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Case Report

Unilateral periventricular heterotopia and epilepsy in a girl with Ehlers–Danlos syndrome

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ABSTRACT

Purpose: Ehlers–Danlos syndrome (EDS), comprising a variety of inherited connective tissue disorders, has already been described in association with various neurological features, particularly with epilepsy and periventricular heterotopia (PH). Until now, there are reports of only bilateral periventricular heterotopia associated with Ehlers–Danlos syndrome.

Methods and results: Here we describe a 1-year, 4-month-old female who came under our care in the Pediatric Emergency Room because of prolonged afebrile generalized seizures, whose clinical picture allowed us to suspect a diagnosis of Ehlers–Danlos syndrome. Neuroradiological investigations showed unilateral periventricular heterotopias, and genetic analyses confirmed the hypothesized diagnosis, identifying in particular a mutation in the COL5A1 gene. After starting anticonvulsant therapy, her seizures showed a good response with seizure control and she had a favorable long-term course.

Conclusion: To our knowledge, this is the first report of unilateral periventricular heterotopia associated with Ehlers–Danlos syndrome. We first hypothesized a mosaicism as the cause of both, a unilateral localization of the heterotopias and a favorable long-term course with good response to anticonvulsant therapy; however, intriguingly, we could not demonstrate a mosaicism as the genetic condition in our patient and the neuroradiological findings and the favorable clinical outcome still remain unexplained.

1. Introduction

Ehlers–Danlos syndrome (EDS) types I and II are well characterized from a clinical perspective, but there are some difficulties in identifying the molecular basis of the disorder because of its genetic heterogeneity, failure of allele expression, and technical difficulties; however, a revision of the classification of the Ehlers–Danlos syndrome based primarily on the cause of each type was proposed, and major and minor diagnostic criteria have been defined for each type and complemented whenever possible with laboratory findings [1]. Ehlers–Danlos syndrome comprises a variety of inherited connective tissue disorders mainly characterized by joint hypermobility, skin fragility, hyperextensibility, and easy bruisability, in association with various neurological features such as disease of the cerebrovascular system, peripheral neuropathy, plexopathy, chronic pain syndrome, spontaneous intracranial hypotension, polymicrogyria, subependymal periventricular heterotopias (PHs), and epilepsy. Some patients may develop different types of epilepsies, i.e., generalized or partial seizures, with different EEG abnormalities [2–10].

In particular, as it concerns the association with neuronal migration disorders (NMDs), three main groups have been described: PH, subcortical heterotopia, and marginal glioneural heterotopia. Periventricular heterotopia is the more frequent alteration described and includes a group of neuronal migration disorders where newly born neurons fail to migrate from their birthplace along the lining of the lateral ventricles of the brain, thereby giving rise to the characteristic ectopically placed neuronal nodules [8].

Accordingly, to the best of our knowledge, there are no descriptions of unilateral PH associated with EDS having been reported in any previously described cases which all report an "exclusively bilateral" localization [2,4,5,7,8–13]. Here, we present a child diagnosed with EDS affected with unilateral PH and associated seizures with a favorable long-term course, in whom a genetic analysis identified a mutation in the COL5A1 gene.

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2. Case report

A 1-year, 4-month-old female came under our care as she presented two afebrile generalized seizures. She was the second child born to nonconsanguineous parents, a 30-year-old mother and a 32-year-old father. The father showed joint hypermobility. Their first pregnancy resulted in a healthy son. The pregnancy of our patient was complicated with maternal hypertension; delivery was spontaneous at 38 weeks of gestation. At birth, she was hypotonic. On clinical examination, she showed joint hypermobility (predominating in her small joints), hyperextensibility, smooth and dry skin, widened atrophic scars on the anterior surface of the legs, muscle hypotonia, easy bruising, and characteristic facial features (epicanthic folds, dilated scars on the forehead, and excess skin over the eyelids); she also had short stature. The neurological examination was normal. Karyotype was normal (46,XX). Skin biopsy was normal on optic examination, but electron microscopy showed rarefaction of collagen fibrils, which were irregular in size. Blood parameters, chest radiography, ophthalmologic evaluation, and two-dimensional echocardiography were normal; psychological evaluation and psychometric examination (Wechsler scale) showed normal developmental and cognitive skills.

The diagnosis of EDS was made following the current Villefranche classification of EDS [1]; in particular, our patient presented the classic type of EDS with mutations in collagen V (mutations in the COL5A1 gene). Interictal EEG showed a nonspecific disturbance of background activity. Brain MRI showed unilateral PH (see Fig. 1A and B).

After these two seizures, she had two additional generalized tonic–clonic seizures (classifiable as "structural and genetic", according to the "etiological categories" provided by the International League Against Epilepsy criteria) and started valproic acid (VPA) monotherapy (22 mg/kg/day). In the following 4 weeks, she had three other afebrile generalized tonic–clonic seizures; therefore, the VPA dosage was increased (35.9 mg/kg/day), with complete seizure control. Seizure-free condition and EEG normalization were reached within three weeks. After three years of treatment, the therapy was gradually discontinued; after the end of anticonvulsant therapy, she continued to be seizure-free for 4 years.

3. Discussion

Ehlers–Danlos syndrome diagnosis and classification into one of the six major subtypes is based on major (skin hyperextensibility, joint hypermobility, skin fragility, vascular fragility, kyphoscoliosis, and scleral involvement) and minor diagnostic criteria [1]. Loss of the elasticity and strength of collagen in EDS presumably contributes to the structural failure in the connective tissue of the various affected organ systems, including the central nervous system (CNS). In some cases with CNS involvement, the association between neuronal migration disorders (particularly PH) and the occurrence of seizures with variable natural course has been reported, ranging from drug-resistant epilepsy to a favorable natural course with complete and persistent clinical picture remission [2–10]. In most cases, management through anticonvulsant medications is sufficient in controlling epileptic seizures, which was what happened to our described case, but in the case of drug-resistant epilepsy with intractable seizures, surgical resection might be indicated. In these cases, the best predictor of surgical outcome is the capacity to localize, by stereoencephalography, the focal epileptic generator, which may or may not include the heterotopic cortex. Resection of the epileptogenic zones from patients with unilateral rather than bilateral PH could show a better outcome; however, since the anticonvulsant therapy was able to control the seizures in our patient, surgical resection was not taken into consideration.

The association of EDS with PH is difficult to explain. Several subtypes of EDS are the result of an impairment of the synthesis of various extracellular matrix (ECM) proteins, including several subtypes of collagen [9–11]. Experimental studies in vitro [1,9–11] suggested that

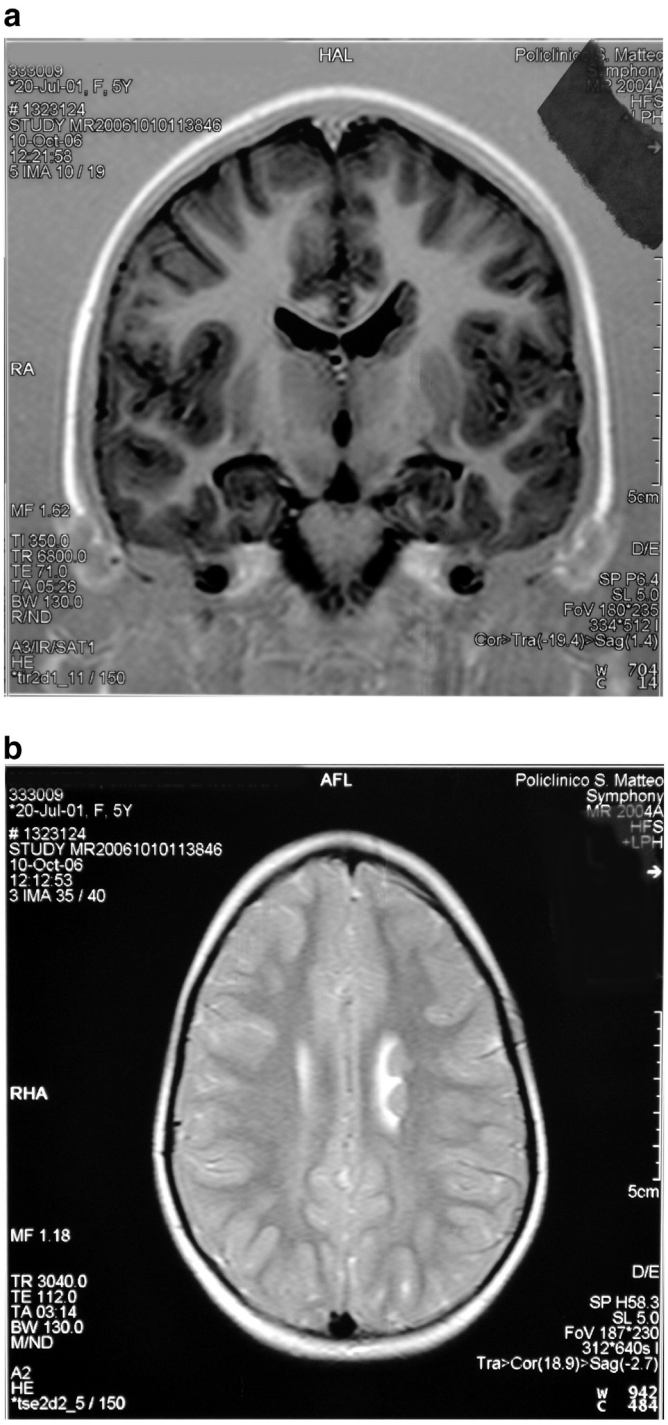

Fig. 1. a—Frontal view: subependymal nodules in the left lateral ventricle, with altered ventricular profile. b—Axial view: mild white matter hyperintensities in the parietal-occipital areas.

regional specification of cerebral cortical neurons during neurogenesis was regulated in part by interactions between epidermal growth factors and ECM proteins, such as collagen type IV. Experimental data have also shown that some subtypes of collagen, including collagen type I and type IV, are implicated in the migration of neurons derived from the neural crest. Accordingly, it has been suggested that EDS diagnosis associated with a disorder in cortical migration and/or organization (PH, for example) might be due to involvement of an ECM protein, resulting in both disorders, EDS and NMD. In fact, it has been reported that the normal migration of primitive neurons away from the periventricular germinative layer zone is prevented by abnormal

collagen, resulting in heterotopic clumps [14]. The collagen acts as a strut over which cells migrate and tissues are organized: a defect in collagen or in another ECM protein, as in the case of patients with EDS, may result in an impairment of the cortical organization [15].

On the other hand, PH not associated with EDS can also be caused by genetic mutations inherited by X-linked dominant (mutations in the filamin A (FLNA)) [15,16] or autosomal recessive (mutations in the ARFGEF2 gene) transmission [15,16]. Neurological symptoms (primarily seizures and dyslexia) are the most common presenting features associated with PH because of FLNA mutations. The classic PH X-linked form, secondary to FLNA mutations, is seen almost exclusively in women and is characterized by bilateral symmetric heterotopic nodules, and the frontal horns are relatively spared and megacisterna magna is common, often in conjunction with cerebellar hypoplasia. In addition, it is crucial to stress that the clinical spectrum of FLNA mutations is wide, however, and missense mutations or mosaicism may result in unilateral forms (also sparing the temporal horn) or nonlethal expression in males [14–16]. Taking into account these latest reflections, we supposed that the "unilateral" PH localization as well as the mild phenotype in our patient could have been the result of a genetic mosaicism, but the genetic investigations did not demonstrate this hypothesis.

Alternatively, the peculiar finding of the unilateral MR localization of the heterotopia not correlating with focal EEG anomalies might suggest that only the macroscopic findings were really unilateral, whereas the epileptogenic substrate could be diffuse with a contralateral hemisphere associated sub-microscopically and not recognized by neuroimaging.

In summary, this is the first case of EDS neuroradiologically characterized by unilateral PH. A favorable natural course, both from a clinical and an outcome point of view (mild phenotype and seizures easily controlled by valproic acid monotherapy) was observed. Most cases of patients with PH from the literature present with epilepsy with a variable natural course and severity which may range from mild (with remission without anticonvulsant therapy) to intractable drug-resistant epilepsy. It is probable that our patient showed favorable seizure control because unilateral PH is less epileptogenic than the bilateral form. However, we were not able to explain in a convincing manner why our patient who presented with the classic type of EDS (mutations in collagen V in the COL5A1 gene) just has an apparently unilateral PH localization. In this respect, we first hypothesized a mosaicism as causing a unilateral localization, but we could not demonstrate this supposed genetic condition in our patient.

Conflict of interest

The authors have no financial relationships to disclose with regard to this article.

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