Role of the cerebellum in the neurocognitive sequelae of treatment of tumours of the posterior fossa: an update

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The lengthened survival of patients with tumours of the posterior fossa has brought awareness of the neurocognitive deficits present in this patient population. In the past, these deficits were thought to be caused by radiotherapy damaging supratentorial structures known to be responsible for cognitive processing. This notion led to the development of new treatment protocols to restrict damage to supratentorial regions by decreasing the radiation dose and the irradiated volume. However, these treatment protocols have only resulted in marginal improvements, sometimes at the expense of long-term survival. Moreover, the current published work reports that non-irradiated patients with tumours of the posterior fossa exhibit similar cognitive impairments to irradiated patients. The growth and treatment of tumours of the posterior fossa also damage infratentorial structures, including the cerebellum. Findings from anatomical, clinical, and neuroimaging studies support a role for the cerebellum in cognitive functions similar to those impaired in patients with a tumour of the posterior fossa. Despite these findings, research focused on the treatment of these patients and on decreasing their cognitive impairments either ignores that the cerebellum has been implicated in non-motor functions or argues against the possibility that damage to the cerebellum might result in cognitive sequelae. Future studies need to address the possibility that the cognitive impairments of patients with tumours of the posterior fossa might be determined by a combination of factors, including damage to the cerebellum. Recognition of the important cognitive contributions of the cerebellum might lead to improved cognitive outcome and quality of life for this patient population.

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Introduction

Tumours of the posterior fossa (figure 1) account for 60% of all childhood intracranial tumours and 20% of adult intracranial tumours, and are the most common types of tumours in children younger than 16 years of age.[1–3] Lengthened survival of patients with certain types of tumours has been attributed to improvements in surgery, radiotherapy, and chemotherapy.[4,5] As a result of this improved survival, there is now an increased awareness of the often progressive neurocognitive deficits present in this patient population. Cognitive declines characterised by impairments in attention,[6–11] memory,[8–10,12–17] executive functions,[9,12] and by loss of intelligence quotient (IQ),[7,10,11,14,16,18–22] have largely been attributed to radiotherapy.[11,15,17,19,21,23–27] This notion has led to the development of new treatment protocols to restrict damage to supratentorial regions by decreasing radiation dose and irradiated volume,[28] or by deferring radiotherapy.[29] However, these treatment protocols have only resulted in small improvements, sometimes at the expense of long-term survival.[21,29–31] Many studies have also reported a decline in neurocognitive function in patients who were never treated with radiotherapy.[1,4,6–10,12,16,22,32–34] As a result, radiotherapy alone does not seem to account for the neurocognitive decline noted in survivors of childhood tumours of the posterior fossa. A new paradigm is therefore necessary to explain these findings and to plan management strategies to improve the quality and length of survival of these patients in the future.

Research has shown important roles of the cerebellum far beyond motor function.[35] Despite these new findings, most textbooks of medical anatomy and neurology,[2,36,37] focus only on the cerebellum's involvement in motor functions and ignore its role in cognitive functions, including those that are put at risk in patients with tumours of the posterior fossa.[12] Knowledge of the cognitive functions of the cerebellum is fundamental to achieve better management strategies for these patients. The purpose of this paper is to describe the role of the cerebellum in cognitive functions by a review of anatomical, clinical, and neuroimaging studies, followed by a discussion of current research on the neurocognitive sequelae of tumours of the posterior fossa, to show the prominent

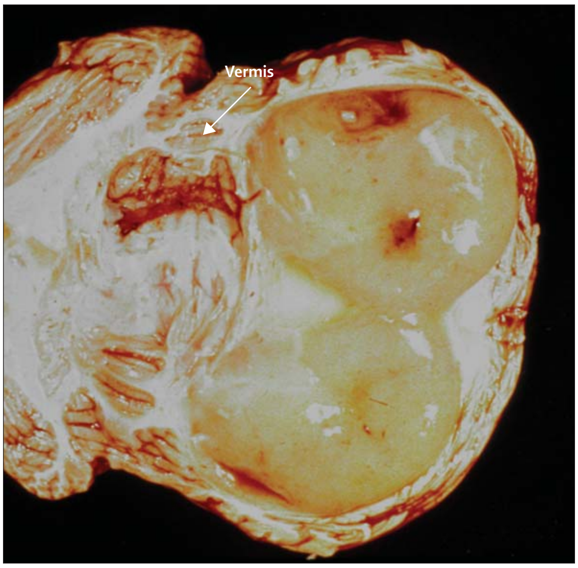

Figure 1: **Cerebellar astrocytoma**
Courtesy of David G Munoz (Division of Pathology, St Michael's Hospital, Toronto, Ontario, Canada.

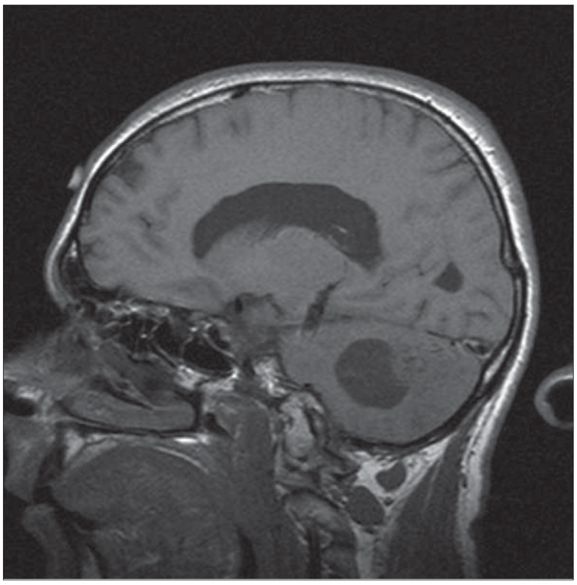

Figure 2: **Sagittal T1-weighted MRI of a patient with a haemangioblastoma in the right cerebellar hemisphere**
Patients with cerebellar pathologies can develop cognitive impairments resembling those caused by damage to the cerebral cortex.

role of the cerebellum in determining these neurocognitive deficits.

Cognitive functions associated with the cerebellum

Patients with tumours of the posterior fossa (figure 2) can acquire damage to the cerebellum from the tumour's growth, during surgical resection of the tumour, due to the effects of chemotherapy and radiotherapy, or from a combination of any of these factors. However, clinicians rarely associate the cognitive deficits frequently noted in these patients with direct cerebellar injury, because the prevailing paradigm in clinical medicine is that the cerebellum's role is restricted to modulating motor behaviour.[2,36,37] In the following sections we review recent evidence from the anatomical, clinical, and neuroimaging published work that has linked the cerebellum to cognitive functions.

Anatomical studies

Classic studies have identified the cerebellum as the portion of the brain in charge of the skilful manipulation of movement.[12] This function still remains the only mentioned role of the cerebellum in even the most recent editions of popular neurology and neuroanatomy textbooks.[2,36,37]

Despite the persistence of this notion, a growing body of evidence, which has been accumulating for over a century, favours an expanded role of the cerebellum. This evidence includes clinical and empirical studies of cerebellar pathology and studies of normal cerebellar function shown by means of advanced neuroimaging techniques, such as functional MRI. Some of the earliest clinical reports date back to the late 1800s and early 1900s, and detail findings from patients born without a cerebellum and those with cerebellar atrophy. In addition to motor dysfunctions, these patients presented with behavioural and mental disorders.[38] However, these reports were largely ignored or dismissed, because at the time the motor role of the cerebellum was already well entrenched.[39]

Several anatomical studies support a non-motor role of the cerebellum. In 1986, Leiner and colleagues[40] traced the phylogenetic evolution of the cerebellum. The phylogenetically newer portion of the cerebellum, including the posterior lobe and the dentate nucleus, was noted to have developed in parallel with areas of the cerebral cortex, important for higher cognitive functions. On the basis of this finding, a proposal was made that because the anterior lobe of the cerebellum, the phylogenetically older portion, was involved in the skilful manipulation of movement, the posterior lobe could be involved in the skilful manipulation of thought.

This theory is in agreement with more recent anatomical findings. In 1997, Zagon and colleagues[41] estimated the human cerebellum to contain over half of all neurons in the brain. This large number of neurons, coupled with millions of fibre tracks, allows the cerebellum to communicate and process information from many brain centres rather than just those involved in motor function.[40] This notion has been confirmed by neuroanatomical and in-vivo fibre-tracking studies in primates and humans.[2,38,42,43] These studies have shown that the cerebellum is a contributing node in an extensive corticosubcortical network. Efferent fibres leave the cerebellar nuclei and reach the cerebral cortex via thalamic projections;[42] fibres from these same cortical areas then return to the cerebellar cortex via pontine nuclei, establishing a series of closed-loop circuits.[38] Some of the non-motor targets of these closed-loop circuits include the prefrontal cortex, the temporal lobe, and limbic structures.[38]

Clinical studies

In addition to the anatomical studies that have outlined the neural substrate through which the cerebellum could manipulate cognitive functions, bedside clinical examinations have elucidated a role of the cerebellum beyond that of motor control. Early clinical studies made use of common neurocognitive tests or experimental paradigms devised to study patients with various brain disorders.[40,44] These studies focused on patients with cerebellar damage. They showed that cerebellar damage could cause deficits in cognitive tasks, such as motor planning, use of visual cues, and creation of mental images, in addition to motor deficiencies. Moreover, patients with damage of the posterior cerebellar hemispheres had no detectable motor impairments. However, these findings were weakened by the small sample sizes and heterogeneous patient populations often used in these studies.[40]