

CASE REPORT

Disturbance of motor development: a manifestation of stroke in early childhood

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SUMMARY

Stroke has been recognised more frequently in children and represents a major cause of morbidity and mortality. It usually has an acute presentation, characterised by focal neurological signs, headache, altered state of consciousness or seizures. We report the case of an 18-month-old male child with motor development disturbance, gait difficulty and preferential use of the left arm with right hemiparesis at clinical exam. Brain MRI showed an extensive damage involving corona radiata, thalamus, posterior arm of the internal capsule and left lenticular nucleus with atrophic retraction of the adjacent cerebrospinal fluid pathways, suggesting old ischaemic injury of the middle cerebral artery territory. Causal research pointed out at methyltetrahydrofolate reductase (MTHFR) C677T heterozygosity. He was referenced to physiotherapy and paediatric neurology consultation with favourable evolution and no recurrence of ischaemic events. Stroke is a relatively rare phenomenon in children; however, we have to consider it as a diagnosis in the presence of focal neurological deficits. MTHFR C677T mutation is considered a prothrombotic factor; however, in the absence of hyperhomocysteinaemia, no direct therapeutic approach is necessary.

BACKGROUND

According to the WHO, stroke is defined as a clinical syndrome that results from irreversible injury to the brain parenchyma, secondary to a vascular abnormality, resulting in death or the development of focal or global cerebral dysfunction.^{1,2} It is, however, a relatively rare disease, with an overall incidence estimated to 2.5–2.7:100 000 children,¹ although it is among the 10 leading causes of infant mortality, with an estimated rate of 0.6:100 000 children per year,^{1,3} which is higher in the first year of life. It also leads to high morbidity and often severe consequences; hence, the long-term evolution and socioeconomic costs involved in follow-up of this disease are currently gaining increasing interest. Over half of the children who survive the present neurological sequel and, in 25% of the cases, focal epilepsy;³ recurrence is reported in about one-third of the children. Epidemiological studies conducted in the UK showed a peak incidence in the first year of life, especially in the neonatal period, as well as a higher risk of cerebrovascular events in boys and African individuals.²

As in adult population, stroke can be classified into ischaemic or haemorrhagic, according to the pathological process involved. Ischaemic stroke is

slightly more frequent (55% vs 45%).^{3,4} Comparatively, haemorrhagic stroke is associated with higher mortality, but lower risk of recurrence.¹

Classically, the clinical presentation is associated with a sudden onset of focal neurological signs and symptoms, correlated with the territory of cerebral blood supply that has been affected; however, the symptoms may install more gradually, particularly in case of a bleeding event that, in addition to the effects of focal ischaemia, must take into account changes in intracranial pressure and cerebral oedema, which may restrict the impact of brain function at distant points. In children, however, conditions attached to age and mechanisms of neuronal plasticity may be able to generate more subacute presentation. About half of children who present with a focal neurological deficit of vascular cause have a risk factor previously identified.³ There are similarities and differences between the predisposing factors to ischaemic or haemorrhagic stroke (table 1). Certain genetic diseases of genetic factors (Down syndrome, homocysteinaemia, sickle cell disease) are risk factors for any type of stroke. In the case of ischaemic stroke, the most frequent predisposing clinical entities are haematological disorders (sickle cell anaemia and thalassaemia) and congenital or acquired heart disease; thrombophilias, such as protein C deficit, antiphospholipid antibody syndrome, factor V Leiden or prothrombin G20210 mutations, are more frequent in the population with ischaemic stroke than in healthy controls.² In the case of haemorrhagic stroke, vascular anomalies and traumatic injuries are the most frequent.

Intermediate risk factors include hypertension, dyslipidaemia, elevated lipoprotein, iron deficiency anaemia and infections. According to some authors, at least one-third of all cases occur with infection,² the majority of cases by vasculitis; the infectious agents most often associated are varicella-zoster virus, cytomegalovirus, enteroviruses, HIV, *Mycoplasma pneumoniae*, *Borrelia burgdorferi* and *Toxoplasma gondii*. Central nervous system infections are also known risk factors for stroke, especially if there is central vein thrombosis. In addition, risk factors include migraine, drug abuse and various metabolic disorders (such as mitochondrial disorders or organic acidaemias).^{4–6}

CASE PRESENTATION

Male child, 18 months old, referred to the paediatric consultation by disruption of motor development, difficulties on running gait and preferential use of the left arm, alterations that were noted by

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Table 1 Risk factors for stroke in paediatric age

Arterial ischaemic stroke	Venous circulation stroke	Haemorrhagic stroke
Vascular	Bleeding disorder	Vascular changes
Focal cerebral arteriopathy	Prothrombotic conditions: factor V Leiden, Prothrombin 20210A)	Arteriovenous malformations
Postvaricella angiopathy	Acquired thrombophilia (eg. Deficit protein C, S, antithrombin III, lipoprotein (a), anti-phospholipid antibody, oral contraceptives, pregnancy/puerperum)	cavernous malformations
Transient cerebral artery	Dehydration	angiomas
Primary CNS angiitis	Iron deficiency anaemia	Hereditary haemorrhagic telangiectasia
Systemic vasculitis (Takayasu arthritis)	Toxic/drugs (contraceptives, L-asparaginase)	Intracranial aneurysms
Cranium-cervical arterial dissection	Chronic systemic disease (IBD leukaemia)	Syndrome/moyamoya disease
Syndrome/moyamoya disease	Nephrotic syndrome	Vasculitis
Blood infection (bacterial meningitis, tuberculosis)	Metabolic disease (homocystinuria)	Neoplastic lesions
Fibro muscular dysplasia		Drugs/toxins (cocaine, amphetamines)
Vasospasm (Call-Fleming syndrome) migraine		Changes clotting
Congenital arteriopathy (eg, PHACE syndrome)		Idiopathic thrombocytopenic
Cardiac	Vascular changes	Coagulation changes
Complex congenital heart disease (cyanotic<<acyanotic)	Infection: acute otitis media, mastoiditis, meningitis, bacterial syndrome Lérié	Idiopathic thrombocytopenic purpura
Cardiac catheterisation	Trauma: fracture skull bones	Haemolytic uraemic syndrome
Surgery	Compression: tocotrauma	Liver disease
Arrhythmia	Iatrogenesis: neurosurgery, ECMO	Consumption coagulopathy
Valvulopathy	Venous malformations, dural arteriovenous fistulae	vitamin K deficit (haemorrhagic disease newborn)
Endocarditis		
Cardiomyopathy		
Intracardiac lesions (eg. atrial myxoma)		
Patent foramen ovale		
Haematological		Trauma
Sickle cell anaemia		Epidural haematoma
Iron deficiency anaemia		Subdural haematoma
Hereditary thrombophilia (eg. Factor V Leiden, Prothrombin 20210A)		Subarachnoid hemorrhage
Acquired thrombophilia (eg, deficit protein C, S, antithrombin III, lipoprotein (a), antiphospholipid antibody, oral contraceptives, pregnancy)		Bruises

CNS, central nervous system; IBD, inflammatory bowel diseases.

his mother only when he starts walking by himself. He was the only child of a first-term pregnancy, which was uneventful; pregnancy was followed by an obstetrician, and the prenatal ultrasonography and serology made did not reveal any significant changes.

The labour was performed at 39 weeks of gestational age, in an obstetric centre, and the neonatal period was uneventful too. There was no pathological background and the chronology of psychomotor development was normal, with major acquisitions in key ages, including the global motor function, with the exception of gait disturbance and precocious motor lateralisation.

Family history was irrelevant, mainly with respect to the occurrence of cardiovascular events early in life, history of miscarriages, consanguinity and history of development, cognitive or neurological problems in other children. On physical examination, neurological assessment a right hemiparesis with hemiplegic gait, decreased muscle strength (grade IV/V) and right hemisphere dominance in the left upper limb were found; the remaining examination was normal with no changes in skin pigmentation, organomegaly, dimorphisms or others.

INVESTIGATIONS

Brain MRI showed an extensive area of encephalomalacia interesting corona radiata, thalamus, posterior arm of the internal capsule and left lenticular nucleus with atrophic retraction of adjacent routes, suggesting old infarction in the territory of middle cerebral artery. No evidence of moyamoya (figures 1 and 2).

Given the evidence of an old ischaemic stroke, aetiological investigation was performed, taking into account the most important risk factors for this disease in paediatric population.

Laboratory tests were made, including haematological and thrombophilia screening, lipid profile and some viral serologies (mainly varicella-zoster virus and echovirus), only revealing methyltetrahydrofolate reductase (MTHFR) 677C> T mutation in heterozygosity with normal values of homocysteine.

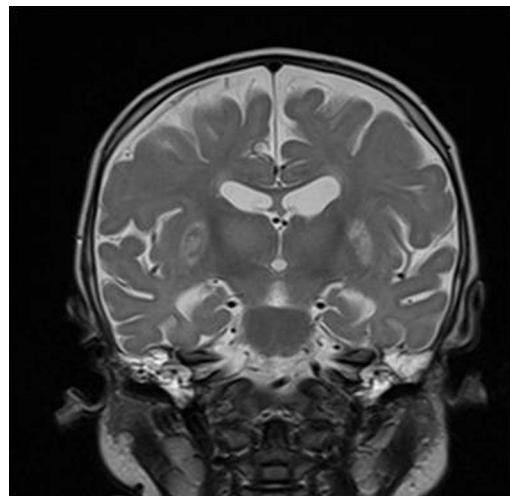


Figure 1 Encephaloclastic injury compatible with old infarction in the territory of middle cerebral artery.

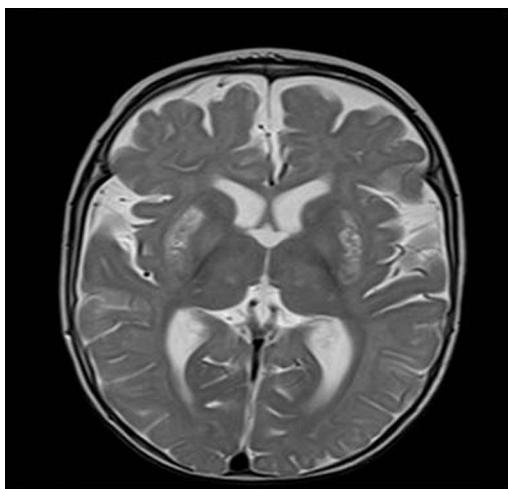


Figure 2 Encephaloclastic injury compatible with old infarction in the territory of middle cerebral artery.

Transthoracic echocardiography was performed and no anatomical or functional alterations were found.

TREATMENT

Set up monitoring plan for medicine and rehabilitation with physical therapy and occupational therapy biweekly with almost a complete recovery of deficits to date.

OUTCOME AND FOLLOW-UP

Maintain follow-up at paediatric neurology consultation, and no recurrence of cerebral ischaemic events was recorded; the development has been age-appropriate, but he maintains the use of the left upper limb predominantly.

DISCUSSION

This case highlights a subacute presentation of a rare disease in children. Stroke in children presents with highly heterogeneous clinical manifestations depending on the age, pathophysiology of the event and the anatomical site of vascular injury. In this case, the time of installation of injury remains difficult to determine; however, we assume the occurrence of ischaemic stroke in the perinatal period, which is more common, with later clinical repercussion, according to normal motor development and myelination phenomena of the central nervous system. In children, the diagnosis is not always made at perfect time, given subtle clinical presentation, often non-specific or subacute, with wide differential diagnosis.^{5,7} The sudden onset of a focal neurological deficit in children is, until proven otherwise, a stroke^{1,2,5}; in this context, neuroimaging should be readily accomplished since it constitutes the first line in the diagnostic approach of focal^{3,6} neurological deficits, with a definitive study made by MRI because of its superiority including greater diagnostic acuity, possible prognostic evaluation, detection of vascular anomalies and better evaluation of the venous system.

There are no consensus guidelines for the evaluation of stroke in children, but systematic approaches including the assessment of haematological, metabolic and cardiovascular risk factors are internationally recommended. In our case, after extensive evaluation, we have only identified MTHFR 677C>T heterozygosity. According to the literature, aetiology of paediatric stroke cannot be determined in one-third of cases.⁸ In other cases, we can consider three main groups of causes/risk factors: vascular, cardiac

and haematological.⁹ Haematological causes include also the prothrombotic stages, inherited or acquired. Among procoagulant mutations, there are genetic polymorphisms of the enzymes involved in homocysteine metabolism, which confer an increased risk of thromboembolic events. Population studies have shown that among these enzymes, homozygosity for mutations of the MTHFR 677C>T is associated with increased risk for not only stroke but also coronary heart disease and migraine-type headache.⁶ Retrospective studies directed at the paediatric population have also shown an association between genetic polymorphisms of MTHFR and cerebral ischaemic events; however, this group of mutations is now considered a minor risk factor, except in the presence of hyperhomocysteinaemia.^{7,10,11}

Despite it representing a low-risk mutation, it becomes important to evaluate this family and to study of genetic polymorphisms associated with MTHFR, a condition that is relevant in this context to identify cases with higher risk not only of thromboembolic events but also risk of other deleterious effects that this prothrombotic mutations in female individuals (which are more prone to obstetric pathology, being reported higher incidence of miscarriage, hypertension, pre-eclampsia or thrombotic events during pregnancy); so, it may be relevant to plan a referral to a genetic consultation with this purpose of study and make the individual genetic counselling.¹⁰

Learning points

- ▶ The presentation of this case is relevant because it makes reference to a rare diagnosis in paediatric population and, more particular still, with a subacute presentation.
- ▶ Brain MRI is the most accurate image testing in the investigation of focal neurological signs.
- ▶ Moreover, besides all the complementary investigation that was made, the only positive finding was an heterozygosity mutation on methyltetrahydrofolate reductase that in this case, with normal homocysteine blood levels, acquires a minor importance for this event, but requires careful family study with the purpose of individual risk and genetic counselling.

Contributors All the authors declare that they had actively participated on the observation of the child, review of the literature and writing of the present article.

Competing interests None.

Patient consent Obtained.

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