■ Case vignette

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Epileptic Disorders

Intractable startle epilepsy in Schuurs–Hoeijmakers syndrome

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Schuurs–Hoeijmakers syndrome is a rare autosomal dominant disorder characterized by dysmorphic facial features, intellectual disability and various physical malformations [1]. The syndrome is caused by *PACS1* mutations, the majority of which are c.607C>T, p.Arg203Trp [2]. More than half of the cases are associated with epilepsy [3], and various seizure types have been reported [4].

Startle epilepsy is a rare form of epilepsy induced by sudden stimuli and was categorized as a reflex epilepsy in the 2001 classification by the International League Against Epilepsy [5]. Startle seizures are mainly caused by unexpected auditory or tactile stimuli and have not been reported to occur in Schuurs–Hoeijmakers syndrome [6, 7].

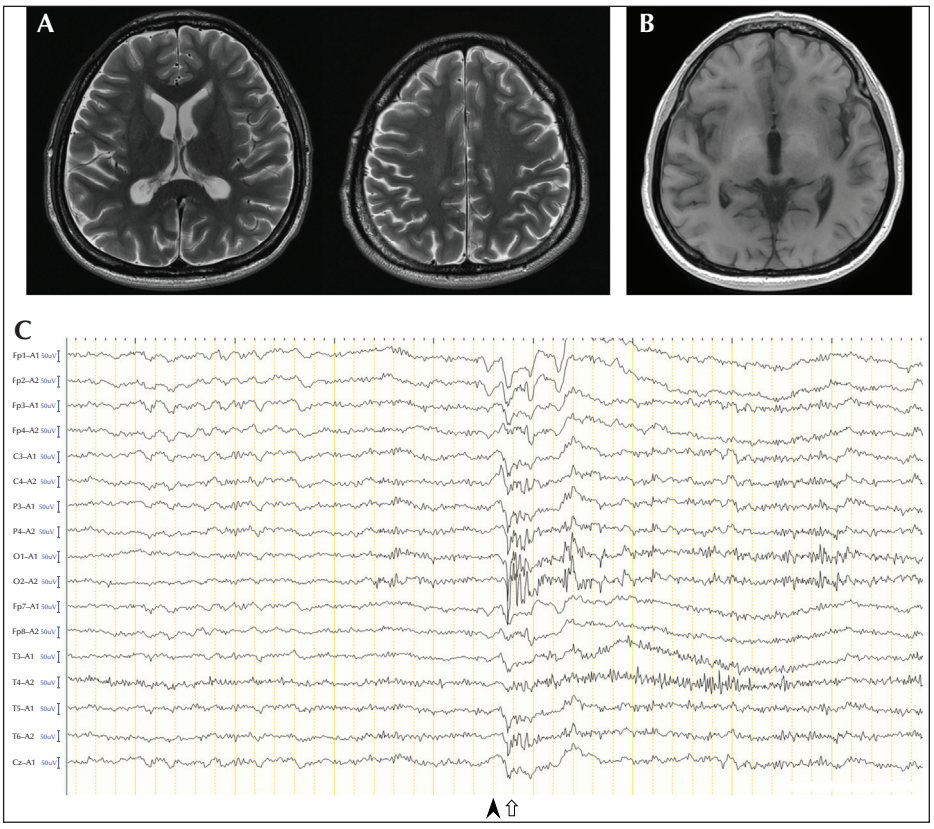
The patient was a 31-year-old male with an unremarkable family history. He presented with severe global developmental delay. His morphological features included a down-slanted palpebral fissure, a thin upper lip and large hands. He had developed epilepsy with generalized tonic seizures at the age of four months, and the seizures resolved without antiepileptic drugs at the age of three years. At around 10 years of age, he developed atonic seizures, which involved knee buckling in response to sudden unexpected noise or touch. The acoustic triggers included other people talking, coughing, ringtones and car horns. Atonic seizures were sometimes followed by a fall (drop attack) and could evolve into generalized tonic-clonic seizures. Interictal electroencephalography frequently revealed right-dominant bifrontal spikes and waves. He was treated with antiepileptic drugs, including valproate, zonisamide, clonazepam, phenytoin, clobazam and lamotrigine. Valproate, clonazepam, phenytoin and clobazam were partially effective. His seizures gradually became intractable to those drugs.

The patient was admitted to our hospital for evaluation at 31 years of age. G-banding showed 46XY with a normal male karyotype. Brain magnetic resonance imaging (MRI) showed whole cerebral and cerebellar atrophies, hyperintensity around the anterior horn of the lateral ventricles on T2-weighted imaging (*figure 1A*), and hyperintensity in the globus pallidus to substantia nigra on T1-weighted imaging (*figure 1B*). Long-term video EEG monitoring was performed. He demonstrated knee buckling immediately after handclap auditory stimulation, and occipital polyspikes were observed (*figure 1C*).

After written informed consent was obtained, whole-exome analysis was performed. A heterozygous *de novo* c.607C>T (p.Arg203Trp) mutation in *PACS1* was found in the patient.

We report a case of Schuurs–Hoeijmakers syndrome with intractable startle seizures. The startle epilepsy from 10 years of age was resistant to antiepileptic drugs. No previous cases of startle epilepsy have been reported in this syndrome, and the refractory nature was considered as a unique characteristic of our case.

Schuurs–Hoeijmakers syndrome was first reported in 2012 in two unrelated



■ **Figure 1.** (A, B) Brain MRI showing T2 hyperintensity around the anterior horn of the lateral ventricles and atrophy in the whole cerebrum (A), and hyperintensity in the globus pallidus to substantia nigra on T1-weighted imaging (B). (C) Ictal EEG showing occipital polyspikes, 0.2 seconds after the onset of auditory stimulus (indicated by the arrowhead). The patient demonstrates knee buckling (indicated by the white arrow).

children with intellectual disability and distinctive facial features [1]. According to a large case series that included 19 patients, seizures were common in this syndrome, occurring in 12 of 19 patients [3]. In this series, seizures responded well to antiepileptic drugs, and in some cases, the medication was discontinued. In other case series, the seizure types included Rolandic epilepsy, focal impaired awareness seizures, absence seizures, generalized and focal tonic-clonic seizures, and drop attacks [4].

The aetiology of startle epilepsy is heterogeneous. Startle epilepsy has been reported in patients with perinatal and postnatal factors [6]. Congenital aetiologies such as chromosomal abnormalities, metabolic diseases and mitochondrial disorders can also cause startle epilepsy [7]. Generally, startle epilepsy is complicated in patients with diffuse brain lesions. Most patients have severe intellectual problems, and their seizures are intractable [7]. Based on intracranial EEG, magnetoencephalography and functional neuroimaging studies, the origin of startle epilepsy is considered to involve the supplementary motor area and primary motor and sensory cortex [8-10]. Our patient presented with intractable epilepsy, severe intellectual disability and diffuse brain abnormalities. Cerebral atrophy, which involves the auditory and primary sensory areas and is a relatively profound abnormality in this syndrome, might be associated with auditory and tactile-induced startle seizures in our patient.

In conclusion, we demonstrate a case of Schuurs–Hoeijmakers syndrome with refractory startle epilepsy. This report adds a new seizure type to this syndrome. In addition, epilepsy in this syndrome may be intractable in some 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 declare.

References

1. Schuurs-Hoeijmakers JH, Oh EC, Vissers LE, Swinkels ME, Gilissen C, Willemsen MA, *et al*. Recurrent de novo mutations in *PACS1* cause defective cranial-neural-crest migration and define a recognizable intellectual-disability syndrome. *Am J Hum Genet* 2012; 91: 1122-7.

2. Miyake N, Ozasa S, Mabe H, Kimura S, Shiina M, Imagawa E, *et al*. A novel missense mutation affecting the same amino acid as the recurrent *PACS1* mutation in Schuurs-Hoeijmakers syndrome. *Clin Genet* 2018; 93: 929-30.

3. Schuurs-Hoeijmakers JH, Landsverk ML, Foulds N, Kukolich MK, Gavrilova RH, Greville-Heygate S, *et al*. Clinical delineation of the *PACS1*-related syndrome – report on 19 patients. *Am J Med Genet A* 2016; 170: 670-5.

4. Stern D, Cho MT, Chikarmane R, Willaert R, Retterer K, Kendall F, *et al*. Association of the missense variant p. Arg203Trp in *PACS1* as a cause of intellectual disability and seizures. *Clin Genet* 2017; 92: 221-3.

5. Engel Jr J, International League Against Epilepsy (ILAE). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001; 42: 796-803.

6. Yang Z, Liu X, Qin J, Zhang Y, Bao X, Wang S, *et al*. Clinical and electrophysiological characteristics of startle epilepsy in childhood. *Clin Neurophysiol* 2010; 121: 658-64.

7. Tibussek D, Wohlrab G, Boltshauser E, Schmitt B. Proven startle-provoked epileptic seizures in childhood: semiologic and electrophysiologic variability. *Epilepsia* 2006; 47: 1050-8.

8. Saeki K, Saito Y, Sugai K, Nakagawa E, Komaki H, Sakuma H, *et al*. Startle epilepsy associated with gait-induced seizures: Pathomechanism analysis using EEG, MEG, and PET studies. *Epilepsia* 2009; 50: 1274-9.

9. Fernández S, Donaire A, Maestro I, Seres E, Setoain X, Bargalló N, *et al*. Functional neuroimaging in startle epilepsy: involvement of a mesial frontoparietal network. *Epilepsia* 2011; 52: 1725-32.

10. García-Morales I, Maestú F, Pérez-Jiménez MA, Elices E, Ortiz T, Alvarez-Linera J, *et al*. A clinical and magnetoencephalography study of MRI-negative startle epilepsy. *Epilepsy Behav* 2009; 16: 166-71.

TEST YOURSELF

(1) Which clinical characteristic is typical of epilepsy in Schuurs–Hoeijmakers syndrome?

A. Most patients respond well to antiepileptic drugs
B. Most patients are intractable
C. Pyridoxine-dependent epilepsy

(2) Startle epilepsy is associated with which of the following clinical backgrounds?

A. Chromosomal abnormalities only
B. Inborn errors of metabolism only
C. Various aetiologies with diffuse brain lesions

(3) What is the trigger of seizures in startle epilepsy?

A. Unexpected auditory or tactile stimuli
B. Photic stimulation
C. Hyperventilation

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