■ Letter to the editor

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Expanding the phenotype of PURA-related developmental epileptic encephalopathy

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To the Editor,

We have read with great interest the report by Solazzi *et al*. (Early-onset bradykinetic rigid syndrome and reflex seizures in a child with PURA syndrome. *Epileptic Disord* 2021; 23: 745-8) [1] who describe a previously unreported child affected by PURA-related developmental and epileptic encephalopathy (PURA-related DEE) harbouring a known pathogenic variant, whose phenotype included two peculiar features, *i.e.* onset of hypokinetic-rigid syndrome at an early age and reflex seizures. The features described by Solazzi *et al*. [1] add to the constellation of phenotypic characteristics that have been previously outlined in PURA-related DEE, such as early-onset hypotonia, gastrointestinal disturbances, severe developmental delay with no language acquisition, poor motricity and epileptic seizures [2]. PURA-related DEE is caused by pathogenic variants in the *PURA* (purine-rich element-binding protein A) gene located on chromosome 5q31, encoding a single-exon transcript that results in a highly conserved 322-amino-acid (AA) protein, Pur-α. Pur-α is crucial for normal postnatal brain development, neuronal cell proliferation and synapse formation.

We recently conducted a study in the largest cohort described so far, including 142 subjects with PURA-related DEE [3]. This study comprehensively delineated and expanded the phenotypic and genotypic spectrum of this DEE and confirmed the main clinical features reported above. In addition, it outlined some phenotypic aspects, *i.e.* the occurrence of a variety of movement disorders and reflex seizures that had been poorly explored or even not reported previously in PURA-related DEE, thus corroborating the findings by Solazzi *et al*. [1]. In Johannesen *et al*.'s study [3], movement disorders such as dyskinesia, hand stereotypies, ataxia, and chorea-like movements, were detected in about 24% of the patients, while a pathological startle response was detected in about 18% of individuals. Overall, these findings suggested that hyperkinetic motor disturbances are common features in PURA-related DEE. However, the observation of an early-onset bradykinetic syndrome by Solazzi *et al*. [1] is indeed a novel finding, not reported previously. In their patient, hypo/bradykinesia was observed at the age of 11 months, associated with limb rigidity, hypomimia and severe global developmental delay. These disturbances, which persisted over time until the age at last observation at seven years, were encompassed in a complex motor disorder characterized by bradykinetic rigid syndrome, limb tremor, stereotypies and a pathological startle response. The study by Johannesen *et al*. [3] showed that non-epileptic paroxysmal motor manifestations and pathological startles can be observed in a significant proportion of patients, both with and without epilepsy, thus lending support to recent observations showing that non-epileptic movement disorders are not an uncommon feature of DEE [4, 5]. In fact, hyperkinetic movement manifestations, such as dystonia and choreoathetosis, are acknowledged as common phenotypic features in subjects with *FOXG1, GNAO1, SCN8A, CACNA1B,* and *STXBP1*-related epilepsy-dyskinesia syndromes [6-10]. Hand

stereotypies also are often reported in children with autism or developmental delay. Although these motor disorders do not bear any diagnostic specificity, a detailed phenotypic description of these phenomena, such as hyperkinetic movements, hand stereotypies and, following Solazzi *et al.*'s report [1], also bradykinetic/rigid features, can be of utmost importance to more precisely define and expand the disease spectrum and increase the early recognition of PURA-related DEE.

Solazzi *et al*. [1] also described reflex epileptic seizures, characterized by a series of spasms lasting several minutes, triggered by showering, tooth-brushing and hand-washing. Reflex seizures were not reported previously in PURA-related DEE. This finding has been confirmed in the study by Johannesen *et al*. [3], who reported seizures triggered by auditory, visual and somatosensory stimuli (such as touch, tooth brushing or hair brushing, pain, associated with evacuation) in about 8% of individuals. Reflex seizures were described as myoclonic or atonic seizures, or "absence-like" episodes. Interestingly, in some patients, a reflex mechanism was observed only for a transitory period, raising the issue of a possible under-estimation of this phenomenon, particularly in those subjects presenting with very frequent seizures, non-epileptic motor disorders and severe intellectual disability. In the series of Solazzi *et al*. [1] and in about 18% of the series of Johannesen *et al*. [3], the clinical picture featured both reflex seizures and a startle response to acoustic stimuli, suggesting that diffuse cortical hyperxcitability might contribute to the pathophysiology of both phenomena, similarly to what has been hypothesized for other forms of genetic encephalopathies, such as encephalopathy associated with pathogenic *KCNQ2* variants which can display exaggerated startle attacks in 38% of individuals [11].

In conclusion, the paper by Solazzi *et al*. [1] adds novel features to the phenotypic spectrum of PURA-related DEE, possibly contributing to an early diagnosis that should ultimately prompt referral of the patients for genetic testing. Furthermore, it highlights the usefulness and need for detailed "deep" phenotyping studies of complex DEEs, not only for more precise and timely diagnosis, but also to ultimately identify genotype-phenotype correlations, at present lacking in PURA-related DEE, and reconstruct the natural history of this condition. The knowledge gained from these studies may be instrumental to delineate appropriate patient populations for pragmatic clinical trials, to ultimately test targeted treatments. In the near future, we may expect advances in deep phenotyping techniques, the "omics" and genetic epilepsy models to significantly impact translational research, bringing precision medicine to the forefront of clinical practice. ■

Disclosures.
None of the authors has any conflict of interest to disclose

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