

cerebrovascular reactivity than normal controls without transient ischaemic attacks or carotid disease was all very well, but did not answer the more relevant question: do patients with severe carotid disease and limb shaking transient ischaemic attacks have more impaired cerebrovascular reactivity than similar patients with 'conventional' transient ischaemic attacks (i.e. loss of function such as paralysis contralateral to severe carotid disease)?

In this issue of *Brain* we now have that empirical evidence, from the well-known cerebrovascular group in Utrecht, for what we had anticipated from the clinical characteristics of the attacks (Persoon *et al.*, 2010). First, the attacks are mostly short, lasting a few minutes, presumably because they can often be aborted by stopping the precipitating activity, even perhaps by just sitting down, or the systemic blood pressure rises spontaneously. Second, as far as the authors could tell, the attacks are usually—but not always—precipitated by something that might lower the systemic blood pressure. Third, patients with limb shaking are more dependent on collateral blood supply distal to the severe carotid disease. And fourth, they have more impaired cerebrovascular reactivity. Of interest is that the patients with limb shaking were more often hypertensive, which does make one wonder whether sometimes their treatment might have been an unrecognized precipitant of the attacks.

So in some patients at least, transient ischaemic attacks are due to focal low flow rather than emboli, and so maybe in the fullness of time we will know whether it is these 'low flow' patients—and not just any patient with carotid occlusion—who benefit from extra- to intracranial bypass surgery.

Life without a cerebellum

The human cerebellum is reported to contain ~85 billion neurons, around half the number in the entire brain (Azevedo *et al.*, 2009). Thus, it is source of considerable wonder that a full adult life is possible in cases where the cerebellum does not develop at all or where only vestigial signs of a cerebellum are present. The first instance of this rare disorder was described in 1831 by Combettes, and again by Ferrier in 1876. Richard Boyd's paper in this issue of *Brain* (Boyd, 2010) is a very interesting addition to the important debate over the significance of cerebellar agenesis for motor development and brain function in such individuals. An important review by Mitchell Glickstein (1994) made the point that in all case reports in which a full clinical description was available, clear motor deficits were present. He stated 'the claim that people with complete cerebellar agenesis can be entirely symptom free is widespread, yet in every documented case there was a profound deficit in the development of normal movement'. He attacked the 'oral tradition' and the 'myth' that 'people who are born without a cerebellum may have no observable symptoms at all'.

In the meantime, I wish we could get our geographical analogy right. The watershed is the high area of land between two river basins; water drains 'from' the watershed, not towards it. It is not therefore an appropriate adjective to describe the potentially low cerebral perfusion and ischaemia between the areas of supply of adjacent cerebral arteries. Unfortunately, to confuse the situation, in North American usage the watershed is the river basin itself, but even that analogy is not right for the ischaemia that may exist where the area of supply of one artery meets the area of supply of an adjacent artery. The boundary zone, between the areas of supply from two cerebral arteries, describes better what we mean.

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Glickstein (1994) remarked that a 'potent source of this myth' arose from a case of neocerebellar hypoplasia first reported in 1940 by J. D. Boyd, Richard Boyd's father. The patient lived to the age of 76 and after he died his unclaimed body was used for dissection at the London Hospital, where the absence of a cerebellum was discovered during an examination for the degree of Master of Surgery. The difficulty that Glickstein had with the 'myth' was the lack of evidence concerning the life, occupation and clinical history of this individual. We both taught in the Anatomy Department in Cambridge at the time Glickstein made his investigation of the brain, which is retained in the Department's teaching collection and still used today. This specimen was clearly labelled 'human brain without cerebellum' and was used every year in the Department's lengthy and detailed course in neuroanatomy for preclinical medical students. In our recollection, it was certainly true that those who taught the course were uncertain as to the capacities of the brain's owner; but that with time the 'myth' was well-established, and as Glickstein (1994) put it 'all members of the Department

thought... that he had normal movement'. The concept that a 'normal' life was possible without a cerebellum was a disincentive for our students to learn the complexities of cerebellar structure and function!

Richard Boyd's paper is based on the rediscovery of his father's papers related to this case, which were found by chance in his brother's garage. The paper sheds important new light on this particular case and questions the 'myth'. Armed with this new information, Richard Boyd revisits the case and confirms the Boyd (1940) anatomical report on the patient, now identified as H. C., and Glickstein's re-examination of the brain in 1994. There is indeed an almost complete lack of cerebellar tissue. The neocerebellum (hemispheres and dentate nuclei) is completely absent, as is the pons, and any evidence of an inferior olive; the cerebellar peduncles are much reduced in size. Structural MRI reveals that there is a small remnant of the paleocerebellum, a vestigial vermis.

Richard Boyd's paper provides a fuller picture of H. C.'s life history. Boyd comments on the remarkable detail of the clinical record that his father was able to acquire in 1939, just a few months after H. C. died (aged 76) as a result of heart disease. The main conclusion of the paper is that the almost complete absence of the cerebellum is compatible with a long and relatively 'normal' life, which included employment as a manual labourer as stated on H. C.'s death certificate. This is what we might refer to as the 'glass half-full' position, and supports the view that there was real substance to the 'myth' after all. However, the glass is also half-empty, and we can probably dispense with the notion that H. C. possessed the degree of motor skill which would have enabled him to work as a 'roof-climbing hod-carrier' (Glickstein, 1994). Indeed, the papers cited by Boyd (2010) include a neurologist's report which noted a number of clinical motor problems which are likely to have resulted from the lack of cerebellum: slurred speech, a squint and problems with gait. The report states that H. C. was 'able to get around unassisted'; in neurological terms that does not seem to indicate normal locomotion (e.g. deficits at levels 0–6 on the Kurtzke Expanded Disability Status Scale could be described as 'able to get around unassisted'). However, some or all of these problems could have been associated with the 'neurological deterioration over the last nine years of the individual's life' (Boyd, 2010), rather than being a direct result of cerebellar agenesis.

Thus, there is potential ammunition here for those supporting both sides of the debate: a case of almost complete cerebellar agenesis, where there were significant motor deficits in line with Glickstein's (1994) view, but not incompatible with a long, useful, albeit simple life. Of course it would have been fascinating to have made a full investigation of H. C. during his lifetime, in the full knowledge of his neocerebellar agenesis. Fortunately such an opportunity has arisen in more recent times. Timmann *et al.* (2003) reported a case of a 59-year-old patient, H. K., with an almost total cerebellar agenesis that was first detected by MRI when the patient presented with sudden loss of hearing. As in H. C., there were also small remnants of the vermis and signs of a vestigial flocculus. On the basis of MRI, the authors concluded that these remnants were of little functional importance.

This patient showed a number of abnormalities in her oculomotor, speech and gait control. She had never learned to read or write and her speech developed late and was slurred. She showed poor dexterity and severely disturbed predictive control of object grasp (Nowak *et al.*, 2006). She could also be described as 'being able to get around unassisted', but showed clear evidence of ataxia. In terms of cerebellar involvement in motor learning, it was interesting that she also showed no evidence of acquiring conditioned eye blinks, a learned behaviour shown to be cerebellar dependent in animals.

A major area of speculation is the role of the cerebellum in cognitive processes. While early studies of the effects of cerebellar lesions did not indicate any form of intellectual deficit (e.g. from Gordon Holmes' detailed studies of cerebellar patients), more recent studies have proposed cognitive functions for the cerebellum (Daum and Ackermann, 1995; Schmahmann and Sherman, 1998). Care should be taken in considering a role for the cerebellum in cognition; impaired motor function could itself interfere with performance on cognitive tests. For example, after cerebellar lesions there is a need to correct movements and posture continually and consciously based on feedback, and this at the least will influence attention. Notably the deficits seen in the performance of patients with cerebellar lesions in these neuropsychological tests tend to be mild, suggesting that a cerebellar role is not critical to cognitive function.

Patient H. K. also showed mild to moderate neuropsychological impairments in IQ, planning behaviour, visual, verbal and spatial memory, visuospatial perception and attention. Timmann *et al.* (2003) point out that these neuropsychological findings could be in part explained by motor performance deficits and 'the influence of impaired motor functions on cognitive development and neuropsychological test performance can neither be excluded nor estimated' (see also Richter *et al.*, 2005). Alternatively, cerebellar agenesis might be accompanied by deficits elsewhere in the brain that are not obvious on the MRI. So there is plenty of evidence here that life without a cerebellum is anything but normal. But (glass half-full) this woman leads a useful though simple life, and is able to work in an electronics workshop.

Perhaps the overall lesson of this fascinating case should be to highlight the remarkable redundancy of the developing human brain that allows at least partial compensation for the absent neocerebellum; certainly the impairments in these cases of cerebellar agenesis are much less severe than those seen in acute cerebellar damage in adults. The surprisingly preserved level of motor function in cerebellar agenesis must reflect the capacity of the extracerebellar motor system, and it is interesting that in cases of cerebellar agenesis, including H. C. and H. K., there are no overt abnormalities in the extracerebellar motor structures. The neocerebellum is known to be massively enlarged in humans compared to animals, including other primates. This evidence, along with a wealth of pathological studies on cerebellar disorders, has led to the view that the neocerebellum underpins particularly advanced human sensorimotor skills such as speech, dextrous manipulation and the manufacture and use of tools. But we surely do not need to revise such a view until we understand how the rest of the

brain networks implicated in these skills compensate in cases of cerebellar agenesis; these remaining networks may operate quite differently in such individuals, and this should be a worthwhile object of future study.

A further speculation: could our expectation that the loss of 89 billion neurons should have much more dramatic results perhaps point to the fact that most of us do not make especially good use of the capacities provided by a fully intact cerebellum? Should we perhaps be measuring the capacities of those rare patients against those brilliantly gifted (and well-paid) musicians and athletes who might be said to have more fully exploited the wonderful skills that their motor network, including the cerebellum, can support? But what about the rest of us who live an increasingly sedentary life where much of the requirement for motor skills has been replaced by electronic wizardry?

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