

## Throat-clearing vocalisations in primary brain calcification syndromes

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Primary brain calcification syndromes are heterogeneous disorders characterized by pathological peri-microvascular calcium deposition in the basal ganglia, subcortical white matter, thalamus and cerebellum.<sup>1</sup> Most are inherited in an autosomal dominant fashion (*SLC20A2*, *XPR1*, *PDGFRD*, *PDGFB*), though recently, biallelic variants in the *MYORG* and *JAM2* genes have been identified as autosomal recessive causes of the syndrome<sup>2,3</sup>.

Clinical manifestations are protean. Some affected individuals remain asymptomatic despite demonstrable brain calcinosis, though most experience progressive neurological decline. Psychiatric symptoms (depression, anxiety, psychosis), movement disorders and cognitive impairment are typical.

Herein, we report 2 patients who displayed grunting/throat-clearing vocalisations as an early manifestation of primary brain calcification (figure 1). The case histories are summarized in Table 1, and further elaborated in the supplementary material. The vocalisations and other clinical features are illustrated in the accompanying videos (Video 1, 2).

Involuntary vocalisations are a primitive form of emotion-driven communication. For many mammals, they are the primary means of conveying anger, fear, satisfaction and mating desire. In humans, they form part of normal early development, prior to the development of language, but may become pathological either through their occurrence beyond specific developmental stages and/or their performance outside of appropriate social contexts<sup>4</sup>.

Generation of vocalisations is critically dependent on the periaqueductal gray matter (PAG) and its efferent projections to the lower brainstem reticular formation<sup>5</sup>. In turn, the PAG receives rostral afferent inputs from limbic and basal ganglia regions, modulating and controlling vocalisation behaviours<sup>5</sup>.

In movement disorder practice, the most commonly encountered vocalisations are vocal tics. These peak in incidence in late childhood/early adolescence, particularly in males, and can be self-limiting (transient/provisional tic disorder,

lasting <12 months) or persistent, either as chronic tics (which generally ease with age) or Tourette's syndrome. In these groups, psychiatric comorbidity- attention deficit hyperactivity disorder, obsessive compulsive disorder or impulse control disorder- is common<sup>6</sup>.

New onset vocalisations in adulthood are unusual, and require close attention. In some, they may represent re-emergence of a childhood tic disorder which had initially dissipated and remained dormant, only to re-emerge in later life<sup>7</sup>. In this setting, a history of childhood tics is extremely helpful. In adults without a past history of tic disorder, or in the presence of other abnormal features on neurological examination, tic-like vocalisations should raise concern for underlying neurodegenerative disorders. Indeed, 'secondary' vocal tics have been described in numerous disorders including Huntington's disease, neuroacanthocytosis, progressive supranuclear palsy, neurodegeneration with brain iron accumulation and others<sup>4,7</sup>. Autoimmune, structural and importantly drug-induced (particularly stimulants e.g. cocaine/amphetamines) are other important differential diagnoses to consider for new adult-onset vocalisations<sup>4,7</sup>.

Involuntary vocalisations have not hitherto been highlighted as a major feature of brain calcification syndromes. Palilalia and echolalia are occasionally reported,<sup>4,8,9</sup> while guttural vocalisations have only been described once previously<sup>10</sup>. Altered limbic-PAG connectivity associated with pathological intracranial calcification may be the driver of abnormal utterances in these cases, and one may surmise that the similar throat-clearing qualities in all cases (table 1) reflects distinct patterns of limbic involvement, leading to preferential activation of PAG neurons controlling guttural sounds. However, in our handful of cases, this hypothesis is difficult to further explore.

Primary brain calcification should be added to the list of disorders which can present with adult-onset vocalisations. Future studies may wish to systematically evaluate their prevalence and pathophysiologic basis in this patient group.

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1 Research project: A. Conception, B. Organization, C. Execution;

2 Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

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**Ethical compliance statement:**

The authors confirm that the approval of an institutional review board was not required for this work. Written informed consent was obtained from all patients for publication of this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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**Figure 1 legend:** CT brain images of Case 1 (A), his mother (B) and his son (C), and Case 2 (D).

**Video legends:**

Video 1. Case 1 demonstrates frequent suppressible throat-clearing vocalisations. He also exhibits gait disturbance including difficulty turning, mild craniocervical dystonia and mirror movements upon finger tapping.

Video 2. Case 2 demonstrates frequent suppressible throat-clearing vocalisations. He also exhibits slowness and interruptions on finger and foot tapping, alongside facial, craniocervical and upper limb dystonia.

**Supplementary material legend:** Detailed clinical history, examination and diagnostic workup of case 1 and case 2

**Table 1:** Demographic, clinical and radiological features of all three cases of PFBC exhibiting involuntary throat-clearing vocalisations

	Age at onset	Sex	Family History	Vocalisations	Clinical symptoms	Areas of calcification	Genetic mutation
<b>Case 1 (see Video 1)</b>	64	Male	Autosomal dominant -affected mother and son	Grunting/throat clearing	Dystonia, cognitive decline, Parkinsonism	Subcortical WM, basal ganglia, thalamus, cerebellum	c.418C>T p.(Gln140*) truncating mutation in <i>PDGFB</i>
<b>Case 2 (see Video 2)</b>	40	Male	Possibly autosomal dominant -mother (depression)	Grunting/throat clearing	Dystonia, Parkinsonism, spasticity, anxiety	Subcortical WM, basal ganglia, Thalamus, cerebellum, pons	Unknown
<b>*Case reported by Kümmer et al. <sup>10</sup></b>	40	Male	Possibly autosomal dominant -mother (Parkinson's disease)	Throat clearing	Depression, impulsivity, seizures, 'frontal' behavioural syndrome, stereotypies, punding	Basal ganglia, subcortical white matter	Unknown

(WM: white matter)



