Issues Surrounding Childhood Stroke : A Case Report and Review of the Literature

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Case Report
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Issues Surrounding Childhood Stroke :
A Case Report and Review of the Literature

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Abstract

Childhood stroke is a neglected area of research, and the lack of evidence makes its management a challenging area for clinicians. The UK childhood stroke guidelines are discussed in conjunction with the American guidelines, and the areas of controversy are highlighted. This case report explores the medical, surgical and critical care issues surrounding the management of paediatric ischaemic stroke in detail, including issues of thrombolysis, anticoagulation, and complications of acute ischaemic stroke. Due to the heterogeneity of underlying childhood stroke aetiology, primary and secondary prevention measures pertinent to this case are also discussed. Finally, recommendations for stroke aftercare are briefly summarized.

Case presentation

A 16-year-old girl presented to the emergency department at 0600 hours in the morning and was noted to have dense right-sided hemiparesis (facial droop, weakness in upper and lower limbs) and global aphasia. As the patient had been asleep since 01:00 h, her symptoms were only observed by family members when she awoke at 5:00 h, hence the exact time of onset of the stroke could not be ascertained.

On admission, the patient's Glasgow coma score was 9 (eye-opening: 2, verbal: 2, motor: 5). She was extremely agitated, hence required intubation and sedation for computed tomography (CT) of her head. The CT scan demonstrated a thrombus occluding the left middle cerebral artery with no distal flow, resulting in a large infarct of the associated territory.

The consensus amongst senior physicians was that the patient was unsuitable for thrombolysis given that the time of onset to that of diagnosis was greater than the three hour time-frame, and that the infarct was at high risk of haemorrhagic transformation due to its large size. She was given a dose of 300mg of aspirin and subsequently arranged for transfer to the intensive care unit at a specialist hospital later in the day.

The patient had a complex cardiac history of a large, congenital ventricular septal defect. She had undergone pulmonary artery banding and a modified Fontan procedure with intra-arterial conduit at the age of 2, and was consequently warfarinised. However, historical medical records revealed poor compliance to warfarin for a number of years. For a period of 5 years from 2003, it was noted that she has not attended any cardiology review appointments for unknown reasons, before being followed up again in 2008. In addition, she stopped taking warfarin about 3 weeks prior to this event through her own volition, which is suspected as the most likely precipitant of the stroke.

Upon transfer to the intensive care unit, the patient was maintained on sedation and mechanical ventilation. Neurosurgeons were consulted regarding concerns of the risk of raised intracranial pressure (ICP) with the possibility of requiring decompressive surgery. It was decided for the patient's intracranial pressure to be monitored by insertion of an ICP bolt.

The patient's ICP had been noted to be continually labile, and continued to require mechanical ventilation. Attempts to withdraw sedation for neurological assessment were complicated with associated rises in ICP, poor cerebral perfusion pressures, and agitation, all of which had to be corrected by reintroducing sedation.

A transthoracic echocardiogram did not reveal an intracardiac thrombus, and showed that the Fontan circulation intact. A magnetic resonance (MR) scan confirmed the diagnosis and did not show significant brain swelling.

On day 9 the patient was reinstated on anticoagulation (warfarin). She was extubated on day 10 as was noted not to require invasive ventilatory support. Over the next few days, she demonstrated steady neurological improvement and her agitation had decreased. By day

13, she was stable enough to be transferred to the stroke unit.

Clinical Problem

Stroke or cerebral vascular event is defined by the World Health Organisation (WHO) as a "focal neurological deficit of cerebrovascular cause persisting for longer than 24 hours or leading to death".[1] Childhood stroke, although relatively infrequent compared to stroke in adults, represents a significant cause of mortality in children and also a major cause of disability. It is estimated that stroke affects 2-3 of 100,000 children per year.[2]

Stroke management has revolutionized in the last decade since the publication of the National clinical guidelines for stroke in 2000. Stroke units in the country are equipped to administer acute treatment, which adults have access to.[3] The management of adult stroke is also well supported by a substantial body of evidence. This is, however, not the case in the management of stroke in children, which is still a neglected area of research. Many areas of acute medical treatment remain controversial. The lack of evidence and experience in dealing with childhood stroke makes the management of childhood stroke a clearly challenging issue, taking into account the significant impact stroke has on a child's future.

Causes of Stroke in children

Part of the difficulty in establishing treatment guidelines can be attributed to the heterogeneity of underlying aetiology in childhood stroke. A wide range of disorders can lead to stroke in children (Table 1). The most common underlying disorders are cerebrovascular diseases and cardiac abnormalities.[4] The ratio of ischaemic stroke to haemorrhagic stroke in children is roughly 1:1 compared to that of adults which is 2:1.

Genetic
Dyslipoproteinaemia (Familial hypercholesterolaemia) Connective tissue disorders (Marfan syndrome) Mitochondrial encephalomyopathies (MELAS, MERRF) Neurofibromatosis type I
Thrombophilic states
Antithrombin deficiency Protein C or S deficiency Clotting factor deficiencies Malignancy Oral contraceptives Diabetes mellitus Sickle cell disease
Cerebral Vascular Abnormalities
Moyamoya disease or syndrome Cerebral vasculitis Arterial dissections
Cardiac Abnormalities
Congential heart disease (Ventricular/atrial septal defect, Fallot's tetralogy, coarctation of aorta) Diseases of heart valves Arrhythmias Cardiomyopathies (MI, myocarditis, atrial myxomas)

Table 1: Some causes of childhood stroke.[4]

Diagnosis, Investigations and Management

Children with stroke can present acutely with hemiparesis, or with more subtle features such as seizures, behavioural alterations and a lower conscious level.[1] Diagnosis of stroke in children can be difficult. Other diseases mimicking ischaemic stroke should be excluded, namely haemorrhagic stroke, electrolyte imbalances such as hypoglycaemia, epilepsy, or brain tumours.[5] For instance, an urgent CT scan may help in differentiating between ischaemic and haemorrhagic subtypes of stroke.

The Royal College of Physicians has published recommendations in 2004 for the diagnosis and management of paediatric stroke (patients age between 1 month and 18 years) to address the lack of published guidance relating to childhood stroke management.[1] The

publication has identified controversial areas surrounding childhood stroke management, but has not committed to giving specific recommendations.

The American Heart Association has also released guidance for childhood stroke management (2008).[4] Despite being more comprehensive than the Royal College's guidelines with recommendations organised into aetiological subtypes, recommendations are similarly based on observational data and are non-prescriptive. Due to the universal lack of substantial evidence in childhood stroke literature, current recommendations are drawn from adult guidelines, theoretical frameworks and anecdotal sources.

The rest of this section serves to summarise the recommendations based on a combination of these guidelines.

Urgent imaging is required for all patients to establish the diagnosis and to aid subsequent management. The main stroke subtypes are arterial ischaemic stroke, venous thrombosis, and haemorrhagic stroke. Imaging modalities which may aid diagnosis and management include MR, CT or ultrasound. In some instances, catheter angiography may be necessary if non-invasive imaging is inconclusive. CT or MR venography studies can be used to investigate for presence of a venous event. Further imaging at a later day (e.g., when MR scan becomes available) may be important in determining cerebrovascular changes.[4]

Additionally, all children with stroke will need to be investigated for causative diseases to aid in management and prevention of recurrent stroke. For instance, patients with arterial ischaemic stroke may require a thrombophilia screen and a transthoracic echocardiogram.[1]

Acute Care

The standard ABCD (airway, breathing, circulation, disability) approach in the emergency care of a child should be employed.

The patient's airway should be secured if there is a suspicion that the patient is unable to maintain his/her own airway adequately. Patients with a low to moderate GCS or brain stem abnormalities are at particular risk. These patients will most likely require endotracheal intubation and anaesthetic/critical care support.[5]

Of immediate concern are the child's oxygen requirements.[5] Hypoxic patients should be supplemented oxygen with their oxygen saturation maintained above 94% to prevent further brain damage, and have their oxygen saturation levels continually monitored.[3]

Depending on the suspected cause of stroke, paediatric neurological or cardiological input is beneficial and should be sought early.[1]

Specific Medical Management

Once radiological confirmation of the stroke diagnosis has been obtained, specific treatments can be considered. This subsection deals with ischaemic stroke.

Thrombolytic therapy

There is currently no consensus on whether thrombolytic therapy is indicated in children with ischaemic stroke. Scant evidence exists for the use of thrombolytic treatment (rtPA) in children.[12,14,15,16] In adults, the risk of haemorrhagic transformation associated with thrombolytic therapy is 6%.[3] The rate in that of children is unknown. One study of 2904 ischaemic child stroke patients with 46 receiving thrombolysis showed "unclear benefit".[2]

One question worth considering in the patient presented in this report is whether she would have benefited from thrombolytic therapy. The paediatric stroke guidelines define childhood as less than 18 years of age.[1] Although it is generally accepted that emergency thrombolysis is not indicated in young children,[6] its indication in patients belonging to the adolescent age group has not been addressed. Individual case reports have shown some success in its use.[7, 8] In adults, treatment with alteplase is recommended in confirmed ischaemic stroke if the time of presentation is <3 hours of stroke onset.[3] Before larger studies on the safety of thrombolysis in children become available, the decision to administer thrombolytic therapy in children has to be an individual clinical judgment.

In practice, thrombolysis is rarely used in paediatric stroke patients. The reluctance of administering thrombolysis may be attributed to the fact that most child stroke cases do no present within 3 hours of onset, and the lack of published evidence regarding the safety of thrombolysis.[9] An American study of[5,8,13] paediatric patients with ischaemic stroke revealed that less than 1% of patients received thrombolytic therapy.[10] The study also showed that aggressive treatment of stroke in children, such as catheter or surgical interventions, are uncommon.

Anticoagulation & Aspirin

Ischaemic stroke is most commonly caused by a thrombotic or embolic event. Furthermore, patients with stroke are at risk of venous thromboembolism associated with immobility. However, patients are also at risk of gastrointestinal bleed, and infarcted brain areas can undergo haemorrhagic transformation in the days following the acute event.[3] These contrasting sets of risks should be balanced up when considering anticoagulation therapy, and should be informed by clinical observations and radiological evidence.

It is recommended that anticoagulation should be started in patients with arterial dissection or venous sinus thrombosis. Anticoagulation in children with cardiac

embolism is controversial (associated with increased risk of haemorrhage) and should therefore be discussed with a relevant consultant paediatrician.[1]

Aspirin 5mg/kg/day is indicated in patients with arterial ischaemic stroke confirmed by imaging, but without radiological signs of intracranial haemorrhage or sickle cell anaemia. Children with specific diagnoses such as sickle cell disease and moyamoya syndrome should be assessed by specialist teams for treatment which may include tranfusions and surgery.[1]

Other Measures

The patient's cardiovascular status should be monitored at least in the initial period. Stroke patients are at risk of secondary myocardial infarction and cardiac arrhythmias. Electrocardiogram changes associated with stroke include ST depression and T-wave inversion. Often blood tests may reveal raised cardiac enzymes. Serious arrhythmias should be treated as they can be life-threatening.[5]

Blood Glucose Control

Hyperglycaemia after an acute ischaemic stroke is associated with poor outcomes. Based on recommendations for adults, blood glucose levels should be maintained between 4 and 11 mmol/l.[3]

Blood Pressure Control

The patient's blood pressure should be controlled within normal parameters. Both hyper- and hypotension are related to poor outcomes.[3]

Hypertension is thought to worsen cerebral oedema, haemorrhagic transformation, and damage to blood vessels. Hypertension spontaneously resolves after the first day of stroke. Whether or not to treat hypertension in the initial presentation of stroke should be judged clinically. An exception is patients who are about to receive thrombolysis should have their systolic blood pressure stabilized below 180mmHg before therapy.[5]

Hypotension can lead to impaired cerebral perfusion and neurological compromise.[5] The patient's arterial pressure should be balanced with the patient's cerebral pressure requirements. This is discussed in further detail in the section on critical care monitoring.

Temperature Control

Acute post-stroke pyrexia is associated with a poor prognosis.[5] It is recommended by the Royal College of Physicians that normal temperatures be maintained below 37.2°C.[3] Pyrexia should be investigated for causes (e.g., post-stroke, infective endocarditis), and patients will need their temperature to be monitored for secondary infections. There is little evidence to support inducing hypothermia in ischaemic stroke despite its purported neuroprotective potential.[5]

Finally, scoring methods such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), when used with the patient's GCS, can aid in identifying seriously ill patients who require more support and possible intensive care services.[11]

Critical Care Monitoring

Patients with declining consciousness should be ventilated and transferred to either a neurosurgical or paediatric ICU in view of the possibility for requiring neurosurgical intervention. A study of 75 patients requiring intensive care support showed that delayed transfer (>5 h) is an independent risk factor of poor outcome.[12] Intensive care units have a critical role in close monitoring of stroke patients after acute measures have been administered and are associated with better outcomes.[10]

Other patients who are considered for transfer to intensive care are those who require mechanical ventilation, invasive treatments, sedation, and/or those who exhibit other serious neurological signs such as seizures. A third of children with stroke will need some form of intensive care.[10]

Intracranial Pressure

Intracranial pressure is the pressure within the cranium relative to atmospheric pressure. It is typically monitored by insertion of an intracranial sensor into a lateral ventricle, thereby sensing the pressure of cerebrospinal fluid within the ventricle. Generally, the cerebral perfusion pressure (CPP) of brain tissue is equivalent to the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), as represented in the equation, CPP = MAP – ICP. In simpler terms, the arterial pressure (MAP) has to overcome the pressure in the cranium (ICP) to drive blood into the brain to perfuse its tissues (CPP). To ensure adequate brain tissue perfusion, the cerebral perfusion pressure (CPP) has to be maintained at a reasonable level. Patients with stroke commonly have raised ICP secondary to post-infarct oedema and haemorrhage. If the ICP is too high, the CPP may fall to a level too low for good cerebral perfusion, further compounding the damage to ischaemic brain tissue. Patients with raised ICP may demonstrate changes in their level of consciousness, which has to be taken seriously.[13]

Malignant Middle Cerebral Infarction (MMCAI) is a serious complication of ischaemic stroke characterized by space-occupying oedema of the infarct area, leading to raised intracranial pressure and subsequent herniation.[14, 15] It is associated with a high rate of death, and surviving patients are left with severe disability. MMCAI tends to occur between 1 and 5 days of stroke onset, and patients deteriorate neurologically with a declining level of consciousness.

Current opinion in the medical community supports the use of decompressive craniectomy in paediatric patients with a fall in conscious level with a substantial MCA infarct.[15] This is in line with the indications for surgical intervention in adults.[3]

It is important to note that there is no evidence to support the use of ICP monitoring in patients with middle cerebral infarction. In fact, ICP monitoring may delay surgical treatment of MMCAI, a point illustrated in a recent five-centre review of 10 paediatric stroke cases with MMCAI.[15] Three of the patients in the study had ICP monitoring in place, and all three patients died of herniation without decompression treatment. Conversely, all patients treated with decompression went on to significant neurological improvement. This is the only article in the medical literature describing the occurrence of MMCAI in children.

Similarly, medical treatments such as mannitol and hyperventilation to alleviate intracranial pressure secondary to large infarct oedema have not been proven and may delay life-saving surgery.[3, 14]

Haemorrhagic Transformation

Haemorrhagic transformation of cerebral infarcts may be symptomatic or asymptomatic, and commonly occurs within the first 14 days of stroke onset. Use of antithrombotic agents, antiplatelets or anticoagulants all contribute to a higher likelihood of transformation.[3]

Seizures

Up to 14% of stroke patients can also present with early (those occurring within 2 weeks of stroke onset) or late seizures.[16] Seizure activity in post-stroke patients is related to poor outcomes.[5] The risks of developing late seizures are associated with large-sized infarcts, early seizures and cortical lesions. Two European studies have cited the rate of seizures in adolescents and young adults aged 15 onwards to be about 6% to 11% in the first year post-stroke.[16] Not all patients will need anticonvulsive treatment depending on the frequency and severity of seizures. Studies have shown that patients with early seizures may not require long-term anticonvulsive medication. Status epilepticus is a life-threatening condition and requires immediate intravenous treatment.[16] Furthermore, patients with late, recurrent seizures are at a risk of falls, and may not be suitable for long-term anticoagulation.

Miscellaneous

Patients in intensive care will need to have adequate nutrition and hydration.[3] Stroke patients are susceptible to infections such as pneumonia and urinary tract infections. This is partly due to immobility and also artificial ventilation, which heightens the risk of aspiration.[17] Immobile patients are also at risk of venous thromboembolism.[3] Hence, the benefits of prophylactic anticoagulation have to be balanced with the risk of cerebral haemorrhage.

Care after Stroke

Patients and their parents often feel isolated due to the limited number of services dedicated to children with stroke. Therefore, an appropriate range of existing paediatric services should be offered to all patients and their carers, with guidance on how to utilize these services.[1]

Long-term Medical Management & Secondary Prevention

It is essential that chronic medical management of stroke is in place. Short-term stroke recurrence rates in children have been reported to range from 8% to 42%, depending on the presence of underlying risk factors.[18] Patients at particular risk of second strokes are those with raised lipoprotein (a), protein C type I deficiency, or vascular abnormalities. Children with stroke should have a clearly delineated plan to reduce their risk of a second event.

The long-term medical management of stroke depends on the underlying aetiology. Some of the factors that should be taken into consideration include dissection of cranial vessels, cardiogenic embolism, prothrombotic states, vasculopathy, sickle cell disease and recurrent stroke while on aspirin.[6]

The consequences of non-compliance with drug therapy can be disastrous, as is seen in this case. The challenging issue is in getting children of young age to understand the rationale behind treatment and the implications of non-optimal anticoagulation. Education has to extend beyond the child's parents or guardians as they may have a more effective role in ensuring that the child takes his/her medication.

Rehabilitation

As with adult stroke victims, rehabilitation is key to functional improvement and recovery. Often, children will need help with reintegrating back into the community and school.

Detailed discussions on each of the rehabilitation services are beyond the scope of this report, but they can be broadly classified into initial and long-term rehabilitation. Initial rehabilitative measures include sensorimotor rehabilitation, speech and language therapy, assessment of cognition, mood and behaviour, and an early assessment of disability.[1]

The Royal College of Physicians has emphasized the need for long-term measures to be integrated with the child's "educational, social and emotional needs". Children will need help in the community and schools, such as special needs in education. Also, the transition of care from paediatric to adult services has to be coordinated, as with the patient discussed in this case. This transition takes place typically between the ages of 16 and 19.[1]

Prognosis of Stroke Patients

The prognosis of stroke patients is variable and dependent on many factors. Very few studies, which have analysed the prognostic data in children, have been found. More than 50% of children with stroke will have long-term cognitive or motor impairment.[19] Haemorrhagic stroke in children is associated with a higher rate of death than ischaemic stroke.[10]

Both a low GCS on presentation and mechanical ventilation for neurological reasons have been cited as independent predictors of mortality and morbidity. Still, critically ill stroke patients who receive appropriate intensive care interventions are more likely to do better than those who did not.[20]

Ethics

All children, regardless of their age, should be consulted if possible in all decisions in accordance with the Children Act 1989. This includes taking their feelings and wishes into consideration. In terms of consenting for any form of interventions, patients have to be assessed for Gillick competence. If the child is deemed to be competent to make a decision, their wishes should be followed.[1]

An issue arising from this case is the fact that the patient had not been reviewed in clinic for a period of 5 years, and it is highly likely that her anticoagulation was suboptimal. This has undoubtedly exposed the patient to significant risks of developing complications due to her underlying heart condition. Ethical dilemmas which extend beyond the realm of paediatric stroke care are illustrated in this example. Whose responsibility is it to ensure that children attend and comply with their medical issues? The three main parties implicated would be the patient herself, her parents or guardians, and healthcare professionals involved in her care. And if the parents or guardians fail to meet the medical needs of the child, should they be accountable? Finally, what social systems are in place to prevent such neglect from occurring? These are difficult questions to pose, but needs to be considered in order to optimize paediatric care and safeguard children.

Another pertinent issue arising from this case is the question of whether a child who voluntarily stops taking medication truly understands the full implication of his/her actions. It is difficult for any child to be on long-term treatment, which the child may feel is meaningless to be on if s/he does not understand the rationale behind treatment and the consequences of not doing so. If a child refuses or stops treatment out of his/her own volition, is s/he fully competent to do so? As members of the healthcare profession, we can pre-empt such behaviour by communicating effectively with the child and his/her family members, especially when the child is old enough to understand. At the same time, we should be sensitive to the environment the child is growing up in if there are concerns that the child might need social support.

Summary

Prevention of stroke is a crucial but overlooked area, as is illustrated in this case. As childhood stroke is relatively uncommon in comparison with adult stroke, children at risk of stroke and their guardians may not fully comprehend the utility of prophylactic medication. In the context of the United Kingdom, robust social healthcare systems have to be in place to ensure that patients under paediatric care have a safe transition to adult care.

The lack of familiarity with childhood stroke also extends to healthcare professionals. Even a classic presentation of stroke in a child can prove to be alarming to a medic. Physicians have to be trained to recognize the signs of stroke and be aware of the immediate steps to take.

Until further research evidence becomes available, the management of stroke in children remains an individualized approach, and will continue to be a highly challenging area.

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References:

1. *Stroke in childhood. Clinical guidelines for diagnosis, management and rehabilitation*, in *Clinical Effectiveness Unit*, P.S.W. Group, Editor. 2004, Royal College of Physicians.
2. Janjua, N., et al., *Thrombolysis for Ischemic Stroke in Children: Data From the Nationwide Inpatient Sample.* Stroke, 2007. **38**: p. 6.
3. *Stroke. National clinical guidelines for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)*, in *Royal College of Physicians*. 2008.
4. Roach, E.S., et al., *Management of Stroke in Infants and Children.* Stroke, 2008. **39**: p. 52.
5. Adams, H.P., et al., *Guidelines for the Early Management of Adults With Ischaemic Stroke.* Circulation, 2007. **115**: p. 57.
6. DeVeber, G. and F. Kirkham, *Guidelines for the treatment and prevention of stroke in children.* The Lancet Neurology, 2008. **7**: p. 3.
7. Cremer, S., et al., *Successful treatment of pediatric stroke with recombinant tissue plasminogen activator (rt-PA): a case report and review of the literature.* Canadian Journal of Emergency Medicine, 2008. **10**(6): p. 4.
8. Noser, E.A., R.A. Felberg, and A.V. Alexandrov, *Thrombolytic Therapy in an Adolescent Ischemic Stroke.* J Child Neurol, 2001. **16**: p. 3.
9. Amlie-Lefond, C., et al., *Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study.* The Lancet Neurology, 2009. **8**: p. 7.

10. Statler, K.D., et al., *Pediatric stroke: clinical characteristics, acute care utilization patterns, and mortality.* Childs Nerv Syst, 2010: p. 9.
11. Riachy, M., et al., *Prediction of the survival and functional ability of severe stroke patients after ICU therapeutic intervention.* BMC Neurology, 2008. **8**: p. 8.
12. Rincon, F., et al., *Impact of Delayed Transfer of Critically Ill Stroke Patients from the Emergency Department to the Neuro-ICU.* Neurocrit Care, 2010. **13**: p. 7.
13. Bhatia, A. and A.K. Gupta, *Neuromonitoring in the intensive care unit. Part I. Intracranial pressure and cerebral blood flow monitoring.* Applied Physiology in Intensive Care Medicine, 2009: p. 9.
14. Huttner, H.B. and S. Schwab, *Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives.* The Lancet Neurology, 2009. **8**: p. 10.
15. Smith, S.E., et al., *Outcome following decompressive craniectomy for malignant middle cerebral artery infarction in children.* Developmental Medicine & Child Neurology, 2010. **53**: p. 5.
16. Menon, B. and S.D. Shorvon, *Ischaemic stroke in adults and epilepsy.* Epilepsy Research, 2009. **87**: p. 11.
17. Worthmann, H., et al., *Linking infection and inflammation in acute ischemic stroke.* Ann. N. Y. Acad. Sci, 2010. **1207**: p. 7.
18. Sträter, R., et al., *Prospective assessment of risk factors for recurrent stroke during childhood—a 5-year follow-up study.* Lancet, 2002. **360**: p. 6.
19. Pappachan, J. and F. Kirkham, *Cerebrovascular disease and stroke.* Arch Dis Child, 2008. **93**: p. 9.
20. Steiner, T., et al., *Prognosis of Stroke Patients Requiring Mechanical Ventilation in a Neurological Critical Care Unit.* Stroke, 1997(28): p. 5.

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