Victoria Neurosurgery

Mr Jeremy Russell
BSc/BE (Hons) MBBS (Hons) FRACS
Cranial and Spinal Specialist

Level 1, 435 Malvern Rd
South Yarra VIC 3141
P: 03 9981 9588
www.drjeremyrussell.com.au

MOYAMOYA DISEASE

What is moyamoya disease?

Moyamoya disease is a rare, progressive, cerebrovascular disease caused by a slow and continuous narrowing of the main arteries to the brain (internal carotid arteries, ICA). This leads to insufficient cerebral blood supply known as ischaemia, and increased risk of stroke or cerebral haemorrhage. Reduced blood flow within these large vessels leads to compensatory development of a tangle of tiny vessels surrounding the carotid artery termination that looks "hazy or smoky" on a cerebral angiogram. This led to the condition being known as moyamoya, Japanese for "puff of smoke". Typically, the disease affects both sides of the brain, however this is not always the case, with approximately half of those who initially present with one sided disease eventually developing moyamoya changes on the other side.

Moyamoya is an extremely rare condition. Its incidence in Australia is not truly known, however is somewhere in the vicinity of one case per million population. It is approximately 10 times more common in East Asian countries. Moyamoya affects people of all ages, however there are two separate peaks incidences, the first at approximate 5 years of age and the second around 45 years of age. Females are affected twice as often as males.

What causes moyamoya?

The direct cause of moyamoya is unknown, though there are likely both genetic and environmental factors involved. The inheritance mode of moyamoya disease is multifactorial and thought to be autosomal dominant with incomplete penetrance. As a result, moyamoya may cluster within families, and in Japan, approximately 10% of patients have a positive family history for moyamoya[1].

More than half of people found to have the characteristic moyamoya vessel findings on angiography have no associated conditions, which is termed moyamoya disease. However, certain diseases have a well-recognised association with moyamoya, and in this setting, the condition is known as moyamoya syndrome.

More common associations (10 – 20%) are:

- Sickle cell anaemia
- Neurofibromatosis type I
- Down syndrome
- Cranial irradiation

Less common associations (<10%) are:

- Hyperthyroidism (Graves' disease)
- Marfan syndrome
- Tuberous sclerosis
- Congenital cardiac anomaly

What are the symptoms?

Moyamoya can occur at any stage of life, though symptom onset is typically between the ages of 5-10 years in children and 30-50 years in adults. Symptoms in moyamoya are due to restriction of flow resulting from the narrowing of the internal carotid arteries. Broadly speaking, symptoms are either directly attributable to brain ischaemia (i.e. stroke,

Victoria Neurosurgery

Mr Jeremy Russell
BSc/BE (Hons) MBBS (Hons) FRACS
Cranial and Spinal Specialist

Level 1, 435 Malvern Rd
South Yarra VIC 3141
P: 03 9981 9588
www.drjeremyrussell.com.au

transient ischaemic attacks (TIAs) and seizures) or indirectly, as a consequence of compensatory mechanisms secondary to the ischaemia (i.e. haemorrhage from fragile collateral vessels and headache from dilated abnormal collaterals).

- Age-related differences
  Most children and adults present with ischaemic symptoms, although haemorrhage may be as much as seven times higher in adults compared to children (20.0% versus 2.8%). Rates of haemorrhage within the adult Asian population is often much higher again. Children present with higher rates of completed strokes and thus permanent neurological deficits, thought to be due to poorer communication of TIA symptoms and subsequent delayed diagnosis.

- Ischaemic symptoms
  Symptoms of ischaemia in moyamoya are typically associated with brain regions supplied by the internal carotid arteries. Thus weakness, sensory changes (tingling and/or numbness), visual deficits, speech deficit and cognitive impairment are common. These symptoms may be transient (TIA) or permanent (stroke). Brain ischaemia may be provoked by hyperventilation and crying (especially in children), as these activities result in reduced carbon dioxide levels which further reduces already tenuous brain blood supply. Dehydration may also precipitate such symptoms.

- Haemorrhage
  Much more common in adults, it is however also described in children. Haemorrhage is typically due to rupture of the fragile compensatory moyamoya vessels, though less commonly may be from an associated brain aneurysm. Most commonly bleeding is within the brain tissue itself (intracerebral haemorrhage, ICH), though maybe within the large fluid cavities of the brain known as ventricles (intraventricular haemorrhage, IVH), or within the smaller fluid spaces overlying the brain (subarachnoid haemorrhage, SAH).

- Seizures
  A common presenting symptom, this may be due to either a stroke, brain haemorrhage or chronic severe lack of blood supply to an area of the brain.

- Headache
  Headache is a frequent presenting symptom. Typically, it is migraine like in quality and often resistant to standard medical therapy. Unfortunately, headaches may persist even after successful revascularisation surgery. It is thought to be due to dilation of the compensatory vessels causing stretch on the painful outer coverings of the brain, known as the dura, though this is not absolutely clear.

- Choreiform movements (children)
  Dilated moyamoya compensatory vessels within the inner part of the brain known as the basal ganglia have been implicated in the development of abnormal jerking or writhing (choreiform) movements in children. These may be very disabling and difficult to treat, though often reported to resolve following revascularisation surgery.

- Cognitive decline
  Seen within more than half the moyamoya patient population, this may be due to either an accumulation of multiple small strokes, or simply from chronic cerebral ischaemia.

What is the prognosis of moyamoya?

The natural history of moyamoya is variable, ranging from a slow and intermittent course, to fulminant and rapid neurological decline. Regardless, moyamoya inevitably progresses in most patients. A 2005 Japanese paper indicated much higher rates of disease progression than previously thought, even amongst asymptomatic patients, and that

Victoria Neurosurgery

Mr Jeremy Russell
BSc/BE (Hons) MBBS (Hons) FRACS
Cranial and Spinal Specialist

Level 1, 435 Malvern Rd
South Yarra VIC 3141
P: 03 9981 9588
www.drjeremyrussell.com.au

medical treatment alone does not alter the disease course. It has been estimated up to two thirds of moyamoya patients will have symptomatic progression over the five-year period from initial diagnosis, with a typically poor outcome without treatment[3]. In comparison, according to a large study involving over a 1000 patients, symptomatic progression may be reduced to as little as 2.6% following surgery[4].

Neurological burden at the time of diagnosis is the major predictor of long-term outcome. Approximately 50 to 60% of affected individuals experience a gradual deterioration of their cognitive function, presumably due to multiple strokes.

Mortality from moyamoya is approximately 10% in adults and 4.3% in children. Death is typically due to a severe brain bleed (intracerebral haemorrhage (ICH)).

How is moyamoya diagnosed?

Moyamoya should be considered in patients, especially children, presenting with unexplained acute neurological deficits or symptoms referable to brain ischaemia. Delayed diagnosis may result in delayed treatment and potential increased risk of permanent disability secondary to stroke. Following an appropriate review of the patient's history and complete physical examination, the presence of moyamoya can easily be confirmed via radiological imaging.

Medical imaging tests will often include the following:

- Computed tomography (CT)
  Rapid and non-invasive test using X-rays to determine if there has been a brain bleed. This is then combined with a separate contrast dye scan called CT angiography (CTA) to show the blood vessels within the brain, looking for the characteristic vessel narrowing and moyamoya phenomena.

- Magnetic Resonance Imaging (MRI)
  MRI is non-invasive, using radio waves and a magnetic field to create brain images without radiation. This process can also show the brain blood vessels using MR angiography (MRA), and give critical information regarding evidence of brain ischaemia and prior stroke. Currently, treatment decisions can often be made based on this alone, without the need for invasive cerebral angiography.

- Cerebral Angiography
  A minimally invasive imaging technique that involves a small puncture within the groin, passing a thin tube up the arteries to the brain and injecting contrast to obtain very high-quality images of the brain blood vessel anatomy, collateral supply and cerebral perfusion timing. Historically integral to diagnosis and decision making, more often this invasive imaging modality is not required for current management.

- Cerebrovascular Reactivity (CVR) testing
  An indicator of brain health, this test assesses the responsiveness of the cerebral blood vessels to alter the brain's blood flow as physiologically required. The normal healthy brain can increase its blood supply approximately 50% from baseline when required. Moyamoya severely restricts this. In particularly severe cases, the blood supply to the diseased region of brain may actually reduce when stimulated, which is known as “steal”, and indicates an especially increased stroke risk . This may be assessed by multiple techniques, including CT-SPECT, MR-BOLD and PET scans, with the aid of a stimulus that naturally increases brain blood flow, such as acetazolamide or carbon dioxide.

What medicines are used in treating moyamoya?

Medication can be used in the treatment of moyamoya, however there is no good evidence they significantly alter the natural history of the disease. More commonly used drugs may include:

- Blood thinners — Aspirin – thins the blood, may help prevent emboli and subsequent stroke

Victoria Neurosurgery

Mr Jeremy Russell
BSc/BE (Hons) MBBS (Hons) FRACS
Cranial and Spinal Specialist

Level 1, 435 Malvern Rd
South Yarra VIC 3141
P: 03 9981 9588
www.drjeremyrussell.com.au

- Calcium channel blockers — Occasionally used to reduce headaches and possibly TIA
- Anti-seizures medications — When patients present with seizures

What neurosurgical treatments are available to treat moyamoya?

Broadly speaking there are two forms of surgical revascularization treatment for moyamoya, both of which typically use the external carotid artery as a source of new blood supply, as for reasons unknown, the disease does not affect this vessel. Aspirin is started one week prior to surgery if the patient is not already on this, as this reduces the risk of the newly fashioned bypass failing.

- Direct bypass

Here an artery from outside the skull (usually one of the two superficial temporal artery , or STA, branches) is *directly* connected to a peripheral artery on the surface of the brain (usually a distal middle cerebral artery, or MCA, branch), and is known as an STA-MCA bypass. The 2 branches of the STA are dissected from the scalp tissues under a microscope to ensure they are not damaged, then set aside. An opening in the skull is then created, called a craniotomy, and the underlying leathery covering of the brain called the dura is opened to expose the brain surface. An appropriate recipient MCA vessel is then looked for under the microscope, aiming for a vessel at least 1mm in diameter. Sometimes this is not available, and only an indirect bypass can be fashioned. If sufficient, the vessel is then prepared for bypass and the 2 arteries sutured together, such that blood flows directly from the STA into the MCA branch. This provides an immediate increase in blood supply to the brain. This operation should only be performed by an appropriately trained and experienced neurovascular surgeon, as it is technically very demanding. In such hands, it is successful more than 95% of the time.

The major risk of the operation is stroke, which can be due to the blood pressure dropping too low during anaesthesia, or from temporarily halting blood flow in the MCA branch to allow the bypass connection to be fashioned. This occurs around 5% or less of cases, and may cause temporary or permanent weakness, sensory changes, or speech difficulty. Other more common risks include post-operative bleeding requiring further surgery (< 5%) and wound healing problems as the main blood supply to the scalp (i.e the STA) has been removed (5 – 10 %). Less common concerns include delayed occlusion of the bypass, seizures, and blood sodium changes. Mortality rates from the procedure are less than 1%.

Link to STA-MCA bypass video: https://www.youtube.com/watch?v=36V7rHLN2ms

- Indirect bypass

Similar to a direct bypass, usually the STA is also used to supply blood to the ischaemic brain, however no direct connection is made between the vessels, and thus blood flow is increased to the brain slowly over time. The most common indirect procedure involves the STA being placed directly onto the brain surface, and over 3 to 6 months' time, small connections form and grow into the brain surface, increasing its blood supply. This is known as an encephalo-dural-arterio-synangiosis, or EDAS, though there are several similar variations to this indirect procedure. Technically much less demanding than a direct procedure, it is still a challenging operation and should only be performed by an appropriately trained neurovascular surgeon. Often children receive an indirect procedure, as their vessels are very small and thus may be too challenging for a successful direct connection. Risk profile is similar to a direct procedure, though typically lower stroke rates are seen as the blood supply to the brain is not temporarily halted like that in a direct procedure.

Link to EDAS bypass video: https://www.youtube.com/watch?v=vYU0bACFhI4

Where feasible, a direct procedure is preferred as it achieves an immediate improvement in brain blood supply and thus symptom improvement. Often a combination procedure can be achieved where the frontal STA vessel is joined directly (i.e. STA-MCA bypass) and the more posterior STA branch is on-layed indirectly (i.e. EDAS bypass), offers the best of both procedures. Long term outcome from all these procedures appears to be roughly equivalent, with clinical improvement typically seen with all variations.

Victoria Neurosurgery

Mr Jeremy Russell
BSc/BE (Hons) MBBS (Hons) FRACS
Cranial and Spinal Specialist

Level 1, 435 Malvern Rd
South Yarra VIC 3141
P: 03 9981 9588
www.drjeremyrussell.com.au

Who is a candidate for these procedures?

Symptomatic patients, in otherwise good general health, who demonstrate a lack of blood supply to the territory involved by the moyamoya vessels, are candidates for a revascularization procedure. Typically, surgery is reserved for those patients who demonstrate cerebral steal on CVR testing (see above), though occasionally it may be offered irrespective when optimal medical management fails to halt symptom progression. Treatment is reserved in asymptomatic patients, who are followed annually with clinical and radiological testing, and offered treatment should their condition progress.

Moyamoya Screening

There is no data to support screening for moyamoya, even in patients with a known affected first-degree relative. In patients with known unilateral disease, there is some evidence that regular interval imaging and follow-up with respect to the other side may reduce subsequent stroke burden and improve outcomes. In patients with one of the more common associations (see above), a low threshold for screening is reasonable.

References

1. Mineharu Y, Takenaka K, Yamakawa H, et al. Inheritance pattern of familial moyamoya disease: autosomal dominant mode and genomic imprinting. *J Neurol Neurosurg Psychiatr*. 2006;77(9):1025-1029.

2. Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y. Incidence and clinical features of disease progression in adult moyamoya disease. *Stroke*. 2005;36(10):2148-2153.

3. Choi JU, Kim DS, Kim EY, Lee KC. Natural history of moyamoya disease: comparison of activity of daily living in surgery and non surgery groups. *Clin Neurol Neurosurg*. 1997;99 Suppl 2:S11-S18.

4. Fung L-WE, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. *Childs Nerv Syst*. 2005;21(5):358-364.

Helpful Links

1. https://www.ninds.nih.gov/Disorders/All-Disorders/Moyamoya-Disease-Information-Page
2. https://www.ahajournals.org/doi/epub/10.1161/01.STR.0000182256.32489.99
3. https://www.youtube.com/watch?v=pVVuZK6xlKY
4. https://www.moyamoyaaustralia.org.au