Reversible Vertical Gaze Palsy in Sodium Valproate Toxicity

We read with interest the report on corticobasal syndrome by Rajagopal et al (1). At times, this neurodegenerative disorder may lead to vertical gaze palsy. We evaluated a patient with valproate toxicity and hyperammonemia and reversible vertical gaze palsy.

A 56-year-old man presented with progressive unsteadiness, drowsiness, and cognitive decline for the past 6 months. Twenty-five years previously, he was involved in a traffic accident and was in coma for 2 weeks. Subsequently, he made partial recovery with recurrent nocturnal generalized tonic-clonic seizures. He was changed to monotherapy with 400 mg of sodium valproate twice daily for 6 months. The patient's relatives noted progressive drowsiness and decline in cognition since the treatment was started. His general health was otherwise excellent, and his last seizure occurred 3 weeks before our evaluation.

On physical examination, the patient needed support to stand and walk. He was drowsy with hypophonic and dysarthric speech. Extraocular movements revealed marked limitation of upward and downward gaze for both saccades and pursuit with preserved horizontal gaze (see Video 1, Supplemental Digital Content 1, http://links.lww.com/WNO/A64). Vestibulo-ocular reflex was preserved, but convergence was absent. Pupils were of normal size and reactive to light. Motor examination showed bradykinesia, rigidity, bilateral postural tremors of hands, and positive pull test. He walked with short steps, moderate stoop, and wide-based gait. His tendon reflexes were brisk, and plantar responses were flexor. Sensory examination was normal.

Complete blood count, renal function tests, profiles of glucose, sodium, potassium, calcium, and thyroid, thyroid antibodies, and B12 levels were normal. Venereal disease research laboratory testing and HIV testing were normal. Brain magnetic resonance imaging showed diffuse cerebral atrophy and bifrontal gliosis. There were no imaging signs of atypical Parkinson syndromes. Electroencephalography showed diffuse mild slowing of background activity of 6–7 Hz theta suggestive of mild diffuse encephalopathy.

His plasma ammonia level was 194 μmol/L (normal, 11–32 μmol/L) with valproic acid level of 109 μg/mL (therapeutic range, 50–100 μg/mL). Sodium valproate was discontinued, and 1,000 mg of levetiracetam twice a day was started. Four days later, vertical gaze for both saccadic and pursuit eye movements had markedly improved (see Video 2, Supplemental Digital Content 2, http://links.lww.com/WNO/A65). Significant improvement also was noted in his rigidity, bradykinesia, and postural imbalance. One week later, he was walking independently.

Partial or total gaze palsy has been described with exposure to phenytoin (2), phenobarbitone (3), and carbamazepine (4). Selective upward gaze palsy has also been described in phenobarbitone poisoning (3). To our knowledge, vertical gaze palsy in valproate intoxication has not been reported. In our patient, complete recovery of upward gaze palsy within few days of stopping valproate strongly suggests a causal relationship. Our patient also had features of parkinsonism, which showed a significant improvement after stopping the medication (5). We did not rechallenge the patient with valproate.

The centers for control of vertical gaze are located in the premotor structures of the midbrain, namely, the rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal. These areas have abundant gamma-aminobutyric acid (GABA) receptors (6). In the interstitial nucleus of Cajal in macaque monkey, medium-sized and large GABAergic neurons have been identified projecting contralaterally to the superior oblique and inferior rectus motoneurons and presumably the contralateral interstitial nucleus of Cajal as well. These commissural GABAergic projections are well suited to inhibit the superior oblique and inferior rectus motoneurons and premotor down-burst-tonic neurons during upward eye movements (7).

Valproate is a well-known GABAergic drug that facilitates glutamic acid decarboxylase, an enzyme responsible for GABA synthesis. At high concentrations, valproate also blocks GABA transaminase in the brain, preventing degradation of GABA. The deactivation of vertical burst neurons by the GABA agonist action of valproate may explain the selective vertical gaze palsy as a result of valproate toxicity (8).

Sarma Gosala Raja Kukkuta, MD, DM
Meghana Srinivas, MBBS
Nadig Raghunandan, MD, DNB
Mathew Thomas, MD, DM
Arvind Prabhu, MD
Mary Laly, MBBS
St. John's Medical College Hospital, Bangalore, Karnataka, India
grk_sarma@yahoo.com

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REFERENCES

16 Syndrome in a Patient With Multiple Sclerosis

We read with interest the report of Connors et al (1) of a case of 16 syndrome with complete horizontal gaze paralysis and facial diplegia caused by a pontine hemorrhage. We describe a patient with multiple sclerosis (MS) who experienced an evolving eye movement disorder, which included internuclear ophthalmoplegia, one-and-a-half syndrome, eight-and-a-half syndrome, fifteen-and-a-half syndrome, and finally 16 syndrome.

A 44-year-old man with a history of hypertension, heavy smoking, and a positive family history of cardiovascular disease complained of double vision upon awakening. Neurological examination revealed bilateral internuclear ophthalmoplegia (INO), which was attributed to a brainstem infarction given the sudden onset and the patient’s vascular risk factors. Magnetic resonance imaging (MRI) of the brain and the intracranial vessels revealed several periventricular white matter lesions but no brainstem abnormality. Three days later, the patient developed drooping of the right corner of his mouth and complained of drooling. Examination revealed a right lower motor neuron facial nerve paresis in addition to bilateral INO. Repeat MRI revealed a nonenhancing lesion in the midline of the dorsal pons (Fig. 1). Two days later, he developed a complete right conjugate horizontal gaze palsy which, coupled with his left INO, produced a one-and-a-half syndrome. Concurrently, he also experienced bilateral facial paresis.

Evaluation for stroke including extensive hematological tests, Holter cardiac monitoring, and transesophageal echocardiography was normal. Cerebrospinal fluid analysis for IgG, oligoclonal bands, and aquaporin-4 antibodies as well as visual evoked responses were normal. MRI of the cervical spinal cord revealed no lesions.

On the 11th day of hospitalization, the patient developed bilateral horizontal gaze palsies with worsening of his facial diplegia. His clinical course in combination with the periventricular white matter lesions was highly suggestive of demyelinating disease. Treatment with methylprednisolone

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**FIG. 1.** Axial fluid-attenuated inversion recovery (A) and sagittal T2 (B) MRI show an area of high signal (arrows) in the dorsal pons ventral to the fourth ventricle.