IS THERE AN ENCEPHALOGRAPHIC TRAIT TO SEPTO-OPTIC DYSPLASIA? (DE MORSIER SYNDROME)

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ABSTRACT

Objectives. Septo-optic dysplasia (SOD), also known as de Morsier syndrome is a rare con-genital syndrome involving variable midline brain structures, characterized by visual impairment, pituitary deficiencies and specific brain abnormalities (especially midbrain malformations). The clinical phenotype is highly variable, from mild to extremely severe. The purpose of this paper is to present the electroencephalographic abnormalities in two clinical cases and correlate with the ones that have been described in the literature in order to find a specific trait of this syndrome.

Methods and results. A 12-year-old girl was hospitalized in the pediatric neurology clinic for focal seizures, developmental delay and cerebral palsy. Clinical examination showed visual dis-turbances (nystagmus and oculomotor nerve palsy), unilateral pyramidal syndrome – left hemipare-sis. Electroencephalography (EEG) revealedbilateral photosensitive epileptic form discharges, but asymmetrical, right more than left, with abnormal, slower background. MRI showed optic nerve hypoplasia and hypoplasia of the corpus callosum. The second case was also a girl, a 7-year-old who had only 2 focal right motor seizures with secondary generalization and developmental delay. Clinical examination showed visual impairment and bilateral nystagmus. The standard EEG evalua-tion didn't reveal any abnormalities, with normal background. Cerebral MRI showedmidline brain defects – agenesis of the septum pellucidum, agenesis of corpus callosum and optic nerve hypopla-sia. Endocrine evaluation for pituitary function showed in the first case – increased thyroid-stimulating hormone and in the second case – decreased IGF1. Antiepileptic treatment was started in both cases, but seizures were refractory to treatment and persistent EEG abnormalitiesstill present in the first case, with good evolution of epilepsy in the second case.

Conclusions. The epileptiform abnormalities associated to SOD are present only if there is an associated cortical malformation.

Keywords: electroencephalography, septo-optic dysplasia, optic nerve hypoplasia, hypopituitarism

INTRODUCTION

Septo-optico dysplasia (SOD), de Morsier syndromeis a rare congenital anomaly, being defined by the association of three or more features of the classical triad: optic nerve hypoplasia, pituitary hormone abnormalities and midline brain defects including agenesis of corpus callosum, absence of the septum pellucid (1). This condition, initial described by Reeves in 1941, then was described by de Morsier in 1956 has an incidence of 1 in 10000 live births, equally affecting boys and girls (2, 3). Only 30% of the patients have the complete triad (4). The phenotype is highly variable and the clinical presentation may be mild to extremely severe.

Most SOD cases are sporadic and several etiologies have been postulated: viral infection, gestational diabetes, environmental teratogens, vascular or degenerative injury, low maternal age and genetic mutations (5, 6, 7). SOD is associated with homozygozity for an inactivating mutation in the homebox gene HESX 1/Hesx1 in man and mouse and with mutation in gene SOX2/Sox2 who plays a critical role in the pituitary, forebrain and eye during human embryonic development (8, 9).

Optic nerve hypoplasia is generally the first manifestation of the SOD. It is important to perform ophthalmological examination to identify the clinical signs of optic nerve hypoplasia: nystagmus

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or strabismus, and if it's unilateral or bilateral, degree of visual impairment and congenital oculomotor nerve palsy uni or bilateral (10).

Hypothalamic – pituitary endocrine deficiencies

Pituitary hypoplasia related to abnormalities of the hypothalamic – pituitary axis, predominant of growth hormone (GH) deficiency resulting in growth failure (11). GH deficiency is followed by another loss of the anterior pituitary function such as: insufficiency of gonadotrophin secretion wich occurs before thyrotrophin releasing hormone (TRH)/tyrotrophin (TSH) or corticotrophin-releasing hormone (CRH)/adrenocorticotrophin (ACTH) insufficiency (12, 13). Diabetes insipidus canalso occur by loss of the posterior pituitary function.

The necessary tests for pituitary evaluation are: thyroid function (level of TSH, free T4), cortisol – level measured at 8 am and if the level is abnormal, proceed with ACTH test or 24 hour cortisol and glucose profile, growth hormone – monitor growth (with CDC growth charts and calculate bone age relative to chronological age) and measure IGF 1, monitor pubertal status – attention to precocious puberty secondary to hypothalamic dysfunction or hypogonadotrophichypogonadism secondary to LH and FSH deficiency. Also is useful to asses'fluid intake and diuresisfor the diagnosis of diabetes insipidus.

Cerebral abnormalities

As mentioned, this genetic syndrome associates different cerebral structural abnormalities, especially on the midline. Imagistic evaluation through cerebral MRI in SOD could reveal agenesis of corpus callosum, absence of the septum pellucid, optic nerve hypoplasia uni or bilateral, hypoplasia of the optic chiasm, abnormal position or size of anterior or posterior pituitary gland, cerebellar hypoplasia, aplasia of the fornix or schizencephaly (14, 15).

Neurological disorders are observed in most patients with SOD and include: developmental delay, mild or moderate mental retardation, focal signs like hemiparesis and epilepsy (16).

As a genetic disease, this syndrome as described has multiple organ abnormalities and this is why for the positive diagnostic besides multidisciplinary clinical evaluation of neurologist, ophthalmologist, endocrinologist and radiologist, there is some specific lab tests evaluation as hormonal functions, cerebral MRI and not the last, but one of the used tests, electroencephalography (EEG). EEG is a common, low-cost test, easy to perform in all ages, which evaluates cerebral function, showing the background of the abnormal brain and also the epileptiform traits.

MATERIALS AND METHODS

In the department of pediatric neurology in a period of 10 years, it has been described only 2 cases with SOD. The both are girls, who had a complex evaluation to confirm the diagnosis of SOD: pediatric neurologists with electroencephalography competence performed the neurological examination and the electroencephalography (EEG), specialized radiologists achieved the brain imaging, pediatric endocrinologist monitored height, weight and pubertal status and did the tests for endocrine function, and pediatric ophthalmologist performed a complete ophthalmological examination.

CASE 1

Liliana is a 12 years – old girl, born at term, weight at birth 1,300 g, unknown Apgar score, the third child of her mother. We do not have any data about family history, age of mother, evolution and type of pregnancy because Liliana is abandoned from her mother and she is in social care services from age of 2. She had a delay in psychomotor development (independent walking at 3 years old) and delay in the language area(the acquisitions were very slow – speech achieved at 4 years old).

The neurological clinical examination showed obesity, visual disturbances (visual impairment, nystagmus and left common oculomotor nerve palsy with ptosis and divergentstrabismus) and unilateral pyramidal syndrome – left hemiparesis disabling, mild mental retardation (Fig. 1).

FIGURE 1. *Left hemiparesis + left common oculomotor palsy*

At the age of 8, she had the first focal epileptic seizure as focal motor type with secondary generalization, for 5 minutes. From then, she has had frequent seizures, all the same and only partially responsive to antiepileptic drugs as valproic acid, levetiracetam, topiramate, lamotrigine, and benzodiazepines.

Her EEG shows abnormal slower background with frequent bilateral epileptiform discharges as spike-wave complexes with photosensitivity, right > left derivations (Fig. 2).

Cerebral MRI shows right large cortical dysplasia with larger and thicker cortex of the right hemisphere that explains left hemiparesis, left focal seizures and mild mental retardation. Besides this abnormalities, it has been described agenesis of septum pellucidum and bilateral optic nerves hypoplasia (Fig. 3).

The other investigations shows left kidney agenesis and increased level of TSH.

The association between midline cerebral abnormalities, hypoplasia of optic nerve and affected

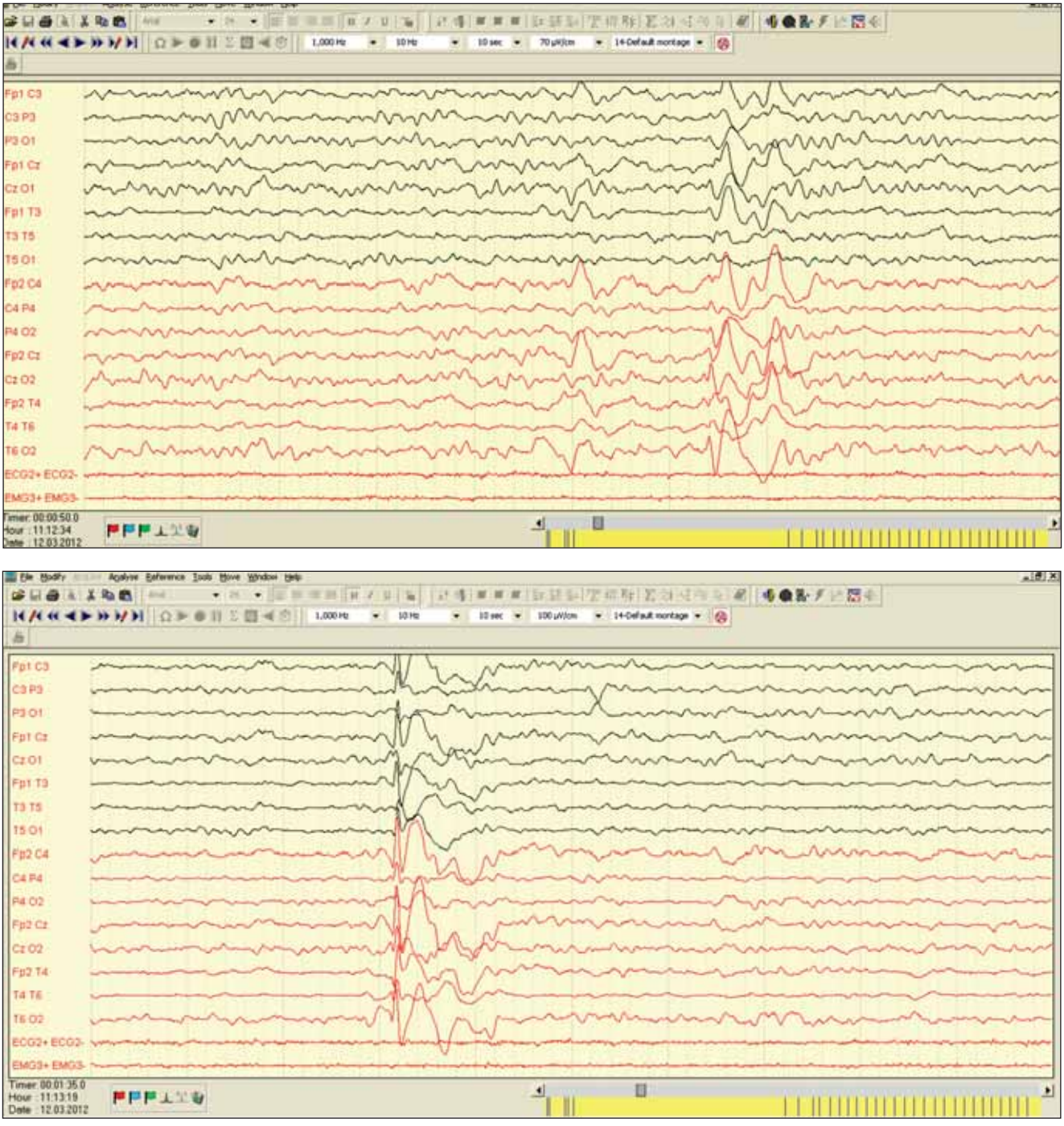

FIGURE 2. *Abnormal, slower background, bilateral epileptiform discharges as spike-wave complexes right > left with photosensitivity*

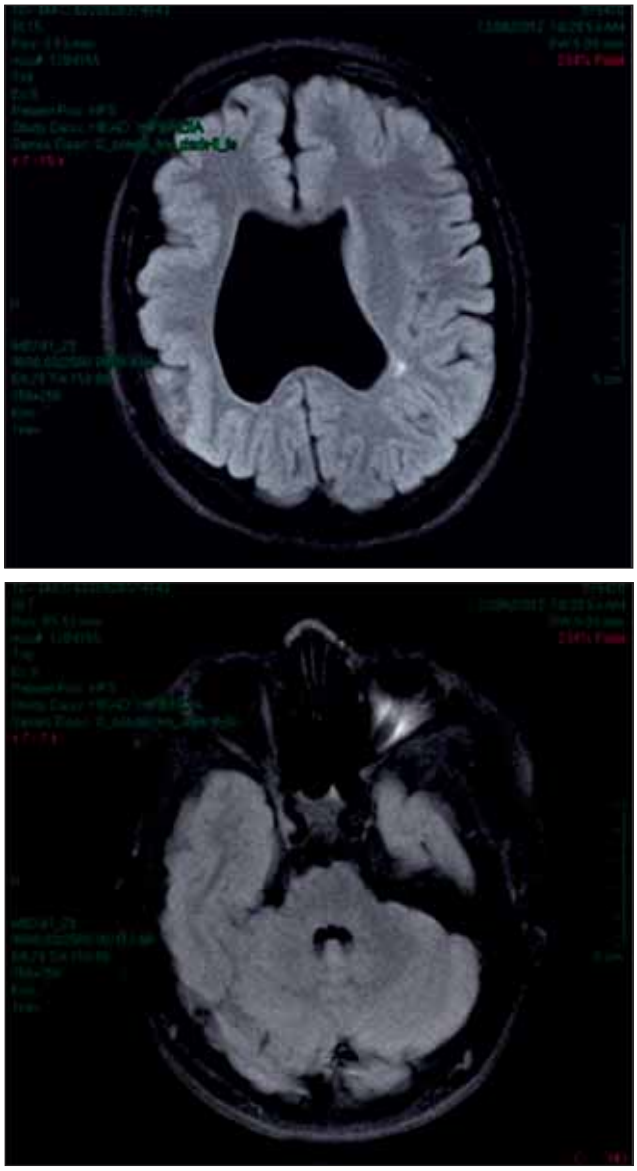

FIGURE 3. *Right cortical dysplasia, agenesis of septum pellucidum, optic nerves hypoplasia*

function of pituitary gland is typical for the diagnosis of septo-optic dysplasia.

CASE 2

Andreea is a 7 years old girl, with normal intellect who came in the department of pediatric neurology for 2 generalized epileptic seizures. Her personal history showed that she is the first child of a healthy family, normal pregnancy, and normal term birth, birth at weight 3500 g, Apgar score-9, no perinatal problems, but she was born with bilateral artrogriposis of the last 3 toes (Fig. 4).

Clinical evaluation shows bilateral nystagmussecondary to very important visual impairment, optic atrophy, normal intellect no other focal deficits (Fig. 5). Because of the visual impairment she is integrated in a special school for blind persons.

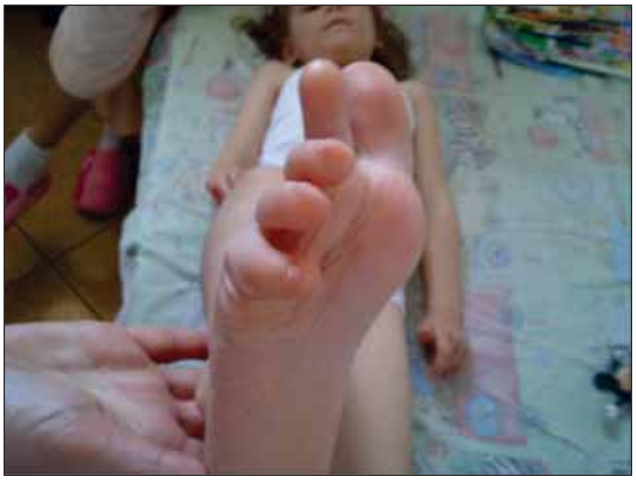

FIGURE 4. *Artrogriposis of the last 3 left toes*

Her personal history related to epilepsy showed one simple febrile convulsion at the age of 1, and two generalized tonic-clonic seizures at the age of 3 and 7. Her standard EEG showed normal background, no epileptiform discharges (Fig. 6). She is

FIGURE 5. *Bilateral visual impairment*

treated with valproic acid with good response, complete control of seizures.

Cerebral MRI showsagenesis of corpus calosum and septum pellucidum besides the abnormalsignal of posterior pituitary gland (Fig. 7).

Endocrineand somatic evaluation shows deficiency of IGF1 which needs substitution with growth hormone.

Association between malformations of cerebral midline with optic atrophy is typical for the diagnosis of SOD. The epilepsy is not a very active trait in this case, with few seizures, easy to control to antiepileptic drug and normal EEG.

DISCUSSIONS

Cerebral abnormalities in SOD are most frequent described as midline defects, plus cortical

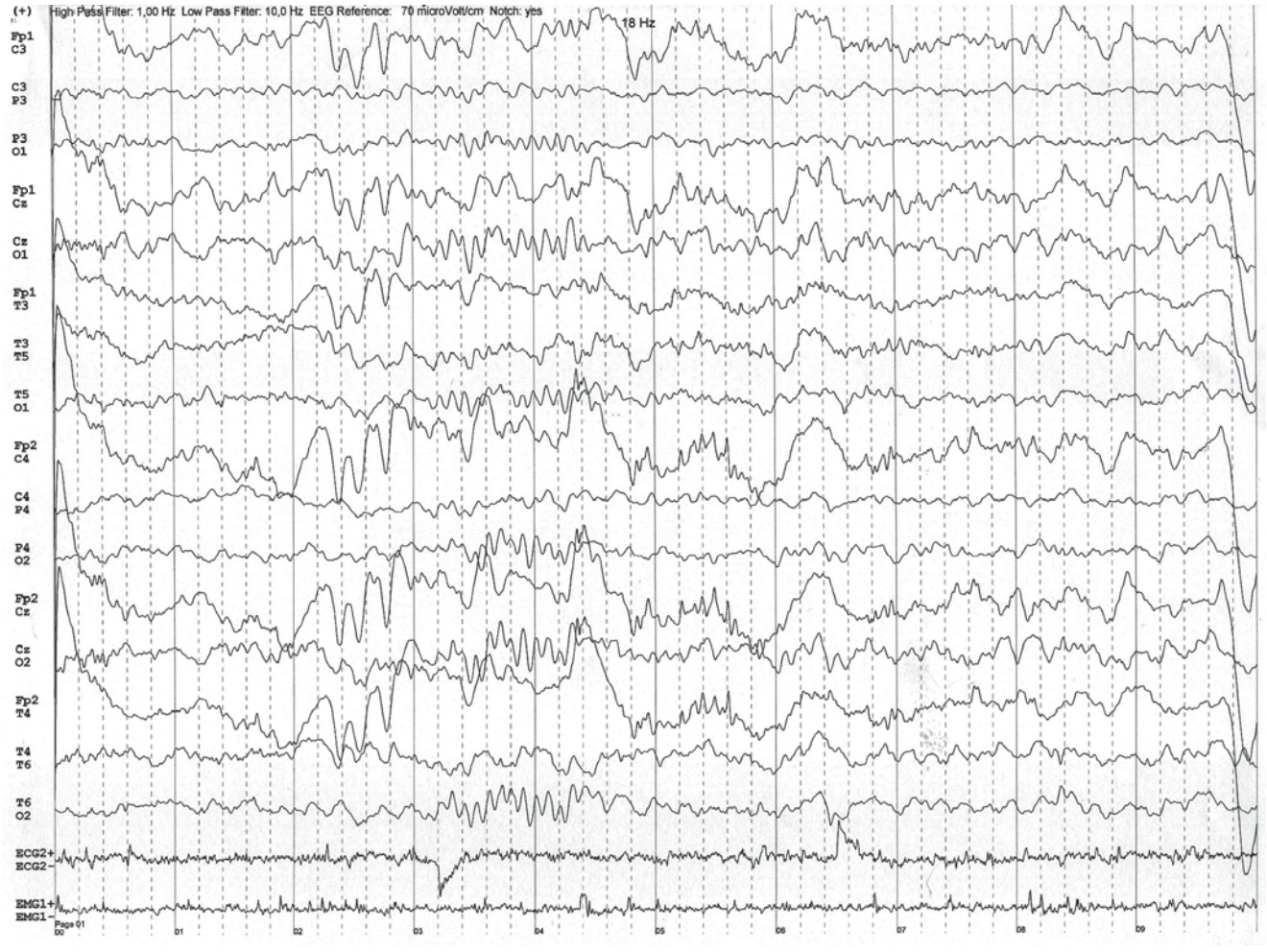

FIGURE 6. *Normal background, no epileptiform discharges*

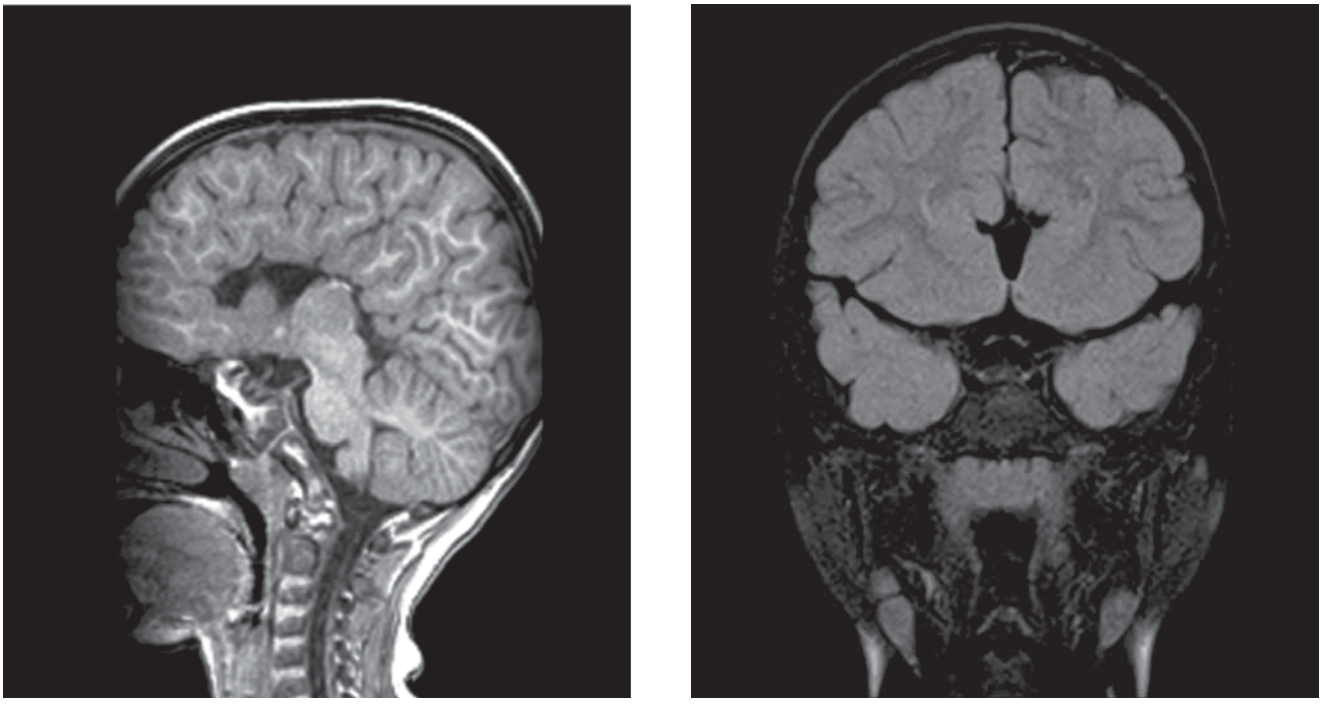

FIGURE 7. *Agenesis of corpus calosum and septum pellucidum, abnormalities of posterior pituitary gland*

malformations and hippocampus malrotation. Imaging anomalies are present in up to 75-80% of the patients with optic nerve hypoplasia, rising up to 90% in those with associated neurological deficits (15).

The presented girls have both optic atrophy associated with typical imagistic anomalies for SOD, but only one has cortical dysplasia, responsible for focal motor deficit, mental retardation and also epileptic seizures, this association being concordant with the relations described in literature (15). The epilepsy is a disease related to cortex and neural transmission, and this is why it's easy to understand the cause of symptoms.

Sener and Miller described association between SOD and cortical dysplasia and named it SOD-Plus. This abnormality can also be distinguished from isolated SOD by the presence of significant global development delay and spastic motor deficits (17, 18).

Seizures and developmental delay can occur due to metabolic and/or neuroanatomical disorders present in patients with SOD, especially in cases with associated hypoglycemia or hypernatremia (19).

EEG represents an active functional evaluation of cerebral activity, the background and epileptiform traits. Background of EEG represents the mark of global cerebral activity. In SOD, it has been described a normal EEGin half of cases (20,21).

The percentage of associated epileptiform cortical malformation to SOD as schizencephaly or cortical dysplasia could explain the number of patients with abnormal EEG traces, the rest of patients with normal EEG but with epileptic seizures, could be explain as abnormal genetic biochemical interneural transmission of excitation.

In the presented cases, only one has abnormal EEG with slower background and bilateral photosensitive epileptiform discharges, right more than left, in SOD-pluscase, the other one has a normal background and no epileptiform discharges.

CONCLUSION

To the question if there is a specific electroencephalographic trait of SOD, we have found that the EEGs anomalies are related to epileptogenic malformations, and not to SOD itself which could associate only epileptic seizure but normal EEG.

This supposition needs to be confirm on large studies with more patients.

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