■ Clinical commentary

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Early-onset bradykinetic rigid syndrome and reflex seizures in a child with PURA syndrome

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ABSTRACT

PURA syndrome is a distinct form of developmental encephalopathy, characterized by early-onset hypotonia, severe developmental delay, intellectual disability, epilepsy and respiratory and gastrointestinal disorders. We report a child with PURA syndrome, harbouring a previously described mutation, whose phenotype included two peculiar aspects: (1) hypokinetic-rigid syndrome, which was part of the clinical presentation from an early stage of the disease, and (2) reflex seizures, consisting of a series of spasms. We provide detailed clinical description and video recordings demonstrating both these aspects that are newly described in PURA syndrome. The early clinical features described here may therefore be included in the complex phenotype associated with *PURA* gene mutations and may help in the early diagnosis of patients. Furthermore, PURA syndrome should be considered in the differential diagnosis of early-onset bradykinetic rigid syndromes.

Key words: *PURA* gene, PURA syndrome, bradykinetic-rigid syndrome, reflex seizures

VIDEO ONLINE

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Mutations in purine-rich element binding protein A (*PURA*) gene have been described in patients with early-onset hypotonia, severe developmental delay, intellectual disability, and epilepsy. Early respiratory and gastrointestinal disorders (congenital and central apnoea, gastro oesophageal reflux, and significant oral feeding difficulties) are frequently associated [1-3]. PURA syndrome is now defined as a distinct form of developmental encephalopathy (OMIM #616158). Epilepsy has been reported in more than half of the cases, presenting usually in the first years of life and including many seizure types (generalized tonic-clonic seizures, tonic seizures, focal seizures, absence seizures, and epileptic spasms), often drug-resistant; however, no specific epileptic syndromes have been associated with *PURA* mutations [4].

Here, we describe a child with a *de novo PURA* variant, already reported in the literature, whose phenotype shares several aspects with those with PURA syndrome, but also includes some new interesting clinical features.

Case study

Our patient was the second male child of non-consanguineous healthy parents; pregnancy and delivery were unremarkable. Feeding difficulties and facial dysmorphisms were evident from birth; at six months, neurological examination revealed axial hypotonia and poor motricity, alternating exotropia and reduced visual acuity; the EEG was normal. At 11 months, the clinical picture was also characterized by hypomimia, limb rigidity and hypo/bradykinesia; severe global developmental delay was documented (QG 32.8 at Griffiths scale). Metabolic tests and brain MRI were normal. EEG showed rare generalized epileptiform elements during sleep. At three years, pyramidal signs (brisk deep tendon reflexes and ankle clonus) became evident, associated with truncal hypotonia and a complex movement disorder (MD), combining bradykinetic rigid syndrome, limb tremor, stereotypies and a pathological startle response (*video [part 1]*). A polygraphic recording during action revealed irregular repetitive EMG bursts in the upper limbs, synchronous and asynchronous on the antagonist muscles, with variable duration (50-200 mseconds); the poor quality of the recording, due to poor compliance, did not allow to precisely define the type of hyperkinetic MD. Brain MRI, repeated at three years, showed only mild delayed myelination in bilateral temporo-polar terminal areas (*figure 1A*). CSF neurotransmitter levels and glycorrhachia were normal. Next-generation sequencing analysis (using a gene panel for MDs) did not reveal any relevant variant.

Since the age of four years, epileptic seizures appeared, occurring initially during showering, tooth brushing or hand washing, characterized by a series of spasms (brief abduction of the upper limbs, followed by repetitive sustained contractions of the four limbs), lasting for several minutes.

We documented a hand washing-reflex seizure on video (*video [part 2]*); the subsequent video-EEG showed generalized periodic spikes-and-waves without clinical correlate.

The child then started having seizures also during sleep, which were documented by video-polygraphic recording, demonstrating brief myoclonic seizures (*figure 1B*) and epileptic spasms, both isolated and in clusters (*figure 1C*).

The child, now seven years old, is seizure-free on valproate and clonazepam. The clinical picture is characterized by severe intellectual disability with absent language and frequent hand stereotypies, without clinical criteria for autistic spectrum disorder. The child is able to walk independently with bradykinetic and ataxic gait; hypomimia, bradykinesia and limb rigidity are still present (*video [part 3]*); neurological examination also reveals pyramidal signs, alternating exotropia and nystagmus. Additional clinical features include chronic constipation and airway complications during anaesthesia procedures (laryngospasm reaction followed by prolonged desaturation). Abdominal and cardiac investigations did not show any organ malformation.

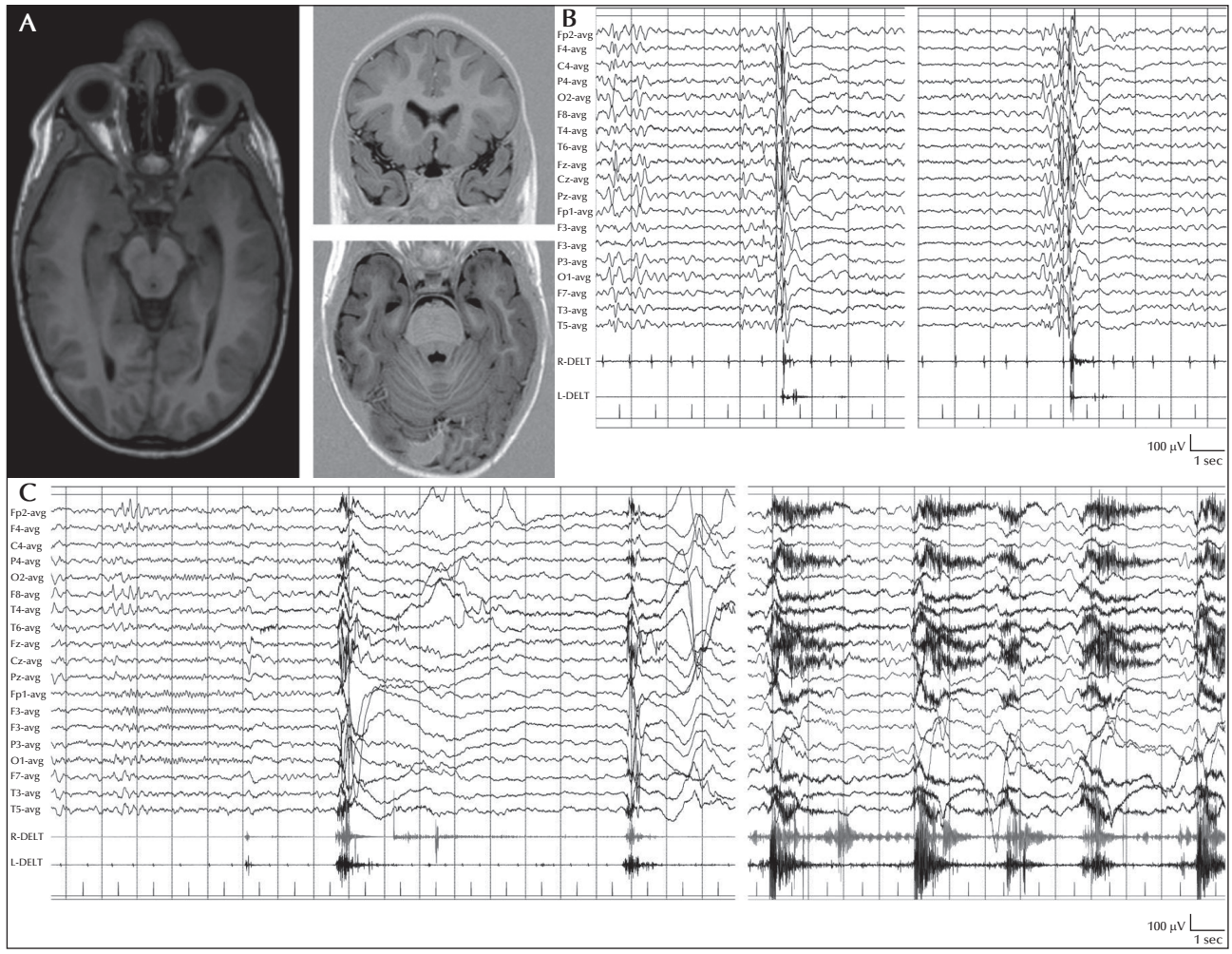
A second targeted 148-gene panel for epilepsy revealed a *de novo* stop-gain mutation (NM_005859.4:c.783C>G p.[Tyr261*]) in the *PURA* gene. Both the DANN (https://cbcl.ics.uci.edu/public_data/DANN/) and the MutationTaster (http://www.mutationtaster.org/) tools predicted this mutation to be disease-causing. The mutation is not reported in the gnomAD control database (http://gnomad.broadinstitute.org/) but is present in the HGMD mutation database (https://portal.biobase-international.com/hgmd/pro/start.php) in a patient with hypotonia and seizures [2].

Discussion

This is a child with PURA-related encephalopathy, harbouring a previously described mutation [2]. Besides some typical clinical features of PURA syndrome (including early-onset hypotonia, early severe developmental delay evolving as intellectual disability with absent language, epilepsy, pathological startle response, and gastrointestinal impairment), two additional aspects make our patient's phenotype particularly interesting.

The first is hypokinetic rigid syndrome: hypomimia, bradykinesia and limb rigidity were prominent features in the child's early clinical presentation and persisted over time, combined with other neurological signs. There have been descriptions of other movement disorders in PURA syndrome (dystonia, choreic movements and ataxia) [4], however, to our knowledge, this is the first case presenting with hypokinetic rigid syndrome. This early feature suggests that PURA syndrome should be considered in the differential diagnosis of early-onset bradykinetic rigid syndromes, as well as in the differential diagnosis of neonatal hypotonia with respiratory and feeding difficulties. It is not surprising that bradykinesia and other movement disorders may be part of the PURA phenotype. Indeed, PUR-alpha protein, encoded by the *PURA* gene and ubiquitously expressed in the brain, has been shown to bind to rCGG repeats at Xq27-28 (fragile X region), suggesting that it might potentially play a role in the development of clinical symptoms associated with fragile X-associated tremor/ataxia syndrome (FXTAS) [5].

The second point of interest is the occurrence of reflex epileptic seizures, also not previously reported in PURA syndrome: the child initially experienced a series of spasms during specific actions (hand washing



■ **Figure 1.** (A) T1-weighted axial and coronal brain MRI sequences performed at three years, showing mild delayed myelination in bilateral temporo-polar terminal areas; (B, C) Polygraphic recordings showing myoclonic seizures related to a diffuse polyspike discharge on EEG (B) and a cluster of spontaneous epileptic spasms during sleep (C). EMG abbreviations: R-delt: right deltoideus; L-delt: left deltoideus.

and tooth brushing). Stimulus-induced epileptic spasms are a rare type of reflex seizures, already described in genetic conditions, including chromosomal abnormalities, Rett syndrome and *CDKL5*-related encephalopathy [6-8]; among the different stimuli that can provoke epileptic spasms, eating is the most frequently described. In our case, triggers consisted of hand washing and tooth brushing, both suggesting a specific sensitivity to somatosensory stimuli, especially prolonged stimuli, as occurs in rub epilepsy [9]. Tooth brushing has already been described as a trigger for seizures, especially in cases of focal epilepsy [10, 11]. In this case, there was no evidence of focal epileptiform activity or clinical signs orienting towards a focal origin of the seizures. It is not clear which specific mechanism underlies this phenomenon; however, we believe that reflex epileptic spasms are probably a manifestation of diffuse cortical hyperexcitability, as in other forms of genetic encephalopathy. Notably, the reported occurrence of an exaggerated startle response in a large proportion of patients with PURA syndrome [4] is in line with the hypothesis of diffuse cortical excitability. In conclusion, this is the first description of both hypokinetic rigid syndrome and reflex seizures in a case of PURA syndrome. The early clinical features described here may therefore be included in the complex phenotype associated with *PURA* gene mutations and may help in the early diagnosis of patients. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to disclose.
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Legend for video sequence

Part 1. Video recording performed at three years of age, showing the complex movement disorder, that combines stereotypies, bradykinesia, limb tremor and ataxic gait.
Part 2. Video recording performed at five years of age, showing epileptic spasms evoked by hand washing.
Part 3. Video recording performed at seven years of age, showing the persistence of bradykinetic rigid syndrome, stereotypies and ataxic gait.

Key words for video research on www.epilepticdisorders.com

Phenomenology: spasm (epileptic), dyskinesias (non epileptic)
Localization: not applicable
Syndrome: epilepsy not classified
Aetiology: genetic disorder

TEST YOURSELF

(1) What are the typical clinical features of PURA syndrome?

(2) How would you describe the movement disorders in PURA syndrome?

(3) What is the form of reflex epilepsy in which a prolonged somatosensory stimulus induces seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.