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The mutation of TBC1D24 associated with epilepsy: About 3 cases

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Abstract

Purpose : The aim of our work is to study the clinical, electrical, imaging and evolutionary profile of epilepsy caused by mutation of the TBC1D24 gene in our patients and to emphasize the interest of genetic counseling.

Methodology : This is a qualitative observational study about 3 cases, highlighting the clinical, electrical, and evolutionary characteristics of the disease.

Findings : In this study we report the clinical history of three patients from two families, hospitalized at the Mohamed V hospital in Tangier, during the year 2022, having in common a first degree consanguinity, a severe epilepsy, pharmaco-resistant, with a very early onset during the first months of life, with several hospitalizations for epileptic seizures, the repercussion on psychomotor development, and schooling was noted with the three children, the genetic study confirmed the presence of mutation of the TBC1D24 gene.

Unique contribution to theory, practice and policy: The cases reported in the literature are not numerous (1) (2) (3). Balestrini et al (1), reported 48 cases, followed for epilepsy related to the mutation of this gene, with a great clinical heterogeneity, and an age of onset in early childhood.

The correlation between the TBC1D24 gene and epilepsy was known for the first time in 2010,it represents a great clinical heterogeneity, ranging from simple epileptic seizure with good cognitive and intellectual development and complete control of the disease, to severe epileptic encephalopathy, so the mutation of this gene can be associated with brain malformations and can be found in several syndromes including DOORS syndrome (which associates deafness, intellectual disability, seizures, onycho-dystrophy, osteo-dystrophy).

This mutation is also described in non-syndromic deafness and in people suffering from various forms of epilepsy, including familial infantile myoclonic epilepsy, progressive myoclonic epilepsy, focal migrating epilepsy and writer's stress-induced paroxysmal rolandic-dystonic epilepsy syndrome.

A panel of genes were searched in particular clinical situations when there are severe epilepsies, consanguinity, or similar family cases, with or without other associated damaged organ, thus the screening of the TBC1D24 mutation is indicated in a wide variety of epilepsies.

Keywords: *epilepsy, TBC1D24 gene, genetic counseling.*

INTRODUCTION

Several studies on the TBC1D24 gene have been carried out, they suggest that it codes for a protein involved in the regulation of synaptic vesicle trafficking and in brain and body construction (2) (4).

The epileptic syndrome linked to the mutation of the TBC1D24 gene, gathers a great clinical variety, the correlation between the phenotype and the genotype is not clear enough. Moreover, several pathogenic variants of this gene have been found (3).

The aim of our work is to study the clinical, electrical, imaging and evolutionary profile of epilepsy caused by mutation of the TBC1D24 gene in our patients and to emphasize the interest of genetic counseling.

Materials and methods: This is a qualitative observational study about 3 cases, highlighting the clinical, electrical, and evolutionary characteristics of the disease.

- **1st case:**

A 5-year-old girl, 2nd of 2 siblings, the elder brother is in a good health, with a history of 1st degree consanguinity.

She presented her first convulsive seizure at the age of 4 months, by the installation of a generalized convulsive state of illness, following a febrile episode, the seizures will be repeated thereafter at a rate of twice a week, with a character sometimes focal sometimes generalized, of the myoclonies, interesting one or two members with lateralization of the glance, of a duration and intensity variable according to the episodes.

Hospitalization in the intensive care unit for generalized convulsive states and a deep post-critical coma were reported, the clinical examination was normal after stabilization, apart from a moderate intellectual deficiency and a strabismus, an electroencephalogram was carried out and came back without any particularity, the magnetic resonance imaging was also normal, the orthoptic check-

up showed a bilateral deep amblyopia with an exophoria-tropia, for which she is followed up in ophthalmology.

The patient was initially put on sodium valproate without improvement, then association of sodium valproate and levetiracetam, the evolution was marked by the repetition of epileptic seizures, following triggers such as lack of sleep, noise, fever and emotion.

Other antiepileptic associations were initiated in the patient: Clobazam, Sodium Valproate, Phenobarbital with persistence of symptoms.

In view of the pharmaco-resistant character of the epilepsy, a genetic study was carried out, by high-speed sequencing of the DNA of a virtual panel made of 9 genes and the analysis in-silico widened to 343 genes responsible for various forms of epilepsies which revealed the presence of the variant NM_001199107:c.457G>A in the homozygous state at the level of the gene TBC1D24, the screening in the parents is requested but not carried out for lack of means.

- **Case N° 2, N°3:**

It is about two twins, the eldest of a sibling group of 3, currently 5 years old, a girl and a boy, having a history of good psychomotor development, a consanguinity 1st degree, the brother died at the age of 10 months because of fever with notion of epilepsy since the age of 5 months undocumented. The beginning of the symptomatology goes back to the age of 5 months for the girl, and 4 months for the boy, by the occurrence of partial convulsive seizures of the myoclonic type, of progressive aggravation in number and duration, put under sodium valprate, clobazam, piracetam, noiafren, without improvement.

At the age of 18 months the twins showed a psychomotor regression along with swallowing disorder, coinciding with the worsening of the seizures.

The clinical examination came back normal in both brothers, except for a hypoacusis in the boy.

The boy's paraclinical exploration showed a normal electroencephalogram, the magnetic resonance imaging revealed an enlargement of the sub-arachnoid spaces. Whereas the girl's electroencephalogram was in favor of a diffuse encephalopathy, and the magnetic resonance imaging showed a diffuse parenchymal atrophy.

Even under treatment the evolution of the seizures was marked by the repetition of the jerks with change of their characters, sometimes generalized, sometimes focal, or limited to palpebral myoclonus. On the other hand, they did not present either onycho-osteo-dystrophy or deafness.

The genetic study through a panel of genes was carried out coming back with the appearance of mutation of the TBC1D24 gene in the homozygous state for the two patients. The screening of the parents finding showed the presence of the same mutation in the heterozygous state.

The parents's genetic counseling revealed a 75% risk of having a sick child.

DISCUSSION :

The mutation of TBC1D24 associated with epilepsy was recently discovered, only about a hundred cases were reported in the literature, and several TBC1D24 variants with their phenotypes were diagnosed, but the exact prevalence is unknown.

Balestrini et al (1), reported 48 cases, followed for epileptic syndromes related to the mutation of this gene, with a vast clinical variability, and an age of onset between 7 months and 8 years, Jing Zhang et al (2), reported a median age of 75 days in a series of Nineteen patients, the age of onset is earlier in our study, it is between 4 and 5 months, The most frequent semiological features of the seizures (1) are myoclonus and focal or generalized clonic seizures, another case reported by Qilin Zhou et al (3) in 2018 presented a continuous partial epilepsy with rare generalized tonic-clonic seizures, so Jing Zhang et al (2) report mainly multifocal myoclonus and continuous partial epilepsy (CPE), in our patients the myoclonus was present in the three children, with a CPE in the brothers

CPE is a form of epilepsy that manifests itself by continuous focal myoclonus, of cortical origin, The frequency of the jerks is variable with an average of 90 per minute.

Hearing loss was frequent in this type of epilepsy, and it could occur and worsen during the follow-up, hypoacusis is noted in only one patient in our work.

The semiological characteristics described in the study of Jing Zhang et al (2) related to the mutation of this gene are the resistance to the treatment, the abolition of the seizures during the sleep, the triggering of the shakes by the fatigue, the fever and the infection. While in our study the seizures are triggered by fever, infection and lack of sleep.

In case N1, sleep deprivation was reported as a trigger for a status epilepticus that required hospitalization in the intensive care unit. Therefore, it is essential to control the triggering factors in order to reduce the frequency and severity of seizures.

EEG and brain imaging findings are highly variable between series, the lack of clear correlation between seizure types and EEG was another interesting feature to report in patients with TBC1D24 mutations (4,5,6), in Jing Zhang's cohort (2), epileptic discharges did not correlate with focal myoclonus in 10 cases out of 19 patients studied.

In the study of Balestrini (1), one third of the patients with the TBC1D24 mutation had an abnormal MRI, in particular, hippocampal sclerosis, vermian hypoplasia, delayed myelination, cerebellar atrophy and cerebellar signal hyperintensity, for the case reported by Qilin Zhou (3), the MRI came back without abnormality, but he suggested that if further exploration, by a post-processing MRI procedure and by a combination of multimodality neuroimaging, restricted cerebral structural abnormalities, potentially epileptogenic can be found , for this patient the post-processing MRI procedure has objectified a slight gray-white blur in the left medial parietal region, Several studies have found cerebellar atrophy or cerebellar atrophy with abnormal MRI signals in patients with

TBC1D24 mutations (7,8,9), in the study of Zing et al (2), MRI abnormalities were found in eight patients, including cerebellar atrophy, cerebral atrophy and abnormal signals in the cerebellum. Two patients had cerebellar atrophy with abnormal signals after prolonged myoclonus induced by infection and fever, in our patients the EEG was abnormal in only one patient showing a diffuse encephalopathy, the MRI came back normal for only one patient, for the second one it showed a diffuse parenchymal atrophy and for the third one it came back in favor of an enlargement of the sub-arachnoid spaces.

The role of the TBC1D24 gene is not clear enough, the researchers are interested in objectifying its action on the central nervous system, therefore, they blocked its expression in the brain of rats during gestation, then they studied the construction of the cerebral cortex in these animals, as a result they found that the neuronal cells migrate much more slowly than normal inside the brain. They arrive late to the right place in the cortex, compared to the control animals, the co-author of the work, Carlos Cardoso, reports: "It is as if we were observing a brain of seven days when it is ten" (10).

This delay is related to a slowing down of the traffic of vesicles that transport proteins and molecules inside the neuronal cell. This traffic directs, for example, membrane receptors or ion channels to reach the membrane. The cells will then lose their polarity, and consequently their orientation during the construction of the brain will be disturbed.

In normal individuals, during development, some of the neurons follow a precise trajectory from the inside to the outside of the brain. This explains the appearance of several layers of the cortex, organized and ensuring different functions. In the presence of a mutation of the TBC1D24 gene, neuronal cells lose part of this capacity. They migrate in all directions and very slowly (10).

The transmission of the TBC1D24 gene mutation and its variants is autosomal recessive, i.e. the disease only appears if the person has the biallelic variants causing the condition.

Because of its recessive transmission, it is essential to do genetic counseling in families at risk, so it is essential to detect first- and second-degree relatives and to avoid consanguinity.

CONCLUSION :

Mutations in the TBC1D24 gene are associated with a range of hereditary, drug-resistant neurological disorders as well as several syndromes, the genotype-phenotype correlation is still under discussion to explain the broad phenotypic spectrum of the disease,

The therapeutic concern is still the huge problematic issue of this disease.

The notion of consanguinity is present in both families in our study, as well as in many families reported in the literature, with a risk of transmission to the offspring, hence the interest of genetic counseling.

PATIENT CONSENT :

Consent to publish the cases reports was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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