CASE REPORT

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Epilepsy in a girl with features of CHARGE syndrome – case report and literature review

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Abstract

Introduction. CHARGE syndrome represents a rare, genetically determined association of birth defects.* The diagnosis of the syndrome is based on the finding of typical clinical symptoms and the detection of mutations in the CHD7 gene.
Case Report. The case of a 13-year-old girl with features of CHARGE syndrome is presented. After birth, the girl was found to have defects that suggested CHARGE syndrome. However, the mutation was not confirmed in the genetic test performed. Despite the presence of all the large CHARGE syndrome criteria in the patient, due to the absence of a genetic mutation, it was not possible to make a complete diagnosis. In addition, the girl had congenital epilepsy, which can occur in CHARGE syndrome but is not characteristic. The onset of epilepsy may also have been independent.
Conclusion. With the discovery of missense *de novo* variants in WDR37, for which epilepsy and other CHARGE-like symptoms are present, perhaps the final diagnosis of the syndrome in the patient described could have been different.

Key words

congenital heart defects, cochlear implants, epilepsy, fetal MRI, CHARGE syndrome, behavioural difficulties

* Explanation of the meaning of CHARGE (syndrome)
Colomba (an eye condition)
Heart defects
Adresia choanae (nasal passsage blocked by bone or tissue)
Retardation (delay) of groewth and/or development
Genital deformities
Ear abnormalities

INTRODUCTION

CHARGE syndrome (CS) is a rare genetic disorder caused by heterozygous mutations in the CHD7 gene with an incidence of about 1 in 10,000 births. There is no gender-coupled expression, therefore both males and females are equally affected [1]. Most cases result from *de novo* mutations in the q12 arm of chromosome 8, which interfere with neural crest cell migration and embryogenesis. The parent of a child with a *de novo* mutation causing CS has a recurrence risk of about 1% – 3% for future pregnancies [2]. The diagnosis of CS is currently possible using the criteria proposed by Blake et al., later modified by Verloes, which increased the importance of the 3C triad (coloboma, posterior nostril atresia, abnormal semicircular canals) (Fig. 1). Other criteria include cranial nerve abnormalities, facial dysmorphia, cardiovascular malformations, tracheoesophageal fistula, and delayed psychomotor and intellectual development [3,4]. CHARGE syndrome is caused by a mutation in the CHD7 gene, the product of which belongs to the DNA helicase-binding protein family. Despite genetic testing in some cases, the mutation in the CHD7 gene cannot be found, a situation that occurs in 5–35% of patients presenting with clinical symptoms [1]. Nevertheless, the absence of a mutation in the CHD7 gene does not preclude a diagnosis, as the diagnosis is ultimately based on the patient's clinical presentation.

Epilepsy is a disease which affects neurons and disturbs inhibitory and excitatory neurotransmission between brain cells. This imbalance causes occuring seizures, which may vary from subtle, absence, to tonic-clonic epilepsy [5]. Epilepsy can occur spontaneously, as an individual disease, or be a part of genetic syndrome. In children younger than 3-years-old, more than a half of diagnosed cases could have genetic etiology, which is found through specialized tests. The percentage of this coincidence increases the younger the infants are diagnosed [6]. Pharmacotherapy is the first choice of treatment in mild epilepsy and should be chosen based on specific syndromes, age, prognosis, and personal factors of thepatient [7]. There are many possible options to consider, but among many efficient drugs the ones which are most commonly used are valproic acid, carbamazepine, lamotrigine and ethosuximide [7,8].

CASE REPORT

The following is a case of a 13-year-old girl with features of CHARGE syndrome. The girl was born from pregnancy one and delivery one by caesarean section, with a normal

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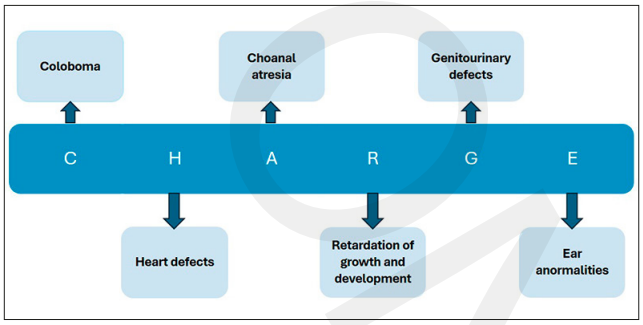

Figure 1. Symptoms of CHARGE syndrome

birth weight (3160 g) and normal body length and head circumference. She received 9 points on the Apgar scale. The first abnormalities were observed in the prenatal period in the form of multiformality. At birth, the girl was diagnosed with defects such as bilateral coloboma, undeveloped right optic nerve, atrial septal aneurysm, posterior nostril atresia, horseshoe kidney, malformed, low-set auricles and hearing loss, which suggested CHARGE syndrome (Fig. 2). However, a mutation in the CHD7 gene was not confirmed in the genetic test performed.

Due to the hearing loss, the patient was implanted with cochlear implants at the age of 2 years – right ear, and at the age of 4 years – left ear (Fig. 3). In addition, the girl had severe visual impairment (-7/-8 diopters without astigmatism) corrected with glasses, a problem with eye movement and defects in her top and bottom vision. To date, she has not had surgery for an atrial septal aneurysm.

After birth, epilepsy was diagnosed based of abnormalities in the EEG recording and clinical symptoms. At the age of 4 years, treatment with sodium valproate was initiated and continued for one year. Due to the observed slowing down of the child's development, it was decided to withdraw the treatment over the next 2 years. Currently, the girl is not receiving pharmacological treatment for epilepsy. Every few months, there are isolated light epileptic episodes of a few minutes' duration with bruising of the skin, stasis and temporary disorders of consciousness without loss of consciousness.

At the age of 3 years, the girl's weight and height were below the third centile concerning the centile grid, and had microcephaly. The patient was observed to have recurrent hypoglycaemia which normalised after the supply of 10% glucose *in venous*. Decreased levels of adrenocorticotropic hormone (ACTH), prolactin and a fairly low level of thyroid-stimulating hormone (TSH) with significantly decreased

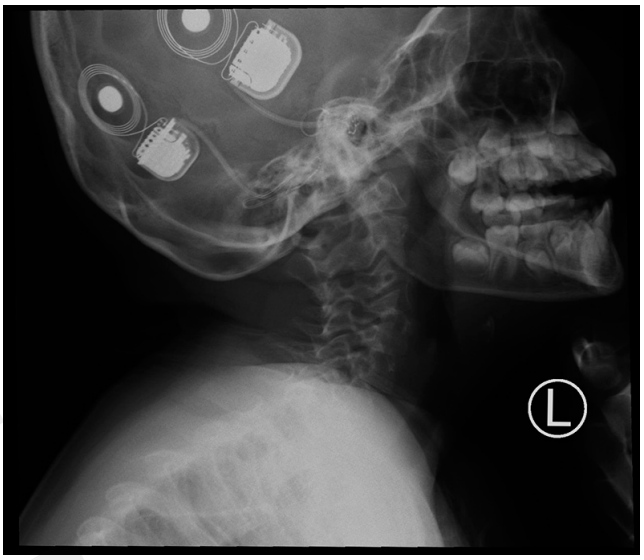

Figure 3. X-ray of the cervical spine- visible cochlear implants

levels of free triiodothyronine (FT3) and free thyroxine (FT4) were indicative of multihormonal hypopituitarism (Tab. 1). As a result, treatment with hydrocortisone and levothyroxine was included.

Table 1. Results of selected laboratory tests from hospitalization at 3 years of age

Laboratory investigation from serum or blood EDTA	Result	Reference range
FT3	1.90 pg/ml	1.95-5.92 pg/ml
FT4	0.87 ng/dl	0.94-1.71 ng/dl
Glucose (measure 1)	58.00 mg/dl	74.00-110 mg/dl
Glucose (measure 2)	40.00 mg/dl	
Glucose (measure 3)	68.82 mg/dl	
Glucose (measure 4)	82.00 mg/dl	
ACTH (measure 1)	6.58 pg/ml	7.20–63.60 pg/ml
ACTH (measure 2)	8.69 pg/ml	
IGF 1	11.5 ng/ml	51–234 ng/ml
Cortisol (a.m.)	21.10 µg/dl	4.30–22.40 µg/dl
Cortisol (p.m.)	6.60 µg/dl	3.09–16.66 µg/dl
Prolactin (measure 1)	1.01 ng/ml	3.60–12.00 ng/ml
Prolactin (measure 2)	3.37 ng/ml	
TSH	1.458 mU/L	0.85–6.5 mU/L

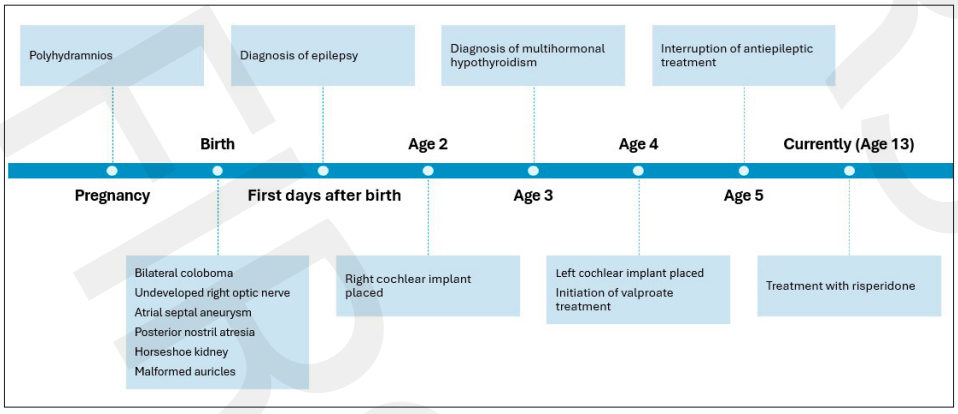

Figure 2. The course of the patient's illness

She is currently taking risperidone due to autoimmune behaviour and remains under the constant care of a cardiologist, neurologist and ophthalmologist.

DISCUSSION

CHARGE syndrome is a very complex syndrome with a broad phenotype and can involve almost all organs and sensory systems. People with CHARGE syndrome have a high risk of co-morbidities and their incidence is extremely variable. Due to the multiplicity of symptoms, clinical problems may also remain undiagnosed [9].

Prenatal ultrasound scans represent the initial diagnostic tool with the potential to indicate the presence of anomalies suggestive of CHARGE syndrome. The most frequently observed findings, which also partially occurred in the described patient, are as follows polyhydramnios, cardiac defects, such as tetralogy of Fallot, double-outlet left ventricle or atrial septal aneurysm, external ear abnormalities, cleft lip and central nervous system anomalies, such as ventriculomegaly, abnormal olfactory sulci and abnormal choroid plexus [10]. In addition, foetal MRI may also be helpful in the prenatal diagnosis of CHARGE syndrome. Early signals on foetal MRI that may indicate CHARGE syndrome include: arhinencephaly, dysplasia or agenesis of semicircular canals and posterior fossa anomalies, short petrous bones, ventriculomegaly, short corpus callosum and ocular asymmetry [11].

The patient was also observed to have a coloboma, which is present in 75 – 81% of patients with CHARGE syndrome; conversely, approximately 15 – 30% of patients diagnosed with microphthalmia/coloboma present CHARGE syndrome [8]. Treating coloboma involves *pars plana* vitrectomy with silicon oil tamponade and endolaser along the margin of the coloboma. It is noteworthy that coloboma is frequently linked to the occurrence of cataracts, and that cataract surgery is associated with an elevated risk of complications [12].

The spectrum of congenital heart defects is highly variable and includes conotruncal defects (31 – 42% of patients), atrioventricular septal defects (13 – 17 %), such as aneurysms (observed in the presented patient), patent ductus arteriosus and aortic arch abnormalities. However, researchers suggest an increase in congenital heart disease in CHD7-positive patients (66–92%) compared to CHD7-negative patients (71%) [13].

In CHARGE syndrome, ear defects and hearing loss are common and often require the insertion of cochlear implants early in life, which occurred in the patient described. A study by Szleper et al. using CT scans showed that a vestigial lateral semicircular canal (SCC) or complete absence of lateral SCC was commonly observed in all patients diagnosed with CHARGE syndrome. The posterior SCC was found to be absent in 95% and the superior SCC in 65%. In addition, cochlear hypoplasia type III was identified as the most common malformation present in 12 ears (60%). Cochlear hypoplasia type II, aplasia with dilated vestibule and vestigial otocyst have also been identified [14]. Prior to cochlear implantation, the type of cochlear anomaly and the anatomical structures of the temporal bone need to be assessed, due to possible vascular anomalies, facial nerve abnormalities or underdevelopment of the bony parts [15]. In addition, it is important to note that if a head imaging study is required in the presence of cochlear implants, MRI cannot be performed. In the case of the described patient, due to the bilateral presence of cochlear implants, an MRI scan was not performed because of the inability to obtain diagnostically reliable images and was replaced by a CT scan.

The patient otherwise has endocrine disorders in the form of hypothyroidism which is not a fixed feature, but may be part of the phenotypic spectrum of CHARGE syndrome including an atypical feature of mutations in the CHD7 gene [16].

In addition, the girl had hypoglycaemia, which is associated with a high incidence of hypoglycaemia in paediatric patients with genetic syndromes, but to-date hypoglycaemia, including neonatal hypoglycaemia, is a feature poorly studied in the literature related to CHARGE syndrome [17]. In addition to this, the girl's ACTH levels were reduced and central adrenal insufficiency was noted, while not a common feature of CHARGE syndrome, routine adrenal function testing in children with CHARGE syndrome is not indicated [18].

The symptoms of epilepsy observed in the patient, including bruising of the skin, freezing in immobility and disturbance of consciousness, suggest the absence of seizures with autonomic components [19]. Notably, epilepsy itself is not a characteristic feature of the CHARGE association but it can also occur. CHARGE syndrome is caused by a mutation in the CHD7 gene, the product of which belongs to the DNA helicase-binding protein family. Despite genetic testing, the mutation in the CHD7 gene was not confirmed in the presented patient, a situation that occurs in 5 – 10% of patients presenting with clinical symptoms [20].

Valproic acid was used to treat the patient's epilepsy and the choice of this drug was based on its properties. However, there is still a lack of randomised controlled clinical trials and prospective studies in the paediatric population with significant benefits in the choice of antiepileptic drug therapy [21]. Valproic acid is a first-generation antiepileptic drug (1960) that exhibits a pleiotropic mechanism of action, enhancing the synthesis and inhibiting the breakdown of GABA, as well as blocking NMDA receptors. Furthermore, it blocks sodium and T-type calcium channels and activates potassium channels, causing neuronal hyperpolarisation [22]. It is a first-line drug used in the treatment of generalized tonic-clonic seizures, myoclonic seizures, absence seizures and unclassified seizures [22]. However, Valproate acid is contraindicated in pregnant women due to the high risk of serious developmental disorders and congenital malformations, such as foetal valproate syndrome, which manifests primarily as neural tube defects, malformations and facial dysmorphic features [23].

A double-blinded study was conducted to compare the side-effects of Vlproate, Etosuximide and Lmotrigine in children with absence seizure. After both 16 weeks and 12 months, a significantly higher rate of attentional dysfunction was observed in patients treated with Vlproate compared with patients treated with ethosuximide or Lmotrigine (49% vs 33% vs 24%, respectively) [24].

Although there is a correlation between the use of valproate in children and the onset of psychiatric and behavioural disorders,such as confusion, aggression, agitation, and attention deficit disorder, it is a drug with a lower rate of psychobehavioural adverse effects (PBAE) compared to the

average of 18 other antiepileptic drugs [25]. Therefore, its use was fully justified for the presented patient. However, due to the observed slowing-down of the patient's development, a slow withdrawal was equally justified.

Furthermore, CHARGE syndrome is associated with many behavioural difficulties, such as autism, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, anxiety and sensory deficits [26]. The presented patient described developed self-destructive behaviours in adolescence, as a result of which treatment with Risperidone, which is increasingly used for behavioural indications in children, was included [27].

CONCLUSIONS

Patients with the CHARGE syndrome phenotype face multiple organ dysfunction including the presence of various comorbidities, such as epilepsy or hypothyroidism. In order to improve their development, patients require continuous therapeutic interventions and multi-specialised care.

Despite the presence of all the large CHARGE syndrome criteria in the presented patient, due to the absence of mutations in the CHD7 gene it was not possible to make a complete diagnosis of the syndrome. In addition, the patient had congenital epilepsy, which can occur in CHARGE syndrome but is not characteristic. Also, the onset of epilepsy may have been independent.

The presented case has been described as 'a girl with features of CHARGE syndrome', which is based on the diagnosis that doctors made throughout the patient's life. However, it is noteworthy that although many patients have some features of genetic syndromes, such as CHARGE syndrome, Peters-plus syndrome, Temtama syndrome and Walker-Warburg syndrome, they can also have features that do not overlap with these known syndromes and their causes remain unexplained [28, 29].

A recently described cause of multi-system syndromic disorder characterised by ocular coloboma with associated other developmental anomalies is *de novo* missense (DNM) variants in WD repeat-containing protein 37 (WDR37) [30]. All individuals with *de novo* missense variants in WDR37 have a clinical phenotype consisting of a bilateral iris and retinal coloboma, developmental delay, as well as additional variable multi-system features [30]. Individuals with *de novo* missense variants in WDR37 may present with epilepsy, hearing defects, congenital heart defects, genital anomalies, dysmorphic facial features, reduced body weight, growth deficits or cerebellar hypoplasia, among others [28, 29, 30, 31].

The pathological symptoms of the described patient were part of the clinical phenotype of people with *de novo* missense variants in WDR37, including epilepsy. In contrast, no information was found in the literature on the association of *de novo* missense variants in WDR37 with multihormonal hypopituitarism, but it was suspect that, due to structural abnormalities in the brain, hypopituitarism could also occur in a patient with this syndrome. For this reason, it was concluded that perhaps with developments in the field of medicine, the patient described in this case report could be diagnosed differently, which is an interesting aspect of the case presented.

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