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Incidental diagnosis of septo-optic dysplasia in an adult: a case report

Marta Leńska-Mieciek[1], Michał Wąsowski[2], Ewa Nagańska[3], Małgorzata Michałowska[1], Urszula Fiszer[1]

[1]Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, Warsaw, Poland
[2]Department of Geriatrics, Internal Medicine and Metabolic Bone Diseases, Centre of Postgraduate Medical Education, Warsaw, Poland
[3]Department of Neurology and Epileptology, Prof. Orlowski's Hospital, Warsaw, Poland

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To the Editors

Septo-optic dysplasia (SOD) is a rare, congenital central nervous system malformation syndrome. It is equally prevalent in males and females, with a reported incidence of 1.9–2.5 per 100,000 live births. Most reported cases are diagnosed in childhood or early adolescence. The diagnosis of SOD is a clinical one that can be made when two or more features of the classical triad of optic nerve hypoplasia, disorders of the hypothalamo-pituitary axis, and agenesis of midline brain structures, are present. There is wide variation in the severity of clinical features. Seizures, developmental delay and cerebral palsy are the most frequent neurological presentations [1, 2]. There is a paucity of data regarding the incidence and clinical features of subtle variants of SOD in adult patients.

We here present the case of a patient who was diagnosed with SOD in the sixth decade of her life. This is, to the best of our knowledge, the first report of an SOD patient with migraine-like headaches as the only neuro-ophthalmological SOD manifestation.

A 56-year-old female was referred to neurological care for severe recurrent headaches of a few weeks' duration. Splitting and diffuse headaches had appeared on the second day of COVID-19 infection. The pain was strong and bilateral and changed its character within a few days. In the emergency department, the patient reported a tension-type, bifrontal headache having lasted for several weeks. There was no evidence of meningitic or encephalitic involvement. The pain met the criteria of the International Headache Society for headaches attributed to systemic viral infection [3, 4]. The patient experienced head traumas at the ages of 17 and 35. She had a history of trigeminal neuralgia, hypercholesterolemia, depression, insulin resistance, obesity and a 40-year history of migraine headaches. The pulsating, severe headache attacks, lasting less than 24 hours, started when she was 17. Symptoms included nausea and vomiting. There were 2–3 attacks per year, but they disappeared in the post-menopausal period. There was also a history of pubertal delay and menstrual irregularity. The patient had been treated using rosuvastatin, metformin, spironolactone, moclobemide, semaglutide, 17-beta-oestradiol and dydrogesterone. There were no abnormalities on the neurological assessment. Funduscopic examination revealed small optic discs suggesting optic nerves hypoplasia. The ophthalmological assessment revealed no other changes. Brain magnetic resonance imaging (MRI) showed abnormalities of the midline structures: agenesis of septum pellucidum, hypogenesis of corpus callosum, falx and optic chiasm (Fig. 1). Electroencephalographic (EEG) activity showed groups of synchronous theta and delta waves, most pronounced over the left occipital, parietal and posterior temporal areas on normal background activity (Fig. 1). Endocrine testing revealed prolactin dysfunction (4.36 ng/mL; normal: 5.18–26.53 ng/mL). *De novo* headache resolved in the patient within one month, and was interpreted as post

Address for correspondence: Marta Leńska-Mieciek, Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, 231 Czerniakowska St., 00–416 Warsaw, Poland; e-mail: mlenska@cmkp.edu.pl

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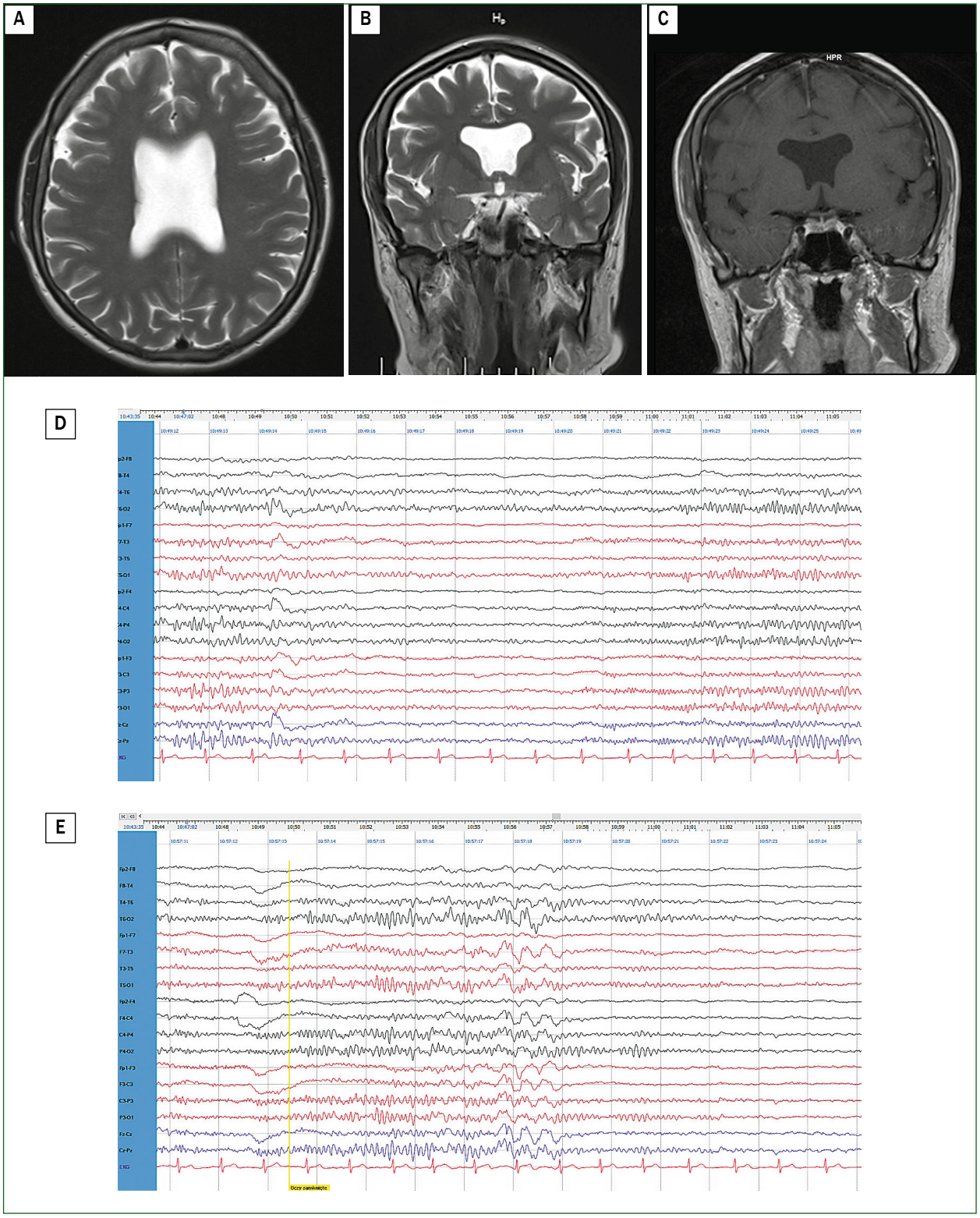

Figure 1. Septo-optic dysplasia. Brain magnetic resonance imaging (MRI); **A.** Axial T2- and **B.** coronal T2-weighted sequences show agenesis of midline structures; **C.** Coronal T1-weighted sequence shows optic chiasm hypoplasia. **D**, **E.** Electroencephalographic (EEG) activity: groups of synchronous theta and delta waves most pronounced over left occipital, parietal and posterior temporal areas on normal background activity

Coronavirus disease-19 headache. The diagnosis of SOD was established.

Less than 50% of SOD patients present all three of the classical triad of features [1, 2]. In the presented patient, two of the triad were present: midline abnormalities of the brain (hypogenesis of septum pellucidum and corpus callosum), and optic nerves hypoplasia.

The precise causes of SOD remain unknown. The phenotypic penetration is highly variable. A combination of genetic predisposition and prenatal exposure to environmental factors are believed to play major roles in its occurrence. The specific genes most frequently involved in the development of SOD are: HESX1, SOX2, SOX3 and OTX2. Very rare familial cases have been described, mostly with autosomal recessive inheritance. Genetic abnormalities have been identified in less than 1% of patients. Whole-exome sequencing (WES) of our patient revealed no pathogenic variants in the 150 genes, according to the Human Phenotype Ontology, associated with septo-optic dysplasia (HP:0100842), absent septum pellucidum (HP:0001331), and optic nerve hypoplasia (HP:0000609).

Some environmental factors (drugs, hormones, alcohol abuse, young maternal age) may play a significant role in the aetiology of SOD. According to the presented patient, there had been no drugs, hormones or alcohol abuse in her mother's history. The mother was aged 39 on the day of the patient's delivery.

Ophthalmological symptoms are the earliest that can be identified in SOD patients. Visual impairment accounts only for 23% of overall reported symptoms [1, 2]. The presented patient had no visual disturbances.

Hypopituitarism is the most commonly reported feature of SOD. Although there was a history of pubertal delay and menstrual irregularity in our patient, she was not diagnosed because of those features. There is no data regarding obesity in SOD adult patients. Its prevalence in SOD children appears to be up to 44% [1, 2]. The presented patient had a history of obesity since adolescence.

Headache affects almost half of patients in the acute phase of COVID-19. As in the presented patient, it begins early in the symptomatic phase and is bilateral of a moderate to strong intensity. The frequent phenotypes are migraine or tension-type headache patterns [3, 4]. The presented patient reported that the headache during the COVID-19 infection had a different pattern to that of previous ones. To the best of our knowledge, the presented patient is the first reported patient diagnosed with SOD in adulthood with migraine-like headaches as the only neuro-ophthalmological presentation.

The clinical features of SOD are very heterogeneous. Most data relates to patients diagnosed in their childhood or early adolescence. Only a few reports are dedicated to adults, and we found only one that presented the incidental diagnosis of a subtle variant of SOD in an adult. This was a patient with a history of migraine headaches and congenital left monocular blindness who was diagnosed with SOD in the fourth decade of his life. A review of this patient's medical record showed no note of endocrine abnormality, developmental delay, or neurological impairment other than left monocular blindness [5].

In our case, there was a history of endocrine abnormalities (pubertal delay, menstrual irregularity) and obesity. The patient was diagnosed with insulin resistance and optic nerve hypoplasia. There was no history of ophthalmological problems or developmental delay. The patient we here present has expanded our understanding of the phenotype of subtle variants of SOD which are diagnosed in adults.

Conflicts of interest: *None.*

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