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Progressive Ataxia and Palatal Tremor Associated With Dense Pontine Calcification: A Unique Case



Intracranial calcifications are associated with a variety of disorders, but marked pontine calcification without an underlying structural lesion has rarely been reported. Here we present a unique case with progressive ataxia palatal tremor (PAPT) associated with marked pontine calcification. A previously healthy 53-year old woman first noticed balance problems, slurred speech, and a constant oculopalatal tremor at age 48. Within 4 years of symptom onset, she progressed to requiring support when walking, developed swallowing difficulties, and intermittently had double incontinence. Cognition was intact. Medical history included type 2 diabetes (dietary management only), hypothyroidism (euthyroid for more than a decade), hypercholesterolemia, and arterial hypertension. She was taking lisinopril, simvastatin, levothyroxine, and fluoxetine. There was no family history of any neurological disorder.

On examination at age 52, she had cerebellar dysarthria and a synchronous ocular-facial-palatal myoclonus. She had titubatory head tremor and torticollis to the left. Examination of extraocular movements showed an elliptical ocular tremor synchronous with the palatal tremor, left lateral rectus palsy, and slow horizontal saccades but normal conjugate vertical eye movements and convergence. She had bilateral gaze-evoked nystagmus and finger–nose ataxia. Her gait was ataxic, requiring the support of 2 people in order to walk (Video 1). Sensation, power, and reflexes were normal. Follow-up at age 53 showed further deterioration of her dysarthria and gait. She is currently wheelchair bound (Video 2).

Routine blood tests including thyroid function, parathyroid hormone, lupus anticoagulant, white cell enzymes,

cholesterol, very long chain fatty acids, and a blood film for acanthocytes were normal. Antinuclear, anti-neutrophil cytoplasmic, voltage-gated potassium channels, anti-glutamic acid decarboxylase, and anti-tissue transglutaminase antibodies were negative. Gastrointestinal biopsy excluded Whipple's and celiac diseases. Genetic tests for Alexander's disease (*GFAP* mutations), spinocerebellar ataxias (SCA 1–6, 12, 17), fragile X-associated tremor ataxia syndrome, common mitochondrial mutations, and polymerase gamma mutations were negative. Cerebrospinal fluid examination showed no abnormalities. MRI showed a paired symmetrical low signal in the posterior aspect of the basis pontis and tegmentum on T2 (Fig. 1A), T1 (Fig. 1B), and FLAIR sequences and cerebellar, pontine, middle cerebellar, and cerebral peduncular volume loss. The low-signal region was confirmed to be calcification on a nonenhanced computerized tomography (CT) scan (Fig. 1C) that also demonstrated some patchy calcification within the rostral medulla. MR angiography and dopamine transporter imaging (DaTSCAN) were normal.

A causative relationship between the calcification and the clinical picture cannot be proven, as also is the case in other disorders with brain calcifications such as Fahr's disease. However, the association of the calcification with the patient's clinical picture is highly likely for many reasons. First, the localization of the calcification cannot be physiologic or incidental, as physiologic or incidental intracranial calcifications are by definition not accompanied by relevant signs and have a different distribution in CT that never involves isolated the pons, particularly to that degree.¹ Second, the localization of the calcification is in keeping with the proposed pathomechanism of PAPT, namely, a lesion involving the Guillan-Mollaret triangle,^{2,3} causing an interruption of the inhibitory pathway from the dentate nucleus to the contralateral inferior olivary nucleus via the superior cerebellar peduncle and central tegmental tract.²

In terms of possible underlying etiology, marked pontine calcification is described typically secondary to tumors or arteriovenous malformations^{1,4–6} or postirradiation,⁷ whereas rarer causes such as Krabbe disease and cerebrotendinous xanthomatosis were excluded in our patient.⁵ There is one case with a similar CT finding reported, but the clinical presentation was different, and the putative diagnosis was multiple system atrophy. However, no DaTSCAN was performed, and the diagnosis remained inconclusive.⁸ In our patient this possibility was excluded phenotypically but also by the normal DaTSCAN.

More widespread abnormal intracranial calcifications in adults can be part of an underlying systemic (eg, hypoparathyroidism, pseudo-hypoparathyroidism, pseudo-pseudohypoparathyroidism, hyperparathyroidism, systemic lupus erythematosus),^{9,10} neurodegenerative (eg, Fahr's disease, diffuse neurofibrillary tangles with calcification),^{11,12} or

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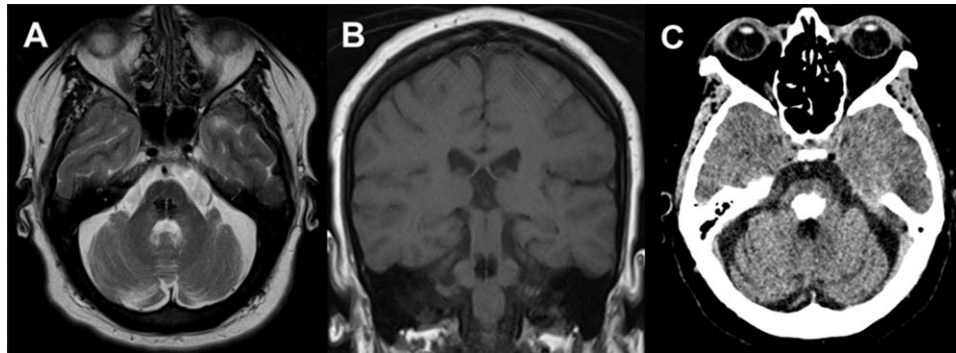


FIG. 1. T2 (A) and T1 (B) show a symmetrical low signal centrally in the posterior aspect of the basis pontis and tegmentum of the pons together with cerebellar, pontine, middle cerebellar peduncular, and cerebral peduncular volume loss. A nonenhanced computerized tomography (CT) scan confirms heavy calcification posteriorly within the pons (C).

mitochondrial disorders (eg, myoclonic epilepsy with ragged red fibers, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), but these conditions were excluded in our patient. Moreover, the calcification in these disorders typically shows a characteristic symmetric striato-pallido-dentate distribution. The brainstem can rarely be involved but is never the predominant localization of the calcification.^{5,13}

Further recognized causes of a PAPT syndrome such as *GFAP* mutations^{14,15} and celiac disease¹⁶ were excluded in our patient, whereas *SCA20*¹⁷ is unlikely in our patient, as there was no family history, and imaging in *SCA20* shows isolated dentate calcification (“dark dentate disease”).

We have described a novel case with marked pontine calcification in the context of PAPT syndrome. The diagnosis of this patient remains inconclusive and is only likely to be obtained at autopsy. We encourage others to report similar cases, as progressive ataxia with or without palatal tremor associated with marked pontine calcification may constitute a novel entity.

Legend to the Video

Video. *Segment 1* shows the patient at age 52, 4 years after disease onset. She has synchronous oculopalatal tremor, also with synchronous movements of facial muscles and the right arm. She has a titubatory tremor of the head. She has cerebellar dysarthria and finger–nose ataxia. There is no bradykinesia. She has marked gait ataxia and can stand only with the help of another. *Segment 2* shows the patient a year later with worsened dysarthria, head titubation, and finger–nose ataxia more in the right than the left. The patient cannot stand even with help of 2 others and is wheelchair bound.

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Prevalence and Impact of Restless Legs Syndrome in University Students

Restless legs syndrome (RLS) is one of the most common neurological disorders. It is characterized by an irresistible urge to move one's legs, the major sensory symptom, and can have an overwhelming impact on quality of life. Apparently changes in central nervous system iron metabolism lead to dopamine dysfunction, which is thought to be responsible for unpleasant feelings and movements of mainly the legs in the evening or during the night.¹

Many epidemiological studies of RLS in the past used different criteria. The consensus on standardized diagnostic criteria of the International RLS Study Group (IRLS-SG) led to agreement on a definition.² These criteria were also used in the REST (RLS Epidemiology, Symptoms, and Treatment) project involving a cohort of several thousand subjects. The prevalence of RLS in the general adult population was 7.2% for individuals with symptoms of any frequency and 2.7% for those with RLS at least twice a week and at least moderate distress (so-called RLS sufferers).³ The occurrence of RLS increases with age in adults,^{3,4} but it is not rare in children. It was reported⁵ that 1.9% of 8- to 11-year-olds and 2.0% of 12- to 17-year-olds met IRLS-SG criteria (0.5% and 1.0% were RLS sufferers, respectively). However, data on the prevalence of RLS in the specific population of young adults have not been available so far.

Three hundred consecutively enrolled students of the Faculty of Medicine, Comenius University Bratislava, participated in our study. They answered 4 specific questions, that is, essential criteria for RLS according to the IRLSSG, in a brief questionnaire that also collected demographic data. If all 4 questions were answered positively, the respondent was considered RLS positive; otherwise, the respondent was considered RLS negative. RLS-positives subsequently completed a second part of the questionnaire that a physician or trained nurse applied. The aim of this part was to confirm the diagnosis of RLS and describe its particular features, a methodology already validated and successfully used in our previous study.⁶ All subjects gave their written informed

consent in agreement with the Declaration of Helsinki, and the local institutional review board approved the study.

All 4 essential IRLS-SG diagnostic criteria were met by 27 of 300 respondents (9%). Almost 78% of RLS-positives were women (Table 1). More than 94% of RLS-positives had only mild to moderate symptoms, occurring on an average of once a month or less. Only 2 (0.7%) reported a moderate or severe average intensity of RLS, occurring at least twice a week (so-called RLS sufferers according to the REST definition). Almost 63% of RLS-positives indicated that their overall quality of life was not affected; the rest reported only mild to moderate impact.

We realize that medical students could be more somatically oriented and sleep deprived. Therefore, they may not be representative of typical people of their age. Nevertheless, our study confirmed that the overall prevalence of RLS in this subgroup is similar to that in the general and a primary-care population.^{3,4} Only 2 of 300 respondents were RLS sufferers. Although prevalent among young adults, RLS does not seem to have a significant impact on the quality of life of this population.

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