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Ischaemic Stroke Post-Varicella Infection: A Vaccine Preventable Disease

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Abstract

Introduction

Ischaemic stroke is an established complication of primary varicella infection. We discuss three cases of post-varicella ischaemic stroke.

Case 1

A 4-year-old boy presented acutely with right-sided hemiparesis. Neuroimaging showed an area of ischaemia centred at the left putamen.

Case 2

A 2-year-old boy presented with ataxia and left-sided hemiparesis. MRI brain revealed abnormal diffusion and T2 flair in-keeping with acute MCA infarct.

Case 3

An 18-month-old boy presented with right monoplegia and intermittent ataxia. CT brain revealed low density lesion in the basal ganglia.

Results

Treatment in each case included methylprednisolone and aspirin, with or without acyclovir. Each patient demonstrated symptom improvement while an inpatient.

Discussion

Varicella associated stroke accounts for almost one-third of childhood ischaemic strokes. With the availability of a safe, effective vaccine for primary varicella the argument for universal vaccination becomes stronger when cases with neurological complications are considered.

Introduction

Stroke ranks in the top 10 causes of death among children in high income countries. [1] Childhood stroke has an incidence of 1-13 per 100,000 per year and a reported mortality of 3-7%. [2-6] It is accepted that over 60% of children have persisting deficits following childhood stroke. [3, 5, 7] The past 20 years have seen a 35% increase in the prevalence of paediatric stroke. [8]

Ischaemic stroke is an established complication of primary varicella infection. [9, 10] The varicella vaccine is effective against acute infection and it also reduces the risk of later complications. [11, 12] The chickenpox vaccine is not part of the routine childhood vaccination programme in Ireland. We present 3 recent cases of childhood ischaemic stroke, linked to previous primary varicella infection presenting to our paediatric emergency department (ED).

Case 1

A 4-year-old male presented following episodes of drooling, limp and confusion. He had been well in school until 2 hours prior to presentation when he developed drooling and a limp. The parent was immediately informed, and the symptoms had resolved by the time they arrived at the school. Approximately 1 hour later at home, he had a 2nd acute neurological episode which manifested as being quieter than usual, drooling and not using right upper and lower limbs. He was brought to the ED where, again, the symptoms had resolved on arrival. A 3rd episode was observed in the department with drooling from the right side of mouth and persistent right hemiparesis. His lowest Glasgow Coma Scale (GCS) score was 13/15.

He was generally healthy. His development was appropriate for age. He had experienced primary varicella infection 3 months prior to this episode. He tolerated his primary varicella infection well with only one day of fever.

An urgent computed tomography (CT) brain was performed which showed an area of low attenuation lateral to the genu of the internal capsule. A CT angiogram was performed which showed a possible reduction in the calibre at the origin of the horizontal section (M1) of the middle cerebral artery, but no obvious filling defect.

The neurology team was consulted, and patient was commenced on oral aspirin, intravenous methylprednisolone and intravenous acyclovir in view of the history of varicella infection. On re-assessment 3 hours post-presentation his GCS was 15/15 but mild right-sided weakness with brisk lower limb reflexes were noted.

There was no further deterioration post admission, however mild right-sided hemiparesis persisted. Word finding difficulties were noted and initially the patient would only speak in short sentences. In-patient therapy included physiotherapy, occupational and speech and language therapy.

Magnetic resonance imaging (MRI) on day 7 of admission confirmed a 3cm area of hyper-intensity centred at the posterior aspect of the left putamen and globus pallidus. This was thought to represent an area of ischaemia secondary to post-varicella vasculitis.

Initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) was positive for varicella. A 7-day course of intravenous steroids was completed. A repeat lumbar puncture 2 weeks into his admission was negative for varicella on PCR. At this point acyclovir was stopped.

A hospital stay of over 3 weeks was required. Symptoms improved throughout admission. On discharge the patient had a very mild residual motor deficit. His speech had improved significantly, approaching premorbid state. Ongoing follow up with multi-disciplinary team input is in place.

Case 2

A 2-year-old male presented with a 2-hour history of failure to habitually suck the left thumb and unsteady gait. A similar episode had been noted the day prior to ED presentation which resolved completely after one hour.

Patient was generally well with no current or recent pyrexial illness. Development was appropriate for age. A primary varicella infection had occurred seven months prior to presentation.

Clinical examination demonstrated an alert child with left-sided hemiparesis, associated drooling and ataxia. Tone and reflexes were normal. CT brain showed no evidence of haemorrhage. CT angiogram showed minor narrowing at section two of the right middle cerebral artery (MCA). MRI brain demonstrated abnormal diffusion and hyper-intense T2 flair within the right putamen, in-keeping with an acute MCA infarct. MRI also revealed an attenuated segment of the MCA consistent with vasculitis.

Treatment was commenced with oral aspirin and intravenous methylprednisolone. Lumbar puncture was not performed. Initial blood tests including coagulation screen were normal. Varicella zoster immunoglobulins confirmed previous infection with IgG >1000 u/ml and negative IgM.

Physiotherapy, occupational therapy and speech and language therapy were provided during his hospital admission. Symptoms improved quickly. Patient was back to baseline on discharge from hospital, six days after presentation. He will continue to be monitored by the neurology team in the community.

Case 3

An 18-month male presented with inability to use his right hand since morning and difficulty crawling, without a history of trauma or fever. His parents had noticed intermittent unsteady gait for the preceding 2 weeks. He had primary varicella infection 5 months earlier and had hand, foot and mouth disease 3 months prior.

A simple febrile convulsion had occurred 4 weeks before presentation and he was treated as an outpatient in accordance with local guidelines. Patient had attained normal developmental milestones.

On clinical examination he was alert and active. His gait was steady with no ataxia. His right hand was held in a fist. There was no facial asymmetry or cranial nerve palsies. Tone in the right upper limb was increased compared with the left, with reflexes present and symmetrical. Power in right upper limb was 3/5 compared with 5/5 in the left. Extensive laboratory investigations were performed, full blood count initially showed leucocytosis with eosinophilia.

CT scan demonstrated subtle low attenuation in the left globus pallidus. Patient was commenced on methylprednisolone, acyclovir and aspirin in the ED. Intravenous acyclovir was continued for 2 weeks.

MRI under general anaesthesia confirmed a small area of diffusion restriction in the left globus pallidus, consistent with ischemia. MR angiography revealed narrowing of the left anterior cerebral artery and left middle cerebral artery. Lumbar puncture was carried out which was negative for varicella zoster PCR.

Motor symptoms improved during the first 2-3 days of his admission. However, he developed a hemi-chorea which persisted at time of discharge; he is being followed by the outpatient paediatric neurology team.

Results

This series presents 3 cases of paediatric stroke occurring as a sequela of primary varicella infection. These 3 cases presented to the ED over a period of 17 months. All 3 cases demonstrated significant clinical improvement while in hospital, but one patient developed a significant complication, chorea. The literature confirms that many children will be left with long-term deficits post-stroke. [5, 7] The 3 cases reviewed demonstrate some variance in management. Patients in Case 1 and Case 3 were treated with intravenous acyclovir and had a lumbar puncture performed. In Case 2 the child did not undergo lumbar puncture and was not treated with acyclovir as his serum showed no signs of active infection. In the literature, benefits and duration of various treatments are debated. A systematic review of reported cases found that 17 out of 29 cases of post-varicella stroke had a lumbar puncture performed. This review also found no difference in outcome whether or not children were treated with antiviral therapy. [13, 14]

In all 3 cases there was a delay in presentation from symptom onset to medical review. The intermittent nature of symptoms or delayed recognition of the seriousness of the symptoms most likely contributed to this delay. The Royal College of Paediatrics and Child Health childhood stroke guidelines provide a comprehensive evidence-based approach to diagnosis and clinical management, along the child's journey from initial presentation, through to rehabilitation and beyond. [15]

Obstacles to accessing hyperacute therapies for suspected paediatric stroke include poor clinical recognition by parents, prehospital and emergency care providers, and the logistical challenges to rapid diagnostic brain imaging. [16]

Discussion

Adult stroke is linked to indirect risk factors such as hypertension or smoking, whereas paediatric stroke is more likely to have a direct risk factor such as congenital cardiac disease, inherited thrombophilia or sickle cell disease. [17] Over 40% of children with ischaemic stroke have at least one direct risk factor for stroke. [18] In contrast to this, in cases of post-varicella stroke, children are much more likely to be previously well. [19] Neurological manifestations of varicella infection have been observed to occur from 1 week to 12 months after primary infection. [20] Askalan et al. reported that varicella-associated acute ischaemic stroke accounts for almost one third of childhood ischaemic strokes.[19] Recurrence of ischaemic stroke or transient ischaemic attacks is reported in one quarter to one third of childhood post-varicella stroke. [11, 20] There is a paucity of data regarding rates of paediatric stroke in Ireland and no incidence rates for post-varicella stroke in Ireland were found.

The varicella vaccine is safe and effective in preventing varicella infection in children. On ten year follow up, the vaccine was shown to be 98.3% effective in preventing primary varicella infection when 2 doses were given. Vaccine effectiveness was also high for a single dose (94.4%); however, children who received 1 dose compared with 2 were 3 times more likely to develop primary varicella infection (2.2% v 7.3%). [11, 12] The World Health Organisation recommends that countries where there is an important public health burden could consider introducing the varicella vaccine into the routine childhood immunisation programme. [21] The varicella vaccine has been used as part of large universal vaccination programmes in other European countries and the USA. [11, 12, 22] In Ireland, varicella vaccines are not yet part of the universal vaccination schedule. Varivax® is the only licenced varicella vaccine in Ireland. It is a live attenuated vaccine, recommended for use in children over 1 year of age and adults. It is given in a 2 dose schedule, at least 4 weeks apart. [23] Acute varicella infection places a substantial burden on Irish hospitals with over 200 admissions annually. Acute varicella infections impact adult health also, with 19% of admissions in those over 18 years of age. Acute varicella infection uses 1100 acute and 160 intensive care bed days each year. [24]

Case reports previously raised the possibility of a link between varicella vaccine and increased risk of ischaemic stroke. As the varicella vaccine is a live vaccine this link was thought to be scientifically plausible. [25] A large population-based study looked at over 3 million children, including 1.14 million that had been given the varicella vaccine. This study demonstrated that children who received the varicella vaccination had significantly lower levels of ischaemic stroke than the unvaccinated children. [11] Therefore this concern is no longer a valid reason to withhold varicella vaccination.

Any child with acute neurological symptoms (intermittent or fixed) consistent with stroke should seek emergency care immediately, with pre-notification to the receiving institution being strongly recommended.

Previous varicella infection should be considered as neurological symptoms can occur up to a year following chicken pox. [20] The management of post-varicella stroke in children remains variable with little high quality evidence to guide management decisions.[13, 14]

Universal vaccination would reduce the burden of hospital admissions for varicella infection in Ireland. [24] With the availability of a safe and effective vaccine against primary varicella infection, the argument for universal vaccination is further strengthened by case series which demonstrate the significant sequelae of infection, such as those detailed in this paper.

Declaration of Conflicts of Interest:
The authors declare no conflicts of interest.

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