Progressive ataxia with oculo-palatal tremor and optic atrophy.

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Common.SubmissionDetails.Abstract:	Progressive ataxia palatal tremor (PAPT) is a rare neurological syndrome characterized by progressive cerebellar ataxia and palatal tremor. Sporadic as well as hereditary forms of PAPT have been described. Whereas sporadic PAPT is typically associated with bilateral pseudo-hypertrophy of the inferior olivary nuclei and progressive cerebellar atrophy, familial PAPT cases show brainstem and spinal cord atrophy in the absence of olivary signal changes on magnetic resonance imaging (MRI). Familial PAPT is often associated with upper motor neuron signs whereas sporadic PAPT cases are associated with cerebellar ataxia. Palatal tremor in the sporadic PAPT cases is characterised by non-periodic, low frequency oscillations (1-3 Hz) of the posterior soft palate, often accompanied by branchial (60%) and/or ocular (30%) muscles oscillations. We report a unique case of sporadic PAPT with bilateral optic atrophy and upper motor neuron signs.
Common.SubmissionDetails.ResponseToReviewers:	We thank both reviewers for favourably reviewing our manuscript. Whilst reviewer #1 felt the emphasis of the discussion should be slightly shifted away from the distinction between sporadic and familial PAPT towards "other neurological abnormalities associated with sporadic PAPT", reviewer #2 emphasized the importance of highlighting the features normally associated with familial PAPT that

	were present in our case of sporadic PAPT. In order to accommodate the valid views of both referees we left the bulk of the discussion untouched and inserted one sentence reminding the reader of the previously described association between sporadic PAPT and other neurodegenerative diseases (highlighted in yellow in the revised manuscript). We hope this is satisfactory.
Common.SubmissionDetails.AuthorComments:	Dear Professor Filippi Re: Progressive ataxia with oculopalatal tremor and optic atrophy On behalf of the co-authors and myself I herewith submit the revised version of the abovementioned case report. Thank you for considering our paper further for publication. With kind regards, Maria Papachatzaki

*Authors' Response to Reviewers' Comments
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Re: JOON-D-13-00941R1 Response to reviewers

We thank both reviewers for favourably reviewing our manuscript.

Whilst reviewer #1 felt the emphasis of the discussion should be slightly shifted away from the distinction between sporadic and familial PAPT towards "other neurological abnormalities associated with sporadic PAPT", reviewer #2 emphasized the importance of highlighting the features normally associated with familial PAPT that were present in our case of sporadic PAPT.

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Progressive ataxia with oculo-palatal tremor and optic atrophy

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Dear Sirs,

A 42 year-old man of Polish extraction presented with a four year history of slowly deteriorating reading difficulties and gait imbalance. There was no evidence for alcohol or recreational substance abuse. Family history was unremarkable.

On examination he had tandem gait ataxia. Power was normal; no atrophies. Deep tendon reflexes were pronounced on the left with ipsilaterally extensor plantar response. He had upper limb past pointing, pronounced on the left.

Visual acuity was 20/60 on the right and 20/80 on the left. Colour vision (Ishihara plates): 13/15 on the right and 10/15 on the left. Humphrey 10:2 perimetry showed reduced sensitivity paracentrally in both eyes. Retinae appeared normal, however both optic discs showed temporal wedge-shaped pallor (Fig. 1). Examination of extra-ocular movements was supported by binocular 3D video oculography (Video 1). Pendular torsional nystagmus in primary gaze was detected, partly attenuated on left gaze. The nystagmus had two components, a baseline, low amplitude (1-2deg), symmetrical, pendular, torsional oscillation (1.7 – 2Hz) and an irregular larger amplitude (2-5deg) nystagmus beating clockwise from the observer's point of view. Both nystagmus components were pronounced in the right eye. The torsional faster component included a large upwards component in the right eye ('left pendular hemi-seesaw nystagmus') [1] (Fig. 1). Non-periodic tremor (2Hz) of the soft palate and posterior pharyngeal wall muscles was evident (video 2).

Optical coherence Tomography of the peripapillary retinal nerve fibre layer confirmed bilateral segmental optic atrophy (Fig. 1). Full- field and multifocal electroretinograms were normal. Amplitudes of pattern reversal visual evoked potentials were bilaterally borderline reduced.

Haematology and biochemistry indices were normal as were vitamin B_{12}, folic acid, thyroid function, syphilis and HIV 1/2 serology, and screening for onconeuronal and other auto-antibodies. Cerebrospinal fluid analysis was normal. Full GFAP gene sequencing failed to support presence of Alexander's disease [2]. Search for spinocerebellar ataxia expansions and/or duplications 1-3, 6, 7, 12 & 20 was negative [3,4] as were searches for mitochondrial mutations associated with (i) Leber's Hereditary Optic Atrophy [5], (ii) Mitochondrial Encephalomyopathy, Lactic acidosis and Stroke-like episodes, (iii) Myoclonic Epilepsy with Ragged Red Fibers, and (iv) Neuropathy, Ataxia and Retinitis Pigmentosa. Genetic testing for Optic Atrophy 1 [6] and Polymerase Gamma Gene mutations [7,8] was also negative.

MRI head and spinal cord showed hyper-intense signal in the medulla oblongata on T_2 weighted images suggesting bilateral pseudo-hypertrophy of inferior olivary nuclei, and mild cerebellar atrophy. MRI of optic nerves suggested reduced optic nerve diameter, pronounced on the left (Fig. 1).

To the best of our knowledge sporadic Progressive Ataxia Palatal Tremor (sPAPT) with bilateral optic atrophy and upper motor neuron (UMN) signs has never been reported. PAPT is a rare syndrome. sPAPT as well as familial (fPAPT) forms have been described. Whilst sPAPT is typically associated with bilateral pseudo-hypertrophy of the inferior olive and progressive cerebellar atrophy, people with fPAPT show brainstem and spinal cord atrophy in the absence of olivary changes. fPAPT is often associated with UMN signs whereas cases of sPAPT are associated with cerebellar ataxia [9]. Palatal tremor in sPAPT is characterised by non-periodic, low frequency oscillations (1-3 Hz) of the posterior soft palate, often accompanied by branchial (60%) and/or ocular (30%) muscles oscillations [10]. In our case palatal tremor was accompanied by oscillations of

branchial as well as ocular muscles to produce left 'pendular hemi-seeshaw' nystagmus. Symptoms and signs were in line with lesions in the medulla oblongata, and an ocular degenerative abnormality, respectively [1]. An association between sPAPT and well described neurodegenerative diseases, for example, multiple system atrophy (MSA) has previously been reported [9]. However, early onset, fairly benign course, and lack of clinical and MRI findings characteristic of alternative neurodegenerative diseases render such association in our patient highly unlikely. Thus, in the absence of clinical, imaging or laboratory findings supporting the diagnosis of a known cause of PAPT, it is possible that our case represents a novel phenotype of sPAPT with bilateral optic atrophy.

Conflicts of interest All authors declare no conflicts of interest.

Ethical standard The authors declare they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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Video 1

3D video oculography of the right eye during fixation to a LED target, initially in primary gaze and then during fixation 15deg to the right, left and back to centre. Note the large, asymmetric, torsional, 'rotatory' nystagmus, which is larger and faster to the left (clockwise from the observer's point of view).

Video 2

Non periodic palatal tremor (~2Hz) with synchronous oscillations of the posterior pharyngeal wall muscles.

Fig. 1

Fundoscopy and ocular coherence tomography (OCT) (a= left eye; b= right eye). Bilateral pallor of the optic disc (*arrows* a1 and b1). OCT of the retinal nerve fibre layer showing defect (summarized in pie charts) in all but the medial section of the left, and the inferior section of the right eye (a2/a3 and b2/b3). T_2 weighted magnetic resonance imaging (MRI) showing bilateral pseudohypertrophy of the inferior olivary nuclei (*arrow* c, *large arrow* e), moderate cerebellar atrophy (*small arrow* d) and optic nerve atrophy, pronounced on the left (*arrow* d). 3D video oculography recordings (f) showing pendular torsional nystagmus in primary gaze. The torsional component was associated with an apparent left and up beating torsional nystagmus (*dashed arrows*). A second smaller amplitude component of the pendular nystagmus was present (*small arrow*) with a frequency of 1.7 - 2Hz.

Figure 1

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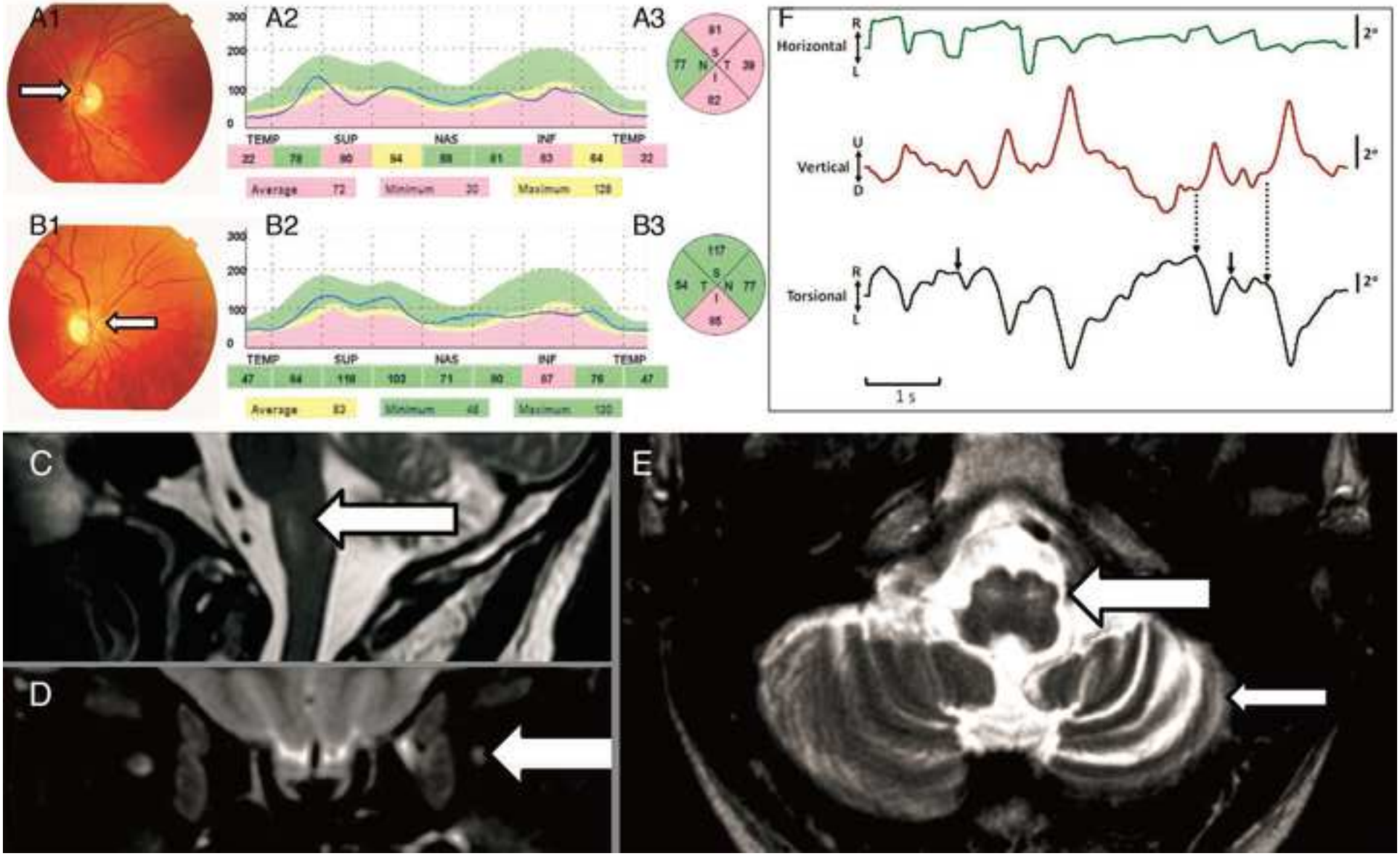

Video 1

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Video 2

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