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RESEARCH ARTICLE

NON-CARDIAC DIGEORGE SYNDROME IN AN ADOLESCENT GIRL WITH EPILEPSY (A CASE REPORT)

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Abstract

22q11.2 deletion syndrome is a fairly common neurogenetic syndrome, presenting with a wide range of clinical. It can manifest as facial dysmorphia, congenital heart defects, thymic hypoplasia responsible for a predominantly cellular immune deficiency, parathyroid and thyroid abnormalities, speech delay, growth retardation and neuropsychological disorders. We report the case of a patient with this deletion presenting with severe hypocalcaemic crises complicated by neurological impairment without cardiac or immune involvement.

Introduction:-

Digeorge syndrome or 22q11.2 deletion (DS 22q11.2) is a genetic disease caused by alterations at the germinal stage of the structures arising from the third and fourth pharyngeal pouches[1].

It is a relatively common genetic disease, with an estimated incidence of between1/3000[1,2]to 1/4000 live births[1,3].

Several clinical signs have been described in relation to this syndrome, dominated by congenital heart disease, atypical facial dysmorphia, intellectual retardation, immune deficiencies and palatal malformations[4,5].

Delays in diagnosis have been observed in patients with a DS 22q11.2 without cardiac involvement. This has led to inappropriate management and adverse outcomes[5,6,7,8,9].

Despite the widespread availability of molecular tests, a delay in diagnosis has been reported, especially in cases where congenital phenotypic characteristics are absent[4,8].

We report a case of DS 22q11.2 withsevere hypocalcaemia associated with poorly controlled seizures and convulsive states mistaken for idiopathic epilepsy. The patient had no cardiac malformations, cleft palate or thymic aplasia. Hypocalcaemia is known to be associated with this syndrome, but its diagnosis is essentially made during the neonatal period or in early childhood because of the very striking clinical manifestations and the very frequent association with cardiac anomalies [5,7].

However, the particularity of our case is that it was diagnosed incidentally until adolescence, underlining the importance of knowing the other clinical manifestations of this syndrome in order to ensure early diagnosis and appropriate treatment.

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Case presentation:
A 16-year-old girl with a history of full-term delivery by the vaginal route, with a history of perinatal asphyxia and poor adaptation to life outside the womb, and delayed psychomotor development: sitting up at the age of three, walking at the age of six, breast-fed with artificial milk for five years, dentition at the age of eight.

Her personal medical history includes epileptic seizures since the age of five, initially on several anticonvulsants (unspecified molecules) and currently on valproic acid. Recurrent seizures with a frequency of approximately one seizure per month. Repeated failure at school and dropping out since the 4th year of primary school.his family history was negative, including no systemic or neurological diseases.

Three years previously, she had been admitted for status epilepticus and was found to have hypocalcaemia, which was treated in emergency and then the patient was lost to follow-up.

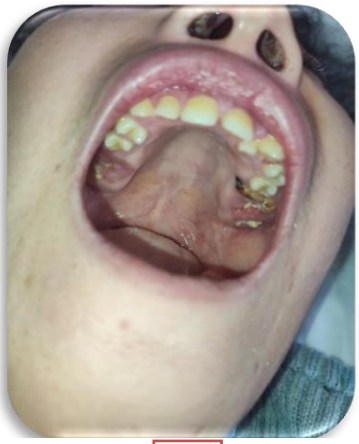
Three days before admission, she had a new epileptic seizure and profound hypocalcaemia (corrected calcium level: 46 mg/L), hyperphosphataemia (P: 74 mg/L) and low serum valproate levels (21.57 ug/dL). In the emergency department, she was given a protocol for correcting severe hypocalcaemia by infusion of elemental calcium.

On admission, the patient was in good general condition, haemodynamically and respiratorily stable, with no clinical signs of hypocalcaemia. The ECG showed a regular sinus rhythm and QTc of 365 ms. On auxological examination, the presence of severe staruro-weight retardation is noted (weight: -2standard deviation,height :-4 standard deviation) (figure 1), normal corpulence; presence of a dysmorphic syndrome with epicanthus, ogival palate, elongated face, hemifacial microsomia, small ears, short neck, acromecria, as well as oral and dental anomalies (figure 2), in a pubescent patient.

Figure 1:- Severe statural delay.

a

b



c

d

Figure 2:- Dysmorphic syndrome consisting of: a- epicanthus, elongated face, hemifacial microsomia, b- small ears, c- ogival palate, d- acromecria.

Biologically, the patient had a corrected serum calcium level of 89 mg/l on a maintenance dose of intravenous calcium element. The etiological work-up was in favour of hypoparathyroidism (PTH: 6.6ng/ml) with hyperphosphataemia (75 mg/l), hypomagnesaemia (17 mg/l) and hypovitaminosis D (22ng/ml). Renal function was normal (CC: 113 ml/min according to the Schwartz formula).

Given this atypical clinical picture and in consultation with the geneticists, 3 main diagnoses were suspected: Sanjad Sakati syndrome, Kenny-Caffey type 2 syndrome and Hypoparathyroidism X-linked syndrome, but Digeorge syndrome had to be ruled out first, given its frequency and the availability of genetic testing.

The genetic study by FISH analysis was in favour of a deletion of chromosome 22q11, confirming the diagnosis of DiGeorge syndrome.

As part of the search for other anomalies observed in this syndrome, the transthoracic ultrasound was without anomalies. In the search for an immunodeficiency syndrome, the haemogram was normal with lymphocytes in the normal range.

In terms of treatment, the patient is treated with calcitriol and calcium supplements with good clinical progress. For these epileptic seizures, the patient was referred to the neurology consultation for further management.

The patient was then referred to the endocrinology consultation for annual monitoring in accordance with the recommendations of the American College of Medical Genetics and Genomics published in 2023[9].

Discussion:-

We presented a case followed for epileptic seizures since infancy with an underlying cause of DiGeorge syndrome with hypocalcaemia, who had no cardiac abnormalities.

DS 22q11.2 is often suspected because of congenital anomalies, mainly cardiac and speech/language deficits, learning/behavioural problems, recurrent infections and subtle dysmorphic features [6,10].Although awareness of DS 22q11.2 has increased, diagnosis is often delayed or missed, particularly in people without congenital heart disease[7,11,12]. This was the case with our patient, who had no signs of heart disease or immunodeficiency, despite a dysmorphic syndrome which remained discreet.

Feeding difficulties, hypocalcaemia and numerous structural abnormalities can also be early warning signs[6].Unfortunately, these signs were present in our patient, but this led to confusion with her history of epilepsy, unmasking the true nature of the hypocalcaemic seizures.

90-95% of people affected carry a sporadic 22q11.2 deletion[1], while 6 to 28% of cases have a familial form with autosomal dominant transmission[1,13].Given our patient's negative family history, the deletion was considered to be sporadic.

DS 22q11.2 syndrome involves more than 35 genes and has a highly heterogeneous phenotype in terms of physical, cognitive and behavioural characteristics[14].

Facial dysmorphia is almost constant but difficult to diagnose because it is usually discreet, consistent with the phenotypic description present in our patient. It includes a tubular nose, protruding at the short root with wide, prominent nasal bridge and anteverted nostrils. The ears are small, poorly hemmed, protruding and low set. The phenotype may be completed by a microstomia with a short philtrum and straight palpebral slits [15].

Certain clinical signs of this syndrome are discovered in the neonatal period, in particular cardiac malformations, thymic hypoplasia and neonatal hypocalcaemia[16]. Congenital heart disease is reported in 75% of cases,it is of the conotruncal type: interruption of the aortic arch, truncus arteriosis, tetralogy of Fallot[17]. Bonnet et al. reported that 50% of conotruncal malformations were associated with Di George syndrome[18].

Congenital hypoparathyroidism is reported in approximately 50% of cases, and may manifest itself as epileptic seizures in 20 to 70% of cases[19,20,21].

In certain situations, hypocalcaemia can mimic a convulsion and be treated with anticonvulsants such as phenytoin, phenobarbital and carbamazepine which further aggravate hypocalcaemia [19,22].This was the case with our patient, who had been treated for a long time with anticonvulsants alone, without knowing whether these seizures were caused by hypocalcaemia or were seizures linked to the syndrome itself.

Neuropsychological signs are frequently reported in DS 22q11.2 [21,22,23]. However, there is little data on the pathophysiology of epilepsy in this syndrome [23].

Otolaryngeal and renal abnormalities and hypotonia are also frequently associated[14]. But they were negative in our case.

Just as the physical phenotype is extremely variable from one individual to another, the cognitive profile of DS 22q11.2 carriers is also heterogeneous. While just under half of children and teenagers show a delay in intellectual development (IQ < 70), the majority have learning difficulties[26].This may explain our patient's repeated failure at school.

Vital prognosis depends essentially on the severity of the congenital heart disease. In the long term, the prognosis depends on the combination of mental retardation and behavioural problems[11].

Conclusion:-

The clinical diagnosis of Digeorge syndrome can be difficult given the heterogeneity of the clinical symptoms, and genetic diagnosis remains difficult due to the molecular complexity. It is therefore essential that paediatricians, endocrinologists, cardiologists and specialists in various fields of medicine are very vigilant for the slightest phenotypic signs pointing towards this syndrome.

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