By Ronald Devere, MD

Pondering a Cerebellar Origin for Cognitive Disorders

Evidence suggests the cerebellum may play a role. Here's a look at the findings.

My youngest son, who is completing his post-doctorate in neuropsychology, called me six months ago. He told me he had attended an international neuropsychology meeting in Hawaii where he went to an hour-long lecture on cognitive dysfunction in cerebellar disorders. He asked me what I knew about the topic. I was quite surprised at the question and realized that I knew very little about this subject despite my long interest and my practice in cognitive and behavioral neurology. As medical students in anatomy and later as neurology residents, we were taught the afferent and efferent pathways connecting the cerebellum and brain stem. Clinically, we were all trained about the role the cerebellum plays in smoothing and coordinating motor function of our extremities and speech. Cerebellar motor testing has been a mainstay of the neurological examination. I do not recall any lectures or clinical teaching cases that discussed cognitive dysfunction in pure cerebellar disorders.

Many papers published in the neurology literature since 1824 have suggested cognitive and behavioral deficits could occur in disorders of the cerebellum. However, these early reports were anecdotal and not proven pathologically. As a result, these early reports were dismissed. I have seen some patients over the years with cerebellar and brain stem strokes who had prominent cognitive disturbances. These were attributed to small white matter lesions or some other cause such as underlying Alzheimer's disease. I never thought a unilateral cerebellar lesion by itself would cause major cognitive dysfunction and decline.

In 1998 Drs. Jeremy D. Schmahmann and Janet C. Sherman of the Department of Neurology of Massachusetts General Hospital and Harvard Medical School wrote the pioneer paper[2] that attempted to answer the question about the role of cerebellar function in cognition. Until this paper, convincing documentation was lacking about the presence of cognitive deficits where pathology was restricted to the cerebellum. The authors studied 20 patients with "pure" cerebellar pathology using bedside mental status and neurological evaluations, MRI or CT scans of the brain, and detailed neuropsychological testing. The age range of their patients was 23 to 68 years with a mean of 50 years. Their patient group consisted of either left, right or bilateral posterior/inferior cerebellar artery strokes, cerebellar cortical atrophy, post infection cerebellitis, and resected vermis tumors of the cerebellum.

To confine the study as much as possible to pure cerebellar dysfunction, they excluded patients greater than 75 years of age with non-cerebellar white matter lesions or infarcts, Alzheimer's disease, Parkinson's disease, seizure disorders, pre-existing psychiatric disorders, history of drug or alcohol abuse, head trauma, and liver or kidney problems. They even excluded patients who had any evidence of upper motor neuron neurological signs, such as bilateral toe signs or asymmetrical reflexes.

Based on bedside cognitive evaluation and formal neuropsychological testing, they found that 18 of 20 patients demonstrated disturbance in executive function, which included poor working memory, motor or ideational set shifting difficulties, and perseverations of actions or drawings. In addition, 18 patients had impaired verbal fluency, which included telegraphic speech and at times almost mutism. There was evidence of decreased verbal fluency, which was unrelated to dysarthria. In 19 cases, visual spatial disturbances were most marked in drawing or copying a diagram regardless of the severity of dysmetria. Naming was impaired in 13 cases. Mental mathematics was abnormal in 14 patients. Verbal learning and recall was mildly impaired in half, and visual learning and recall were decreased in a third of the patients tested. Two had ideational apraxia. Also of note, personality and behavioral changes were noted in 15 cases. This included flattening of affect and dysinhibition, which included inappropriate comments and impulsive actions. Some had regressive child-like behavior. Those patients who had strokes improved with time (nine to 10 months) but many had mild residual executive dysfunction. Patients who had cerebellar cortical atrophy continued to slowly decline. The authors coined "the cerebellar cognitive affective syndrome" to describe these kinds of patients.

Connecting the Dots

What is the anatomical substrate of the cerebellum and its pathways that correlate with these important clinical findings? First, the cerebellum accounts for over one

half of the brain population of neurons. The cerebellum receives input from all levels of the central nervous system. If you remember your anatomy of the cerebellum, it is divided into two main hemispheres, each made up of anterior and posterior lobes and the midline vermis and flocculo nodular node. Based on clinical observation and functional neuroimaging, the tasks of language, memory, attention shifting, planning behaviors, and motor function have been mapped to different areas of the cerebellum. The motor aspects of cerebellar function appeared to predominately involve the anterior lobes. Cognitive function, including visual perception and language, involves the posterior lobe, and behavioral function involves the vermis and flocculo nodular node.

The motor regions of the cerebral hemisphere project via the pons to the anterior lobe of the cerebellum and back again, and its function is to smooth out motor activity. The dorsal, lateral and medial prefrontal regions of the brain, including the frontal language area, project to the posterior cerebellum with cerebellar efferent pathways projecting back to the same region via the cerebellar thalamic and thalamocortical circuit. These pathways would certainly play a role in executive and language function. Cerebral projections from the posterior, inferior and superior parietal cortex and superior temporal cortex also project to the posterior lobe of the cerebellum and back, playing a major role in visual perception, including copying and construction of diagrams. Projections from the anterior singular cortex and posterior hypothalamus, and serotonin and dopaminergic brain stem nuclei project to the vermis and back. These pathways play an important role in behavior and emotion. It appears the cerebellum modulates mood, intellectual function and motor function through its connections with the cerebral hemisphere and brain stem.

As clinical neurologists, what are the implications of this information? First, cerebellar disorders by themselves are associated with cognitive abnormalities and gradual decline. The core features are executive, spatial, linguistic and affective changes. Arousal and alertness are usually not involved. Remote, episodic, and semantic memory is usually preserved, and new learning may be only very mildly affected. Aphasia, apraxia, and agnosia, which are standard cortical phenomena, are usually spared. Of importance is the awareness that these characteristics in cerebellar disorders can be easily picked up on office or bedside examination such as using the MMSE or a standard battery of neuropsychological testing.

When evaluating patients with cerebellar motor disorders and finding behavioral and cognitive impairment, we should not jump to the conclusion the patient must have cerebral pathology as well. Remember, patients with Alzheimer's and other dementia can have cerebellar and brain stem strokes, which can worsen their dementia without clinicians concluding that multiple cerebral strokes have also occurred. Patients with a recent cerebellar stroke evident clinically and on neurological imaging, who also show frontal lobe/visual perception and mild memory impairment on evaluation, and have nonspecific changes or normal MRI of the cerebral hemisphere, should not be diagnosed with a frontal variant of Alzheimer's disease or multi-infarct dementia without further close observation. The cerebellar cognitive disorder will not likely apply to patients who have spinal cerebellar genetic disorders because these patients also have cognitive impairment due to cerebral involvement as part of their disease.

Here Comes the Sun

On another topic, wouldn't it be interesting and exciting if we could improve cognitive function and behavior by simply increasing the brightness of light in the domiciles of patients with Alzheimer's and other dementias? This is exactly what was done by a group of physicians in the Netherlands. Riemersma-van der Lek, et al.[6] reported in the *Journal of the American Medical Association* on a a randomized study of 189 cognitively impaired patients in 12 group care facilities conducted over a

three to five-year period. Their concept of a group care facility is that each patient had their own apartment where they slept but spent most of the day in a common living room supervised by caregivers. Of the 189 cases, 63 percent had probable Alzheimer's disease, 11 percent had multi-infarct dementia, and the remainder had frontal dementia, Lewy Body dementia, alcohol dementia or a dementia of undetermined cause.

Two light conditions were used in the study. First was the exposure to 1000 lux in the common living room from 9am to 6pm daily. This amount of light in previous unrelated studies was shown to synchronize circadian rhythm in healthy people in isolation and patients with moderate to severe dementia. The placebo group had light of 300 lux. Melatonin 2.5mg versus placebo was also given in the evening and randomized. The study was over a mean of 15 months up to a maximum period of 3.5 years. The placebo and active study groups were essentially equal except for mild differences in the MMSE, withdrawn behavioral scale, and agitation index. Results of this study showed light reduced cognitive deficits by five percent; that is, there was an increase in the MMSE score of 3.5 points. The light also reduced depression by 19 percent and attenuated functional limitations by 53 percent.

Melatonin had no effect on the depression rating, but adversely affected care-giving ratings of withdrawn behavior and mood. However, it reduced sleep onset latency by 19 percent and increased the total sleep duration by six percent. When melatonin was combined with bright light it reduced agitated behavior by nine percent, improved sleep efficiency by 3.5 percent and reduced nocturnal restless by 10 percent. The combination of light and melatonin helped to maintain sleep efficiency by 85 percent. The authors feel that enhancement of the function of the circadian timing system occurs and often takes two or three months with this treatment.

The nice thing about this treatment is that it is easily done in either the group home or private setting. The light had no side effects and improved mood, behavior, sleep and functional limitation. **PN**

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