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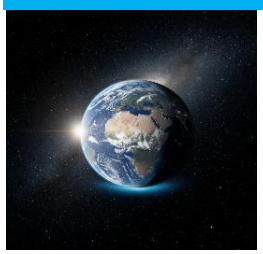

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TBC1D24 mutations- opening the DOORS to the associated syndromes

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Abstract

Introduction

TBC1D24 mutations encompass a vast variety of very rare disorders, which can manifest in a wide array of manifestations. The phenotypes include the most common DOORS syndrome, as well as Developmental and Epileptic Encephalopathy with other epileptic syndromes, DFNB- Autosomal recessive nonsyndromic hearing loss and DFNA- Autosomal dominant nonsyndromic hearing loss. With the increasing availability of the genetic studies, there has been a steady increase in the cases reported in the literature, showing a growing increase in the importance of this mutation in developmental diseases.

Aim

To summarize current knowledge about the pathophysiology of the TBC1D24 mutations, clinical manifestations, their epidemiology, diagnosis and potential treatment of the patients with the focus on most common signs and symptoms.

Material and methods

A systematic literature review was conducted through PubMed database and Google Scholar, using the keywords “DOOR syndrome”, “DOORS syndrome”, “TBC1D24”, “Developmental and Epileptic Encephalopathy”, “DEE”, “Autosomal recessive nonsyndromic hearing loss”, “Autosomal dominant nonsyndromic hearing loss”, “DFNA” and “DFNB”.

Keywords: TBC1D24 mutation; DOOR syndrome; Developmental and Epileptic Encephalopathy; Deafness; Genetic;

Introduction

TBC1D24 mutations were firstly associated with the DOOR syndrome. First descriptions of the syndrome were made in 1961 by Feinmesser and Zeilig, who described two siblings coming from a consanguineous marriage with deafness and characteristic dysplastic nails. In 1975 Cantwell described a girl with a characteristic tetrad of symptoms and invented an acronym DOOR syndrome [1]. Later more cases were described in the literature and an additional S was added, which stands for seizures, characteristic in patients with this syndrome. In 2001 a family with FIME (Familial Infantile Myoclonic Epilepsy) was described and later the gene responsible for this disease was mapped [2], [3]. Since then with the advance of molecular studies this mutation has been found as an underlaying cause of more cases of developmental problems and more diseases have been associated to it, such as Nonsyndromic Hearing Loss and Developmental and Epileptic Encephalopathies [4].

The purpose of this study is to review the available bibliography about these syndromes and summarizing the known pathogenesis, epidemiology, clinical manifestations, diagnostic challenges, differentiation between them and possible treatment options for the affected people.

Pathogenesis

TBC1D24 (which stands for TBC1 domain family member 24) with its locus on chromosome 16p13.3 codes a variety of differently spliced transcripts containing a N-terminal Tre2/Bub2/Cdc16 (TBC) domain. It is uniquely linked to a C-terminal TLDc (TBC, LysM and catalytic domain) and by binding small Ras-related GTPase ARF6 takes part in vesicle endo- and exocytosis, especially at synaptic sites and during the development of neurons [5]. It also plays a role in reducing oxidative stress in neuronal cells by binding of the TLDc with other proteins, such as e.g OXR1 (Oxidation resistance 1) [6], [7] TBC1D24 was found to be mainly expressed in the cerebral cortex and hippocampus, as well as in cochlear epithelium and plays a role in neuronal migration, branching and maturation in embryos, as well as neuronal signal transmission [6], [8].

Several mutations have been found in this gene, yet absence or presence of the symptoms should be taken into consideration. Most of them are single substitutions with very rare cases of

microdeletions, causing loss of the function of both of the genes, which leads to increased neuronal excitability, deteriorated exocytosis of the neuronal vesicles and higher susceptibility to oxidative stress [7], [9]. Due to pleiotropy of the genes the exact correlation between the mutations and the phenotypes of the disorders is hard to establish. Moreover, TBC1D24 mutations are in some cases a part of a broader spectrum of overlapping mutations, which makes it harder to pinpoint to a specific syndrome [10], [11].

Clinical features, epidemiology and diagnosis

a. DOORS syndrome

DOORS syndrome is considered to be an ultra-rare disease, with around 50 cases documented worldwide from many ethnicities e.g. Indian, Pakistani, Chinese, Japanese, Moroccan, Turkish, Polish, Brazilian as well as others [4]. 7/26 of studied individuals came from consanguineous marriage, and only in 13/46 of those patients a TBC1D24 mutation could be identified. In some individuals mutations of ATP6V1B2 (17%), GPI biosynthesis genes (17%) as well as others were found; in 13/46 cases no direct genetic etiology has been found [9], [12].

5 distinctive major features are distinguished in this syndrome: Deafness, Onychodystrophy, Osteodystrophy, Intellectual delay and Seizures. Deafness is sensorineural and congenital; it can be either partial or total in both ears. Onychodystrophy comprises a wide array of structural, textural and shape deformations of the nails in both hands and feet as well as their hypoplasia or aplasia [13], [14]. Osteodystrophy is marked by abnormal development of the bones of the fingers and toes. It can manifest itself by the presence of an accessory or rudimentary phalanx in fingers or toes, which can cause them to be disproportionately longer than others, while on the other hand some phalanges can be hypoplastic leading to their abnormal shapes and sizes. A triphalangeal thumb has been described in one third of the affected individuals. Both onycho- and osteodystrophy affect hands and feet equally. Intellectual disability has been reported in all individuals, in most cases, moderate or profound, with reported autism spectrum disorder, language and motor skills impairment in some cases [15], [16], [17]. Seizures are common among the patients, with the first onset in the first year of life, often tonic-clonic, but sometimes partial or myoclonic. They are sometimes progressive in nature, with an increasing frequency or severity and, in some cases, are resistant to antiepileptic drugs leading to status epilepticus and death. In 33% of cases hyperintensive T2 MRI signals were described, especially in

cereberall cortex, with other findings such as delayed myelination and punctate T2 hyperintensive foci [9]. In 7 out of 11 cases of the DOORS syndrome with TBC1D24 mutation abnormal 2-oxoglutarate secretion was found in urine. Some authors divide the DOORS syndrome depending on the presence or absence of 2-oxoglutaric aciduria into more severe type I (with aciduria) or milder type II (without aciduria), while others do this division depending on the severity of neurological and developmental symptoms. Nevertheless, there is no strict consensus about this division [13]. Other nonspecific symptoms include optic nerve (29% of cases) and peripheral neuropathy with hypo- or areflexia (with 4 cases identified), as well as coarse face features like long, prominent philtrum, downturned corners of the mouth, large nose with bulbous tip, wide nasal bridge and anteverted nares [14].

Tab. 1. Rare features of the DOORS syndrome [9], [13], [14], [18]

Ophthalmic	Musculoskeletal	Internal organs	Other
Myopia Astigmatism Convergent strabismus Nystagmus Cataract	Microcephaly Brachycephaly Sagittal craniosynostosis Dental anomalies (24%) Frontal bossing	Cardiac defects 16% (Fallot's pentalogy, ASD, PDA, complete heart block) Genitourinary anomalies 16% (hydronephrosis, nephrocalcinosis, unilateral renal agenesis, cystic dysplastic kidneys, ambiguous genitalia)	Hypothyroidism Hypochromic microcytic anemia Thrombocytosis Parkinsonism

Diagnosis of this syndrome relies on the previously described characteristic phenotypical pentad, as well as on gene targeted testing of the TBC1D24. In individuals with most characteristic features the sequence analysis should be used firstly as its yield appears to be the highest. When there is no variant detected, in the next step gene-targeted deletion or duplication analysis should be performed [4]. Clinical features of the DOORS syndrome overlap with the DDOD (deafness- onychodystrophy) syndrome, as well as Zimmermann- Laband syndrome

(ZLS). These include deafness (rare in ZLS), onychodystrophy and in ZLS intellectual disability with seizures. In some cases a straightforward diagnosis is hard to establish, especially due to the fact that DDOD and DOORS syndrome both can have ATP6V1B2 mutations. What differentiates these syndromes is the absence of seizures in both and gingival hypertrophy and scoliosis in ZLS. Moreover patients with DDOD can have normal cognitive functions, whereas in ZLS and DOORS syndrome most of the patients have developmental delay [19] Molecular studies should be done to seek pathogenic variants of ATP6V1B2 (DDOD), ATP6B1B2, KCNH1 and KCNH3 (ZLS) [4]. Coffin-Siris syndrome (CSS) should also be taken into consideration in differential diagnosis. This autosomal dominant syndrome also presents itself with intellectual disability (98%), hypoplasia of distal phalanges and nails (especially in fifth finger) (65-80%), seizures (50%) and hearing impairment (45%). Other symptoms include feeding problems, hypotonia and frequent infections in most cases of CSS, as well as scoliosis and internal organ defects. Nevertheless, the symptoms can often overlap and genetic screening including CSS-specific genes like ARID1A, ARID1B, ARID2, SMARCA2, SMARCA4 and SMARCB1 should be considered in differential diagnosis [20]. Other syndromes that should be considered are Temple-Baratsier syndrome (intellectual disability, seizures and nail hypo/aplasia in thumbs and toes) and Mabry syndrome (intellectual disability, seizures, short terminal phalanges and onychodystrophy) [4].

b. Autosomal Recessive Nonsyndromic Hearing Loss (DFNB86)

Nonsyndromic sensorineural autosomal recessive hearing loss is a disorder that affects individuals without any other symptoms that can be associated with the aforementioned hearing loss and lead to diagnosis of a syndrome. It is the most common cause of congenital deafness among the children, with 75-85% of cases inherited in autosomal recessive manner and affecting approximately 1 in 500 live births [21], [22], [23]. This variant has often an early onset and 61 mutations inherited in this manner have been found to date. Studies have shown that some patients affected by prelingual profound deafness (with hearing threshold of over 90 dB HL) have recessive TBC1D24 mutations, with some of them presenting with compound heterozygosity [24], [25]. 3 Pakistani families (2 consanguineous), 3 Moroccan, one consanguineous Arabian and several unrelated individuals from different ethnicities have been reported [4]. TBC1D24 mutation should be taken into consideration when diagnosing this type

of congenital hearing loss to improve the knowledge of true prevalence of this mutation in this syndrome.

c. Autosomal Dominant Nonsyndromic Hearing Loss (DFNA65)

Autosomal dominant nonsyndromic hearing loss (DFNA) is a more heterogenic disorder than the previous one, with hearing loss onset beginning often later in life and with most of the patients having at least one parent affected by it. 15-24% of cases of nonsyndromic hearing loss are transmitted in autosomal dominant manner [22]. More than 50 genes have been associated with autosomal dominant hearing impairment, among which is TBC1D24 [26]. Individuals with this specific mutation often present the first symptoms in adulthood (second and third decade of life) and they start initially in high frequencies. The progression is bilateral and leads to either moderate or profound hearing loss later in life [27], [28]. The number of patients with this mutation is considered to be underestimated by some authors, therefore testing for this mutation should be considered when diagnosing the patients with this illness [28].

d. Epileptic syndromes

Epileptic syndromes among children are rare, with cumulative incidence varying between 169 to 239 in 100 000, however roughly one third of the patients cannot be classified to a specific syndrome [29]. TBC1D24 mutations show a vast variety of heterogenic phenotypes of epileptic syndromes usually affecting infants and young children. Familial Infantile Myoclonic Epilepsy (FIME) was the first described epileptic disease associated to this gene [6]. The onset of seizures among the patients started between the first 24 hours of life and 36 months. The characteristic pattern involved spontaneous or triggered myoclonic focal, bilateral or massive seizures with preserved consciousness that could last between minutes to several hours of status myoclonicus. They had high frequency, with several attacks every day in infancy and childhood, but regressed over time in adolescence to a few seizures per week in adulthood. Only two out of eleven patients described had moderate intellectual disability, the rest showing normal psychomotor development [3], [30]. Progressive myoclonic epilepsy (PME) has also been associated to this gene in some cases, yet it is one of the rarest causes of this syndrome [31]. Only 2 cases of PME have been documented with certainty, while 5 patients coming from a consanguineous family had most probably this mutation, yet it hasn’t been directly proven [32]. First onset of symptoms

appeared in the first 2 months of life in most patients, all of them having full-developed epilepsy by the age of 7 months. The manifestations included prominent myoclonus, cereberall ataxia, developmental delay and in one case profound sensorineural deafness. The seizures could be either spontaneous (twice to multiple times a week) or caused by frequent infections (which could lead to status epilepticus lasting for days). With the age progression a deterioration in motor and cognitive skills was documented and most of the patients showed profound developmental delay. Most of them died early between the ages of 1,5 to 9 years [32], [33]. EPRPDC is another form of manifestation of the mutation, which stands for Rolandic Epilepsy with Paroxysmal Exercise-Induced Dystonia and Writer's Cramp. The patients suffered from Rolandic Epilepsies, which are characterized by unilateral facial seizures that include facial twitching and stiffness, as well as oropharyngeal symptoms like drooling, hypersalivation and gargling noises. Additionally sporadic dystonia of neck, trunk or extremities occurred during excretion, especially characteristic forearm dystonia that prevented them from writing. 6 such cases have been reported, 3 of them coming from one family and reaching adulthood with relatively good development [34], [35]. Another interesting case was described in Japan, where a child had myoclonus with the spinal cord origin and a sporadic (1 episode) of cortical seizure [36]. Some of the cases can be classified into a broader term of Developmental and Epileptic Encephalopathies (DEE), which encompass both developmental encephalopathy and epileptic encephalopathy [29]. Most of them were clonic or tonic, which could be focal, multifocal, unilateral, generalized or alternating. The most typical characteristic is drug-resistance, early onset (typically in the first 3 months of life; one patient had the first onset of seizures in the first day of life) and often early death. One of the types of the DEE is EIMFS which stands for Epilepsy of Infancy with Migrating Focal Seizures. These patients showed migrating focal seizures that migrated in one hemisphere or between both [37], [38]. Other types of seizures include focal, multifocal and generalized epilepsy with most of the cases also starting within the first year of life. Cerebellar atrophy was also described in many patients, who had abnormal signals in MRI as well as in EMG and EEG, some of them having ataxia [39]. This mutation should be considered especially among the patients with a very early onset of epilepsy and differentiated with other disorders. A differential diagnosis of FIME and PME should include Neuronal ceroid lipofuscinoses, MERRF (Myoclonic Epilepsy with Ragged Red Fibers), POLG-, PRICKLE1- and SCARB2- related disorders as well as Unverricht-Lundborg disease. DEE is associated to more than 250 different genes with vast heterogeneity among the patients,

nonetheless TBC1D24 should be a part of a multi-genomic next-generation sequencing panel when diagnosing DEE [11]. Moreover, an EEG and EMG should be performed in every patient so that an origin and severity of the seizures can be mapped and documented. A direct correlation between the localization of the mutation and the clinical outcome is still an open field to research [38].

Treatment and prevention

To date no causal treatment has been developed for the patients with these disorders, although anti-oxidative treatment including N-acetylcysteine amide and α-tocopherol showed good results *in-vivo* in reducing the number of seizures [34]. Epilepsy associated to mutations of TBC1D24 is often drug-resistant (62,5% of cases). A part of the family with FIME had good outcomes of treatment with either phenobarbital or sodium valproate, while some patients didn't even need any antiepileptic medication. One patient had a good response to phenytoin and clobazam, and two other to zonisamide. The patient with spinal myoclonus was successfully treated with oral baclofen [36]. Nevertheless most of the patients needed to take 2-3 drugs simultaneously to achieve at least some control of the seizures. The most common drugs used were sodium valproate, leviracetam, lamotrigine, clobazam, carbamazepine, clonazepam, phenobarbital, phenytoin and topiramate in various combinations and with different outcomes [4], [40]. All patients with this syndrome should be under regular neurologic surveillance and treatment should be adjusted properly to the symptoms and responsiveness. Early introduction of treatment is crucial to at least reduce the impact of epilepsy on the developing brain [13].

All patients with DOORS syndrome, as well as those with Nonsyndromic Hearing loss should be evaluated as quickly as possible by a team consisting of an otolaryngologist, an audiologist and a speech-language pathologist, all of them with an experience in pediatric patients, to asses the hearing loss and to eventually propose a treatment plan including hearing aids, or cochlear implantation, speech rehabilitation and to give prognosis. Patients with DFNA should avoid excessive exposure to intensive sounds, not to worsen the hearing loss [26].

Developmental delay should be managed by a multi-disciplinary team according to the recommendations and available means in each country. Treatment should be started as soon as possible and should include speech, physical, operational and psychological therapy. Quality and quantity of interventions should be adjusted proportionately to the disability to improve as

many functions as possible [41]. Other evaluations should include ophthalmologist to assess vision impairment, pediatric cardiologist and nephrologist to assess the possible cardiac and genitourinary defects, dentist to evaluate dental anomalies, as well as other specialties according to individual symptoms [4].

After diagnosing the patient with TBC1D24-associated disease or syndrome, the family of the proband should be given a genetic counselling. Parents of the proband should be tested for the mutation. With the exception of Autosomal Dominant Nonsyndromic Hearing Loss, all other aforementioned illnesses are inherited in autosomal-recessive manner, so both parents can be suspected to be heterozygous; if one of the parents is found to be negative with the mutation, mosaicism or de novo mutation should be suspected. Siblings of the proband should be tested as well whether they are carriers or free of the mutation (unless they are affected as well- then test should be conducted to confirm the diagnosis). When it comes to DFNA at least one parent can be affected, but the negative family history doesn't rule out the mutation. Siblings and children of the proband should be counseled as well. In all cases, family planning and potential risks should be addressed during the consultation and all of the doubts and questions should be addressed [4], [42].

Conclusions

Patients with TBC1D24 mutation can exhibit a vast variety of symptoms, especially developmental, neurological and audiological, creating a very heterogenic group of diseases and syndromes requiring multi-disciplinary approach. With the advancement of molecular studies, more cases can be properly diagnosed and associated to this specific group, but more research should be done to correlate the type of mutation and severity of symptoms, as well as on causal treatment in these syndromes, which could improve prognosis for some patients. Control of the symptoms is sometimes difficult to achieve, because some patients can respond poorly to the treatment, while others respond perfectly, therefore their management should be done in expert clinic with experienced staff.

Disclosure

Author's contribution

Conceptualization - Kacper Szada-Borzyszkowski

Methodology - Konstancja Owczarenko

Software - Kacper Szada-Borzyszkowski

Check - Konstancja Owczarenko

Formal analysis - Kacper Szada-Borzyszkowski

Investigation - Konstancja Owczarenko

Resources - Konstancja Owczarenko

Data curation - Konstancja Owczarenko, Kacper Szada-Borzyszkowski

Writing - rough preparation - Kacper Szada-Borzyszkowski, Konstancja Owczarenko

Writing - review and editing - Konstancja Owczarenko, Kacper Szada-Borzyszkowski

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