causing "brain attack" symptoms, or acute onset focal neurological dysfunction, with particular emphasis on childhood stroke, because early recognition is essential to improve access to thrombolytic treatments which have improved outcomes in adults. Clues to diagnosis of specific conditions are discussed. Symptoms and signs which discriminate stroke from mimics are described, highlighting differences to adults. Haemorrhagic and ischaemic stroke have different presenting features which influence choice of the most appropriate imaging modality to maximise diagnostic accuracy. Improvements in the care of children with brain attacks requires coordinated approaches and system improvements similar to those developed in adults.

Key words

Neurological, emergency, cerebrovascular disease, childhood stroke, clinical neurology.

Additional key words: brain attack.

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Key points

1. Triage nurses and emergency physicians play key roles in differentiating uncommon but serious conditions such as stroke, from more common and benign conditions such as migraine, in children presenting with acute focal neurological deficits or brain attacks.
2. Clinical diagnosis influences decisions about timing of investigations including emergent neuroimaging and the most appropriate treatments. Bedside tools have been developed to assist paramedics and emergency physicians to discriminate stroke from mimics but their diagnostic utility has not been adequately tested in children.
3. Development of paediatric brain attack protocols are urgently needed to improve care of children with neurological emergencies and increase access to time critical interventions such as thrombolytic therapy in ischaemic stroke.

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Introduction: Brain attacks in children

Paediatric neurological emergencies include status epilepticus, stroke, acute raised intracranial pressure, traumatic brain injury, central nervous system infections, acute demyelinating disorders and acute flaccid paralysis. Some of these conditions present with altered conscious state whereas others present with sudden onset focal neurological or "brain attack" symptoms which may include weakness, speech, sensory or visual disturbance, headache or ataxia. In adult public education campaigns the term brain attack is used synonymously with stroke because of mechanistic similarities to heart attacks. This review will focus on differentiating uncommon but serious causes of brain attack symptoms such as stroke, from more benign conditions such as migraine, and discuss approaches to investigation and management.

The spectrum of paediatric conditions causing brain attack symptoms differ from adults.

Whereas adults with brain attacks are diagnosed with stroke in three quarter of emergency department (ED) presentations[1-3] children presenting with brain attack symptoms generally do not have a stroke.[4] Yet, it is critical to identify these children who require urgent neuroimaging to improve access to hyper-acute therapies such as tissue plasminogen activator and endovascular treatments.[5-9] A recent study of children presenting to an Australian tertiary paediatric ED found that migraine was the most common cause of sudden onset focal neurological symptoms and signs, accounting for 28% of cases. First febrile or afebrile seizures

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were the second most common diagnosis in 15% of children, followed by Bells Palsy in 10%, ischaemic or haemorrhagic stroke in 7%, and conversion disorders in 6% of children.[4]

In addition the paediatric conditions which mimic stroke differ from adults, and disorders such post infectious cerebellitis are only encountered in children.[4] Another study describing the spectrum of disorders mimicking paediatric stroke in an inpatient setting found that serious neurological conditions accounted for almost two-thirds of cases, with diagnoses including posterior reversible leucoencephalopathy, vascular abnormalities, inflammatory disease, intracranial infection, metabolic stroke, tumours, drug toxicity and idiopathic intracranial hypertension.[10]

Clues to specific neurological diagnoses in children presenting with brain attack symptoms (Table)

Migraine is a common neurological disorder of children and teenagers[11, 12] and is typically associated with unilateral throbbing headache. Associated symptoms may include nausea, photophobia and phonophobia.[5-9] Migraine headaches can be of shorter duration than adults and are frequently bilateral in children. Auras are less common than adults and typically consist of a mix of positive and negative visual symptoms, and less commonly sensory symptoms.[13] Simple analgesics are the mainstay of acute treatment in younger children but triptans can be considered in teenagers.[14] Clues to childhood migraine diagnosis include a positive family history, *gradual* onset of neurological symptoms, which usually resolve within 15-30 minutes,

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followed by headache which builds in intensity. Focal weakness, speech disturbance, confusion and altered consciousness are unusual. Red flags which warrant urgent neuroimaging include sudden onset severe headache associated with stroke and focal neurological deficits which are not resolving.

Focal seizures can be followed by a Todd's paresis and may be difficult to differentiate from stroke. Todd's paresis typically occurs in the context of known focal epilepsy and resolves within a few hours. Therefore children with no prior history of seizures whose neurological deficits are not resolving should undergo urgent neuroimaging because seizures are a common presenting symptom of stroke,[15-18] encephalitis, and acute disseminated encephalomyelitis. There are well developed protocols for emergency management of seizures (https://www.apls.org.au/page/about-us) based on good evidence from randomised controlled trials.[19-22]

Diagnosis of Bells palsy is fairly straightforward but requires careful examination by the emergency physician to ensure weakness involves the upper and lower facial muscles and *absence* of other neurological signs referable to the brainstem.[23] There is good evidence to support use of steroids in adults[24, 25] but data are lacking in children.[26]

Conversion disorders are probably the most challenging group of patients for non-neurologists because the child's neurological symptoms are by definition unexplainable from a neuroanatomical perspective. Conversion disorders typically occur in children over the age of 8

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years[27] and present with multiple neurological complaints including weakness, speech, sensory or visual disturbance, seizures, collapse, inability to walk or abnormal gait.[28, 29] Clues to diagnosis include examination findings which are inconsistent with the complaint, signs which vary from one examination to the next or which do not conform to neuroanatomical pathways. Input from colleagues with specific expertise in neurological examination and knowledge of neuroanatomy is often required and non-urgent neuroimaging is sometimes indicated to exclude more serious organic conditions.[27]

Childhood brain tumors can present with focal neurological deficits, often referable to posterior fossa structures but they are usually associated with non-abrupt onset of symptoms unless there is a bleed into the lesion. Similarly acute disseminated encephalomyelitis (ADEM) typically has non-abrupt onset, often following an identifiable prodromal infection. Clues to the clinical diagnosis of ADEM include encephalopathy, seizures and *multifocal* neurological deficits referable to more than one location within the central nervous system.[30] Magnetic resonance imaging is the neuroimaging investigation of choice and typically shows multifocal lesions involving white matter, deep grey matter and sometimes the cerebral cortex. High dose corticosteroids are the mainstay of treatment.[30]

Childhood stroke is the most time critical of all neurological emergencies

Childhood stroke may be less common than other causes of brain attack symptoms but it is associated with high personal cost to affected children and their families,[31] because more than

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half of survivors have long-term impairments that interfere with normal development and lifestyle.[32-34] Licencing of tissue plasminogen activator in 1996 was a watershed moment for treatment of stroke in adults. The ischaemic penumbra is the biological target of thrombolytic treatments in acute stroke. Brain tissue which is destined to go onto infarction can be salvaged if blood flow is restored by vascular recanalisation.[35] As a consequence there is a major focus on reducing time delay to stroke diagnosis. Thrombolysis is established as an effective treatment if given within 4 and a half hours of from symptom onset, based on evidence from multiple randomised controlled trials.[36] Very recently several adult studies have confirmed the effectiveness of endovascular treatments (such as intra-arterial lysis and mechanical thrombectomy), when given within 6 to 12 hours from symptoms onset.[5-9] Therefore rapid radiological confirmation of diagnosis within 6 to 12 hours of symptom onset is the key to accessing thrombolytic or endovascular treatments to reduce the long term impact of stroke. Adult emergency stroke management guidelines recommend radiological confirmation of diagnosis within 45 minutes, decision to thrombolyse within 60 minutes and admission to a stroke unit within 3 hours.[37]

Delays to stroke diagnosis in children are much longer than adults with three studies reporting delays of more than 20 hours.[38-40] Systems of care do not currently exist for childhood stroke. In contrast to well-developed protocols for other neurological emergencies such as status epilepticus the Advanced Paediatric Life Support (APLS) guidelines do not contain algorithms for

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identification, investigation or management of children with brain attack symptoms relevant for stroke. (https://www.apls.org.au/page/about-us) Reasons for delayed presentation of children with stroke are poorly elucidated but include failure to call an ambulance, short duration[41] or mild symptom severity[38] and poor awareness of stroke amongst paediatric physicians.[39] Strategies are urgently required to reduce long term morbidity by improving identification and acute treatment of childhood stroke.

Clinical features which distinguish childhood stroke from mimics

Clinical differentiation of stroke from mimics is the first step in reducing treatment delays. More common presenting features of stroke include hemiparesis (22-100%), headache (16-45%), altered mental state (12-24%), speech disturbance (28-55%), altered consciousness (24-52%) and seizures (11-58%).[16, 41-45] Age at presentation influences the clinical presentation with seizures, altered mental state and non-focal signs being more likely in infants.[16, 43]

The frequent occurrence of seizures in childhood stroke[15-18] is a notable difference to adults.[1, 46]. This difference may reflect age related cortical hyperexcitiability or decreased inhibitory influences in the developing brain. In adults seizures are more likely to occur with mimics and are used as a predictor variable for mimic diagnosis in prehospital and emergency department bedside stroke recognition tools.[46-48]

Sudden onset symptoms of focal weakness, speech disturbance and headache and signs including face, arm, hand and leg weakness, dysphasia, dysarthria, inability to walk and altered

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conscious state are associated with increased odds of stroke. In contrast absence of focal signs on examination is with decreased odds of stroke.[49] Presenting clinical features differ by stroke subtype. Arterial ischaemic stroke is more likely to present with focal limb or face weakness, speech disturbance, limb incoordination or ataxia whereas haemorrhagic stroke is more likely to present with headache, vomiting and altered mental state.[50]

Bedside recognition tools improve accuracy of stroke diagnosis in adults

Whereas stroke recognition tools have been developed to improve paramedic[47, 48, 51] and emergency physician accuracy in differentiating stroke from mimics in adults[46] no such tools exist in children and a preliminary analysis of adult bedside tools in childhood arterial ischaemic stroke found that they had lower sensitivity than reported in adult studies.[52]

Emergent imaging is the key to confirming diagnosis and selecting appropriate treatments

Standard adult stroke protocols recommend CT imaging to identify intracranial haemorrhage because it is a contraindication to thrombolysis.[37] The higher a priori probability of stroke in adults means there is a low likelihood of inappropriately administering thrombolytic treatment to someone with a stroke mimic. In contrast mimics are more common in children and therefore specificity of brain imaging is very important. Computed tomography has the advantage of greater accessibility to emergency physicians. It is adequate for identification of intracranial haemorrhage but has poor sensitivity for detection of acute brain ischaemia,

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ranging from 16% to 56% in paediatric studies.[38-41, 50] Therefore MRI is the diagnostic modality of choice for suspected arterial ischaemic stroke.[53]

Rapid MRI in adult stroke in the ED may allow more accurate positive identification of stroke and mimics.[54] The latter finding is particularly relevant to children given the lower a priori probability of stroke. However the need for sedation in young children presents an additional challenge in the paediatric emergency setting.

Computed tomography is also relatively insensitive to detection of demyelinating lesions, acute encephalitis and detection of posterior fossa tumors due to bony artefact from the base of skull. Therefore MRI is also the neuroimaging investigation of choice for children with suspected ADEM, viral encephalitis and posterior fossa tumors.

Management of neurological emergencies in the ED

Urgent interventions are required for several serious neurological disorders. Treatments may include antibiotics for meningitis, antiviral agents for encephalitis, anticonvulsants for status epilepticus, immunotherapies for acute disseminated encephalomyelitis and transverse myelitis and mannitol, steroids or neurosurgical interventions for raised intracranial pressure. Acute treatment of childhood stroke currently focuses on normalisation of physiological parameters and early initiation of secondary preventative anticoagulant or antithrombotic treatment. Paediatric stroke management guidelines do not currently recommend tPA usage in children because there is a paucity of efficacy and safety data for tPA in children.[55, 56]

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Conclusions and future directions

The spectrum of disorders causing paediatric brain attack symptoms differ to adults with migraine, seizures and Bell's palsy being the most common conditions. The presenting symptoms and signs which discriminate stroke from mimics are similar to adults but seizures are a common presenting feature of stroke in children and therefore they are not discriminatory for mimics. This represents an important difference from adults and means that bedside stroke recognition tools, which are widely used by paramedics and in the ED, may not be as accurate in children to differentiate stroke from mimics. Haemorrhagic and ischaemic stroke have different presenting features which influence the choice of the most appropriate imaging modality to maximise accuracy of radiological diagnosis. Children presenting with sudden onset headache, vomiting and coma have a higher probability of haemorrhagic stroke and CT is the most appropriate acute neuroimaging modality. Children presenting with sudden onset focal symptoms and signs have a higher probability of ischaemic stroke and MRI is the preferred first imaging modality.

Better and earlier diagnosis of brain attacks, in particular the differentiation between stroke and non-strokes, are crucial for developing the capacity to offer thrombolysis to select children with ischaemic stroke to improve long term outcomes.

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