Palatal Tremor Revisited: Disorder with Nosological Diversity and Etiological Heterogeneity

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ABSTRACT: This case series aimed to describe clinicoradiological, electromyographic, and etiological spectra in palatal tremor (essential = 1; symptomatic = 26). Patients with symptomatic palatal tremor had 2 to 10 Hz arrhythmic electromyographic bursts, a spectrum of changes in inferior olivary nucleus, with/without lesions in Guillain Mollaret triangle, and varied etiologies (genetic = 9, vascular = 6, trauma = 3, infections = 3). Exome sequencing showed variations in POLG, WDR81, NDUFS8, TENM4, and EEF2. Clinical phenotypes of patients with POLG, WDR81, and NDUFS8 variations were consistent with that described in literature. We highlight salient magnetic resonance imaging features, electrophysiological observations, and diverse etiologies in a large cohort of palatal tremor.

RÉSUMÉ: Le tremblement du voile du palais revisité: diversité nosologique et hétérogénéité étiologique. Le but de cette série de cas était de décrire le spectre clinico-radiologique, électromyographique et étiologique du tremblement du voile du palais (essentiel chez 1 patient, symptomatique chez 26 patients). Les patients qui présentaient un tremblement symptomatique du voile du palais avaient des bouffées électromyographiques arythmiques de 2 à 10 Hz et une gamme de changements dans l’olive bulbaire inférieure, avec ou sans lésion dans le triangle de Guillain-Mollaret. L’étiologie était variée chez ces patients: génétique chez 9, vasculaire chez 6, traumatique chez 3 et infectieuse chez 3. Le séquençage d’exomes a mis en évidence des variations dans les gènes POLG, WDR81, NDUFS8, TENM4 et EEF2. Les phénotypes cliniques chez les patients porteurs de variations dans POLG, WDR81 et NDUFS8 étaient conformes à ceux décrits dans la littérature. Nous soulignons les principales caractéristiques à l’imagerie par résonance magnétique, les observations électrophysiologiques et les étiologies diverses chez une grande cohorte de patients présentant un tremblement du voile du palais.

Keywords: Essential Palatal Tremor, Genetic, Inferior Olivary Nucleus, Symptomatic Palatal Tremor

Table 1: Clinical Features and Brain Magnetic Resonance Imaging Observations in Patients with Palatal Tremor (n = 27)

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Age/Gender</th>
<th>Diagnosis</th>
<th>Tremor of additional muscles</th>
<th>Inferior Olivary Nucleus changes</th>
<th>Hyperintensities/lesions in brain MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ocular</td>
<td>Larynx</td>
<td>Tongue</td>
</tr>
<tr>
<td>1</td>
<td>20/F</td>
<td>EPT</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>30/F</td>
<td>Ophthalmoplegia and ataxia. Mitochondrial cytopathy, POLG variation</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>44/F</td>
<td>Ophthalmoplegia, ataxia, and seizures. Mitochondrial cytopathy, POLG variation</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>13/M</td>
<td>Optic atrophy and spastic ataxia. WDR81 variation</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>50/F</td>
<td>Ataxia. EEF2 variation</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>9/M</td>
<td>Recurrent encephalopathy and ataxia. Mitochondrial cytopathy, TENM4 variation</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>16/F</td>
<td>Optic atrophy and spasticity. Leucoencephalopathy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>54/F</td>
<td>Fever triggered ataxia. Mitochondrial cytopathy</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>31/F</td>
<td>Episodic ataxia and optic atrophy. Suspected mitochondrial cytopathy</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>17/M</td>
<td>Ataxia, peri-oral dyskinesias, and generalized dystonia. Mitochondrial cytopathy, NDUFS8 variation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>51/M</td>
<td>Recurrent stroke</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>55/M</td>
<td>Pontine bleed</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>35/M</td>
<td>Pontine bleed</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>43/M</td>
<td>Stroke</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>39/F</td>
<td>PCA aneurysm &amp; infarct</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>16</td>
<td>35/F</td>
<td>Takayasu arteritis</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>44/F</td>
<td>Post head injury</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>32/M</td>
<td>Post head injury</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>19/M</td>
<td>Post head injury</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>44/M</td>
<td>Atypical demyelination</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>31/M</td>
<td>Atypical demyelination</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>53/M</td>
<td>CNS toxoplasmosis</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>48/M</td>
<td>Tubercular pachymeningitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24</td>
<td>24/M</td>
<td>CNS tuberculoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25</td>
<td>57/M</td>
<td>Granulomatous lesion of pons</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>50/M</td>
<td>Glioma of middle cerebellar peduncle</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>27</td>
<td>56/F</td>
<td>Fourth ventricular epidermoid cyst (post op status)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

BL: Bilateral; CNS: Central Nervous System; EEF2: Eukaryotic Translation Elongation Factor 2; EPT: Essential Palatal Tremor; GMT: Guillain Mollaret Triangle; MRI: Magnetic Resonance Imaging; NDUFS8: NADH:ubiquinone oxidoreductase core subunit S8; NV: Not Visualized; PCA: Posterior Cerebral Artery; POLG: Polymerase Gamma; TENM4: Teneurin Transmembrane Protein 4; UL: Unilateral; WDR81: WD Repeat-Containing Protein 81
Brain MRI showed abnormalities of the inferior olivary nucleus (ION) in the form of: (1) hyperintensity with hypertrophy (bilateral = 10, unilateral = 5) and (2) hyperintensity without hypertrophy (bilateral = 4, unilateral = 1). In three patients, ION could not be assessed because of lesions in the brainstem that were large and/or contiguous with ION. Additional observations included signal changes involving (1) brainstem in the region of GMT as well as a region outside the GMT (n = 17), (2) brainstem in the GMT only (n = 4), (3) a region outside the GMT only (n = 2), and (4) normal (n = 4) (Figure 1).

In the present study, the relatively high proportion of patients with genetic causes could be due to referral bias because we are actively involved in research in mitochondrial and other neurogenetic disorders (Supplementary Data). Patients 2 and 3, with ataxia, ophthalmoplegia, and palatal tremor, had variations in POLG1. Although patient 2 had compound heterozygous variations (W478 + E1143G), patient 3 had homozygous variation (W478S). The W478 variant in POLG1 is consistently associated with the clinical phenotype of ataxia and PT in the European population, either in the homozygous state or in the compound heterozygous state with the polymorphism E1143G. Patient 4 had homozygous variation in WDR81, which has been previously reported in families with autosomal recessive cerebellar ataxia, mental retardation, and disequilibrium syndrome type 2 (Online Mendelian Inheritance in Man [OMIM] #610185). The presence of oculopalatal tremor in our patient expands the clinical spectrum of WDR81 mutations. Patient 10 had juvenile-onset Leigh syndrome and compound heterozygous variation in the gene encoding the NDUFS8 subunit of complex I of the mitochondrial respiratory chain; this was further supported by the presence of isolated complex I deficiency in skeletal muscle. Homozygous and compound heterozygous variations in NDUFS8 are recognized causes of Leigh syndrome (OMIM #256000).
We have earlier reported the association of inferior olivary hypertrophy (IOH) with Leigh syndrome and underlying SURF1 variation, but examination for PT could not be carried out because the cohort consisted of children only. PT associated with mitochondrial disorders and mutations in POLG and SURF1 has been reported. We believe that the presence of IOH in an appropriate clinical setting may provide clues for an underlying mitochondrial etiology. Patients 5 and 6 had heterozygous variations in EEF2 and TENM4, respectively, that are associated with autosomal dominant spinocerebellar ataxia-26 (OMIM #609306) and hereditary essential tremor (OMIM #617636). Because our patients’ phenotypes did not conform to that described in the literature, the causal role of these variations remains to be established. Other heredodegenerative causes for IOH and PT reported in the literature include spinocerebellar ataxia, Alexander disease, neuroferritinopathy, GM2 gangliosidosis, and progressive ataxia palatal tremor, among others.

Earlier reports indicate that SPT develops after a varying interval of a few weeks to several years following brainstem injury. Anatomical changes evolve sequentially in the ION. Increased signal in the ION in T2 and proton density sequences is followed by hypertrophy; this coincides with the development of PT. Three patients with infarcts in our cohort reported an interval of 1.5 to 10 months between the initial stroke and onset of ataxia. We presume that this may be the interval needed for IOH to develop after brain stem injury and therefore PT. This is a putative statement; we have not examined these patients serially. Pathologically, six stages are described in the evolution of IOH that correlate with MRI changes. The spectrum of MRI changes in ION noted in our study may be a reflection of different stages in evolution of IOH; we have only cross-sectional data on the clinical features and MRI changes.

In our study, nystagmus synchronous with PT, i.e., oculopalatal tremor, was noted in 20 patients. Ocular movements may be vertical and pendular or horizontal and torsional and may be symmetric or dissociated. Oculopalatal tremor produces oscillations, which is sometimes distressing. PT may also be associated with rhythmic movements of face, larynx, and diaphragm, as was noted in a few patients in our study. Rarely, vocal cord and facial tremor have been described. Deuschl et al. reported that the frequency of PT was 120 to 130 jers per minute, with variable involvement of the pharynx, diaphragm, vocal cords, face, and eyes. Electrophysiological recordings in subsequent studies showed a much lower frequency of 2 Hz. In our study, PT was arrhythmic and the frequency ranged from 2 to 10 Hz.

The GMT is formed by fibers that link the dentate nucleus with the contralateral red nucleus, central tegmental tract, and ION. Increased glucose metabolism in the medulla, encompassing the region of ION and increased blood flow to the ION and dentate nucleus, have been demonstrated. The “dual mechanism” hypothesis elucidates the role of ION and deep cerebellar nuclei in PT. ION is the “pacemaker” oscillator. A lesion in the GMT causes transynaptic deafferentation, loss of inhibitory \( \lambda \)-aminobutyric acid afferents, and compensatory increase in presynaptic terminals of deafferented IOH. Electrotomographic coupling of dendrodendritic gap junctions facilitates synchronized oscillations of neurons in ION. Further, abnormal soma-somatic gap junctions in IOH increase the strength of electrotomographic coupling. Specific T-type calcium channels that are expressed on neurons of ION modulate their oscillations. The low amplitude signal from the ION is subsequently amplified by the deep cerebellar nuclei.

IOH may occur without a lesion in the GMT and may or may not be associated with a lesion outside the GMT. In the present study, abnormal ION in the form of hyperintensity with or without enlargement was the isolated observation in three patients, whereas, in another two subjects, a lesion was noted, but outside the GMT. Thus neuronal pathways outside the GMT may have a role in IOH. Earlier instances of PT developing in the presence of cortical lesions without brainstem or cerebellar involvement highlighted the role of cerebral cortex in the generation of IOH and PT. In our cohort, two patients did not have IOH abnormality; thus, PT may develop without MRI changes. Besides this, PT as a clinical correlate is seen in only a proportion of subjects with IOH. We did not assess other patients with IOH who did not have PT. To add to the enigma is the observation made in other studies that IOH that develops after stroke or trauma and eventually resolves, whereas PT persists. In vivo studies delineating connectivity of ION to GMT as well as other areas of brain and spinal cord in health and disease is now possible using advanced MRI techniques such as diffusion tensor imaging and functional MRI. This may shed light on this intriguing topic.

In conclusion, we report a fairly large cohort of patients with PT from a single center. PT is a movement disorder known for its nosological diversity and etiological heterogeneity, linked by a common anatomical substrate (i.e. the ION). We highlight newer etiologies including uncommon genetic variations underlying PT. A spectrum of changes was noted in IOH ranging from unilateral or bilateral hyperintensity with or without hypertrophy to normal findings.

Acknowledgments and Funding
The study is supported in part by a grant from Indian council of Medical Research to PSB (Grant No. 54/9/2012-HUM-BMS).

Disclosures
PSB discloses support from the Indian council of Medical Research (grant no. 54/9/2012-HUM-BMS). The remaining authors have nothing to disclose.

Supplementary material
To view material(s) referred to in this article, please visit https://doi.org/10.1017/cjn.2017.273

References