

Paroxysmal Tonic Upward Gaze at Adolescence: A Girl with Prader-Willi Syndrome

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Paroxysmal tonic upward gaze (PTUG) is a childhood oculomotor syndrome characterized by episodes of conjugate upward deviation of the eyes. Its pathogenesis is unknown and the etiology is heterogeneous. PTUG has been reported only in children younger than 9 years. Prader-Willi syndrome (PWS) is a complex neurogenetic, multisystem disorder caused by the absence of paternal expression of imprinted genes on 15q11-q13. Ophthalmologic phenomena are common in the syndrome, including myopia, strabismus and amblyopia, but PTUG has not been described in PWS. We describe a 13 year old girl with PWS who had recurrent episodes of PTUG.

PATIENT DESCRIPTION

A 13 year old adolescent female with PWS due to a paternal deletion on 15q11-q13 was treated from early age with an early-intervention holistic program and had received growth hormone treatment from the age of 6 months. Developmentally, she achieved most milestones as expected; she attended special educational frameworks due to mild mental retardation, learning disabilities and autistic spectrum disorder. She manifested obsessive-compulsive behavior, behavioral problems and attention deficit hyperactivity disorder pharmacologically treated with

fluvoxamine, risperidone and methylphenidate, respectively. Food-related issues were under control. The girl had strabismus since birth which was corrected surgically at age 6 years.

At the age of 13, two episodes of sustained conjugate upward deviation of the eyes occurred, with neck flexion and down-beating saccades with no ataxia; during these episodes consciousness was maintained [Figure 1]. These episodes lasted 12 hours and resolved spontaneously. On examination, several days after the second episode, her weight was 39.6 kg (37th percentile), body mass index 21.2 (82nd percentile), and physical examination, aside from central hypotonicity, was normal. Neither PTUG movements nor ataxia was observed. Ophthalmologic examination revealed: right eye – hypertropia that was comitant in left, right, up, and down gaze; and left

eye – myopia and amblyopia. There was no stereo vision.

Electroencephalogram (EEG) was normal, and no epileptic activity was recorded. Brain magnetic resonance imaging (MRI) was normal. Genetic testing for mutations on the *CACNA1A* gene on chromosome 19 revealed no pathology.

COMMENT

PWS is a complex neurogenetic, multisystem disorder with a prevalence of 1/15,000 to 1/30,000, caused by a lack of expression of genes on the paternally inherited chromosome 15q11.2-q13. Ophthalmologic morbidity is common, and includes myopia, strabismus, esotropia, exotropia as well as reduced visual acuity, iris hypopigmentation, amblyopia, refractive errors and astigmatism [1]. Despite the variable ocular abnormalities PTUG has not been reported in individuals with Prader-Willi syndrome.

Paroxysmal tonic upward gaze in childhood is characterized by episodes of sustained conjugate upward deviation of the eyes with neck flexion, down-beating saccades in attempted downward gaze, and normal horizontal eye movements. Ataxia, in some cases, accompanies PTUG. Consciousness is maintained during these episodes and neurological exam is usually intact. PTUG appears usually before age 1 year or during early childhood. The oldest child described is a 9 year old boy [2,3]. The duration and frequency are variable: episodes usually last seconds, but in rare cases they can continue for more than 24 hours. The frequency ranges from daily episodes to once in several months. Exacerbations are common during febrile illnesses or after

Figure 1. Episode of upward deviation of the eyes and neck flexion



vaccinations [2]. The episodes are relieved by sleep and disappear spontaneously. Ataxia, ocular disability, language problems, mild cognitive or even (rarely) severe cognitive disorder may remain [2].

There is controversy in the literature regarding the efficacy and need of drug treatment for PTUG. Drugs that have been tested are L-DOPA, ACTH, acetazolamide, and antiepileptic drugs such as valproic acid, carbamazepine and benzodiazepines [2,3].

Although the etiology of PTUG is obscure in most cases [2], a genetic basis of PTUG was identified in some instances. There are a few familial cases with autosomal recessive and autosomal dominant inheritance [4]. A mutation in the *CACNA1A* gene, on chromosome 19, causing calcium channelopathy was reported in five cases. *CACNA1A* is linked to other paroxysmal disorders, such as benign paroxysmal torticollis of infancy, episodic ataxia, hemiplegic migraine and paroxysmal vertigo [4].

In addition to our patient, PTUG has been reported in two other children with chromosome 15 abnormalities. The first was a 3 month old infant with partial tetrasomy of chromosome 15, and the second, a 2 year old girl with Angelman syndrome caused by a maternal deletion of 15q11-13 [5]. PTUG was described in two other imprinting disorders: one was a case of a 2 week old boy with Beckwith Wiedemann syndrome [3] and the other was the above

mentioned girl with Angelman syndrome [5]. Although the vast majority of cases with PTUG show no brain abnormalities on imaging [2,4], there are rare case reports of demyelinating pathology [4], upper brain stem lesions, periventricular leukomalacia, hydrocephalus and a vein of Galen malformation [3]. EEG and metabolic findings are generally normal, but association with epileptic disorders has been reported [2,4]. Due to the early onset of PTUG some researchers hypothesized that it may be caused by either immaturity of eye movement control or secondary to a channelopathy, or due to neurotransmitter depletion [2,3]. Fukumura et al. [5] speculated that the dopaminergic abnormalities present in Angelman syndrome may cause PTUG [5].

In our case, the cause of PTUG is unclear: there was no clinical or laboratory evidence of epilepsy, structural brain anomalies, *CACNA1A* gene abnormalities, or maturational abnormalities in eye movement control. The girl was treated for years with fluvoxamine, risperidone and methylphenidate (MPH) before the PTUG onset. Fluvoxamine can cause, in rare cases, ophthalmologic adverse effects such as amblyopia, and risperidone is known to cause blurred vision, conjunctivitis and reduced visual acuity. MPH works through dopaminergic pathways, which were hypothesized to explain the pathophysiological basis of PTUG; nonetheless, our patient was

treated with MPH for years at the same dosage. Neither of these drugs was reported to cause PTUG.

In summary, we describe a 13 year old adolescent with PWS who had PTUG, the oldest case reported. Genetic causes may elucidate the etiology of PTUG in some cases. Imprinting genetic disorders and abnormalities on chromosome 15 should be suspected in cases with PTUG and developmental disorders. Further genetic and epigenetic studies may shed light on the precise etiology of PTUG.

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