Clinical commentary with video sequences

Paroxysmal tonic upgaze of childhood with co-existent absence epilepsy

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ABSTRACT – Paroxysmal tonic upgaze (PTU) is a childhood oculomotor syndrome of unclear etiology characterized by episodic tonic upward eye deviation with neck flexion. Neuroimaging findings are often normal and the electroencephalography during episodes is typically normal. We describe a 2-year-old boy who presented with macrocephaly, hypotonia, developmental delay and episodes of eye fluttering, head nodding and unresponsiveness. Video-EEG captured absence seizures and he was treated with valproate, which led to improvement of his seizures. However, two weeks after treatment, he developed paroxysmal episodes of “eyes up and chin down” movements lasting for hours at a time which were captured by home video. The episodes were relieved by sleep and exacerbated by fever, stress and even tactile stimulation. Increasing the dose of valproate resulted in increased frequency of the episodes. A repeat video-EEG disclosed the non-epileptic nature of these events. Discontinuation of valproate dramatically decreased the episodes. This case illustrates that paroxysmal tonic upgaze of childhood may co-exist with early onset absence epilepsy. Furthermore, valproate treatment may be associated with the development or unmasking of PTU suggesting that the pathophysiology of PTU may involve abnormal GABA neurotransmission.

Key words: paroxysmal tonic upgaze, absence epilepsy, valproate, video-EEG, non-epileptic, movement disorder

Paroxysmal tonic upgaze (PTU) of childhood was first described by Ouvrier and Billson in 1988. It is an age-related oculomotor syndrome of unknown etiology characterized by paroxysmal episodes of conjugate upward eye deviation with neck flexion, down-beating saccades in attempted downgaze, normal horizontal eye movements, diurnal fluctuation, relief by sleep, exacerbation by illness, varying degrees of ataxia and essentially normal neurologic investigations (Ouvrier and Billson 1988; reviewed in Ouvrier and Billson 2005). Its paroxysmal nature and the absence of epileptiform activity on electroencephalography (EEG) during the episodes suggest that it can be classified under non-epileptic paroxysmal movement disorders in children (Roubertie et al. 2007). Yet, an association between movement disorders and epilepsy has long been demonstrated (Berkovic et al. 2000, Guerrini et al. 2002) and the use of video-EEG has indeed provided strong support for this association.

We now describe a 2-year old boy who presented with macrocephaly, developmental delay, hypotonia and absence seizures. While being treated...
with valproate, he developed the classic features of PTU. This case suggests that PTU may co-exist with absence epilepsy. Furthermore, it also demonstrates that valproate may potentially unmask the occurrence of PTU and shed some light on its pathophysiology.

Case study

Our patient was a 26-months-old adopted boy who presented to us for a second opinion regarding his episodic conjugate tonic upward eye deviations. He was born full term by vaginal delivery with a birth weight of 7 lbs and 9 oz and APGAR scores of 9 at both one and five minutes. Maternal history was significant for developmental delay, epilepsy and depression with intake of valproate during pregnancy whereas paternal history was significant for cognitive impairment and, therefore, the newborn was given up for adoption. At age 4 months, he presented with hypotonia, developmental delay, hearing loss and macrocephaly. Neurologic investigations consisted of metabolic workup and genetic testing, including chromosomal analysis, DNA testing for Fragile X syndrome and subtelomere analysis, which were all unremarkable. Cranial magnetic resonance imaging at 6 months of age showed signal hyperintensities in the periventricular white matter and insular region suggestive of delayed myelination as well as mild sulcal and extra-axial fluid space prominence, consistent with benign macrocephaly of infancy (figures 1A,B).

At age 16 months, he began to manifest episodic eye fluttering, head nodding and unresponsiveness lasting for few seconds occurring multiple times per day. Video-EEG showed a background activity of 5-6 Hz (figure 2A). Interictally, frequent generalized spike and wave paroxysms were noted. His habitual events were captured and these episodes were associated with bursts of generalized 3 per second spike and wave activity (figure 2B) consistent with absence epilepsy. He was treated initially with topiramate which dramatically decreased his seizures. However, four months later, he developed poor appetite and his medication was changed to valproate. Two weeks later, he developed a new kind of paroxysmal event described as episodes of “eyes up and chin down” movements and these were captured on home video (see video sequence). The event consisted of paroxysmal episodes of sustained, conjugate, upward eye deviation with neck flexion (chin down) associated with down beating eye jerks on attempted down gaze and relatively normal horizontal eye movements. During these episodes, which lasted for an average of 4 to 5 hours each, he was completely responsive and was interactive. The episodes were typically exacerbated by fever, stress, fatigue and even tactile stimulation, such as touching him with a blanket. They were relieved by sleep or even by a short nap. He was re-evaluated and repeat video-EEG captured both his absence seizures and the tonic upgaze episodes of his eyes. Repeat cranial MRI at age 18 months was normal (figure 1C). The valproate was gradually increased to 60 mg/kg/day, but the medication dramatically worsened his tonic upgaze episodes, both in frequency and duration. Ethosuximide was added at 15 mg/kg/day but this did not relieve his paroxysmal upgaze. He was then brought to us by his adoptive parents for a second opinion.

Developmentally, he held his head at 7 months, sat alone at 11 months, walked at 25 months, babbled at 9 months, and started speaking words at 11 months. At the age of 26 months when we first saw him, he could speak 10 words and make 8 signs. He had an ataxic gait and fine motor incoordination. On physical examination, he was macrocephalic with head circumference of 52 cm (90th percentile). He had very good social interactions. Cranial nerve examination was normal. He moved all of his extremities equally and spontaneously. He had normal muscle tone, bulk and range of motion. Deep tendon reflexes were normal in all extremities bilaterally. He had mild truncal ataxia, and walked with an ataxic gait. No nystagmus was

**Figure 1.** A and B) Fluid attenuated inversion recovery (FLAIR) sequence cranial magnetic resonance imaging of our patient at age 6 months showing some signal hyperintensities in the periventricular white matter and insula suggestive of delayed myelination as well as mild sulcal and extra-axial fluid space prominence, a finding consistent with benign macrocephaly of infancy. C) T1-weighted cranial magnetic resonance sequence at age 16 months showing normal findings. There were no structural lesions in the midbrain or the cortical structures.
Figure 2. A) Electroencephalography (EEG) at age 16 months in a longitudinal bipolar montage showing a background activity of 5 to 6 Hz. B) Ictal electroencephalography (EEG) was captured showing burst of 3 per second generalized spike and wave activities associated with eye fluttering, head nodding and unresponsiveness.
noted. Repeat video-EEG captured the paroxysmal episodes of tonic upgaze of the eyes associated with neck flexion, and confirmed that these episodes were non-epileptic events consistent with PTU. No absence seizures were captured. The patient was weaned off from his anti-seizure medications resulting in immediate and dramatic improvement of his PTU episodes. From daily episodes, he went down to having episodes every other day to having no episodes for two days. However, within 2 weeks of the medication tapering process, absence seizures recurred. Ethosuximide was initiated. Currently, patient’s absence seizures are well controlled. He would still have intermittent PTU episodes but these are significantly less frequent and less pronounced.

**Discussion**

Our case highlights several new insights about paroxysmal tonic upgaze of childhood. First, PTU can co-exist with absence epilepsy. Secondly, valproate treatment may either trigger or unmask the development or occurrence of PTU.

Since the first description of four cases of PTU, there have been 49 reported cases in the literature; however, the disorder might still be unrecognized or undiagnosed. The clinical features have also been expanded. Cases of PTU associated with psychomotor retardation and MRI findings of hypomyelination have all been described (Sugie et al. 1995, Hayman et al. 1998, Blumkin et al. 2007). The association of PTU with epileptic seizures has been reported in a few instances. There have been cases which were associated with febrile convulsions (Echenne and Rivier 1992, Hayman et al. 1998, Verroti et al. 2001). In the series of Hayman et al. (1998), only one child had a history of epilepsy, PTU and EEG findings of generalized epileptiform discharges. Guerrini et al. (2002) have described two siblings with PTU with co-existent absence epilepsy. In these two patients, PTU began first followed by the development of absence epilepsy. Conversely, in our case, absence seizures occurred first followed by the development to PTU.

Another interesting issue in our case is whether valproate triggered or unmasked the development of PTU. This has never been reported in the literature, although various antecedent factors have been described in PTU, including febrile illness, immunization (Ouvrier and Billson 1988, Hayman et al. 1998, Spalice et al. 2000, Verroti et al. 2001), car travel (Sugie et al. 1995, Hayman et al. 1998) and recently, proprioceptive stimulation such as light tapping of the forehead (Karam et al. 2003). The pathophysiology of PTU is poorly understood. Ouvrier and Billson (1988, 2005) hypothesized that the neuroanatomical substrate of PTU is the upper dorsal midbrain, particularly the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Since PTU is paroxysmal and not usually associated with structural brain lesions, a neurotransmitter disorder or a “channelopathy” is suspected (Ouvrier and Billson 2005). Hayman et al. (1998), on the other hand, speculated that this condition is analogous to the pathophysiology of epileptic spasms as proposed by Chugani et al. (1992) who, based on positron emission tomography findings, proposed that an alteration in cortical-subcortical interaction may be present in epileptic spasms and noted that the timing of this disorder coincided with the onset of cortical maturation. Similarly, PTU may be an age-related manifestation of immaturity of the corticomesencephalic control of vertical eye movements.

The link between the development of PTU and valproate has not been fully elucidated. Although there were three cases of PTU who had history of fetal exposure to valproate (Echenne and Rivier 1992, Campistol et al. 1993, reviewed in Ouvrier and Billson 2005), the causal relationship between valproate and PTU has not been identified. However, based on an experimental animal study, a potential link can be proposed. Horn et al. (2003), by using tract-tracer methods combined with immunocytochemistry or in situ hybridization, investigated the location of gamma-aminobutyric acid (GABAer)ic premotor neurons in the riMLF and the interstitial nucleus of Cajal (IC) in macaque monkeys. They observed that very few small GABAer neurons are present in the riMLF, and none of them was found to project to the oculomotor nuclei, suggesting that the projections of the riMLF to the oculomotor neurons are exclusively excitatory. However, in the IC, medium-sized and large GABAer neurons were identified projecting contralaterally to the superior oblique and inferior rectus motor neurons and presumably the IC of the other side, suggesting that these commissural GABAer projections inhibit the superior oblique and inferior rectus motor neurons and possibly the premotor down-burst-rectus neurons during upward gaze. Since valproate enhances GABA neurotransmission (Johannessen, 2000), it is possible that valproate potentiates the GABAer neurotransmission in the IC causing imbalance and excessive excitation of the motor neurons projecting to the superior rectus and inferior oblique responsible for the upgaze. We therefore propose that aside from the riMLF, a neurochemical disturbance in the IC may also be implicated as one of the neuroanatomical substrates in the pathogenesis of PTU particularly in cases triggered by valproate treatment.

Legend for video sequence

An episode of paroxysmal tonic upgaze captured by home video. The child presents with paroxysmal tonic upgaze and was able to eat, and follow commands.
References


