Introduction

Lysosomal storage disease is caused by the deficiency of a single hydrolase (lysosomal enzymes). GM2 gangliosidoses are autosomal recessive disorders caused by deficiency of β-hexosaminidase and Tay-Sachs disease (TSD) is one of its three forms.

Objective

To perform a review of the state of the art on TSD and describe its definition, epidemiology, etiology, physiopathology, clinical manifestations, as well as advances regarding its diagnosis and treatment.

Materials and methods

A literature search was carried out in PubMed using the MeSH terms “Tay-Sachs Disease”.

Results

After the initial search was conducted, 1233 results were retrieved, of which 53 articles were finally selected. TSD is caused by the deficiency of the lysosomal enzyme β-hexosaminidase A (HexA), and is characterized by neurodevelopmental regression, hypotonia, hyperacusis and cherry-red spots in the macula. Research on molecular pathogenesis and the development of possible treatments has been limited, consequently there is no treatment established to date.

Conclusion

TSD is an autosomal recessive neurodegenerative disorder. Death usually occurs before the age of five. More research and studies on this type of gangliosidosis are needed in order to find an adequate treatment.

Keywords: Tay-Sachs Disease; Gangliosidoses; Hexosaminidase A; Enzymes; Jews (MeSH).

Introduction

Lysosomes contain a wide variety of active hydrolytic enzymes known as hydrolases, including glycosidases, phosphatases, sulphatases, lipases, proteases, phospholipases, and nucleases. (1) Deficiency of only one of these hydrolases results in the inability to degrade macromolecules and, as a consequence, a lysosomal storage disease. (1,2)
There are two isoenzymes of β-hexosaminidase: hexosaminidase A (HexA), a heterodimer formed by two subunits (α and β), and hexosaminidase B (HexB), a homodimer also formed by two subunits (β- and β-). (1,3) There are also three forms of GM2 gangliosidosis: Tay-Sachs disease (TSD), Sandhoff disease (SD) and GM2 activator deficiency. (1) Specifically, this article describes TSD, which is caused by the deficiency of the HexA subunit α. (4)

TSD was first described in 1881, but its etiology remained unknown for a long time, and affected newborns could only be diagnosed after the first clinical manifestations. (1,5) That changed in 1969 when the deficiency of the hexosaminidase enzymatic activity was discovered, allowing the initiation of the assessment of carrier states. (5-6) Large-scale detection in specific ethnic groups decreased its incidence by 90% in the USA, mainly in groups where the rate of the disease was higher, as in people of Ashkenazi Jewish descent. (5) For this reason, Tay-Sachs disease is considered a prototype disease for targeted ethnic evaluations. (5)

TSD occurs most often in children with intellectual disability, skill regression, dementia, paralysis and blindness, and it, usually, leads to death by age 5. (7) If an individual is Jewish —or even if s/he has a Jewish grandparent—, is aged between 18 and 44 years old and plans to have children, the probability that they have the disease is 1 in 3 100 live births. (8,9)

Recent technological advances and demographic changes are modifying the way professionals study and explore TSD. A research by Lazarin et al. (10) reveals that 40% of TSD carriers in their cohort were from non-targeted ethnic groups. (10) In addition, marriages between different ethnic groups result in more complex genetic diversity, so a traditional DNA analysis has low sensitivity (5); however, sequencing promises greater sensitivity and specificity, with the potential to become a leading tool in carrier state screening and thus increasing its effectiveness to further decrease the incidence of TSD. (5)

Having an updated literature review on TSD is of great importance, since there is little relevant information available to the medical community due to its rare nature. With this in mind, the objective of this research is to provide information so that it can be a useful tool to know and understand this pathology for proper diagnose and treatment. In this article, the reader will find information on the epidemiology, etiology, physiopathology, clinical, diagnosis and management of this disease.

**Materials and methods**

A literature search was made in PubMed using the MeSH term “Tay-Sachs Disease”, obtaining 1 237 results in total. Citations were filtered, according to study type, in case reports, clinical trials, controlled clinical trials, narrative reviews, meta-analyses, systematic reviews, letters to the editor, classical articles, editorials, historical articles and journal articles, and also according to language (English), obtaining 666 results.

The search was conducted in December 2017 and was filtered by date of publication, without exceeding five years, retrieving in 45 results. Eight of the references were beyond the search and date range as they were original publications of the first findings of the disease; however, those articles included MRI observations or clinical manifestations of importance that contained information relevant to the review and deserved to be included.

A total of 53 articles were selected, and their abstracts were read in their entirety. In addition, a book bibliography was included since this information allows clarifying important epidemiological data. Figure 1 shows the flow chart of the review articles.

**Results**

Of the 54 sources used to carry out the literature review, 53 were articles and 1 was a book. Among the 53 articles, 31 were original investigations, 4 were narrative reviews, 9 were case reports, and 9 were letters to the editor. Table 1 provides a characterization of the most significant documents for the study.

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**Figure 1.** Search flowchart.

Source: Own elaboration.
Tay-Sachs disease (TSD) is an autosomal recessive, neurodegenerative disorder that is part of a group of three lysosomal storage diseases known as gangliosidoses. GM2. (4,7,11) These diseases are caused by a defect in GM2-catabolism, which is in turn caused by the deficiency of the lysosomal β-hexosaminidase A (HexA) enzyme, whose function is to transform ganglioside GM2 into ganglioside GM3 (4,11,22), thus triggering the abnormal accumulation of gangliosides GM2, mainly in neurons; this leads to cell death and to the development of the disease. (4,23-26)

In April 1881, Warren Tay, a British ophthalmologist, general surgeon and dermatologist, presented the case of a 12-month-old boy to the Ophthalmological Society of the United Kingdom. (27) From the age of 3 weeks, the baby presented with generalized progressive weakness and “symmetrical changes in the region of the yellow spot of each eye” (27, p1); Dr. Tay wrote: “I found the optic discs apparently quite healthy, but in the region of the yellow spot in each eye there was a conspicuous, tolerably well-defined, large white patch, more or less circular in outline, and showing at its center a brownish-red, nearly circular spot, contrasting strongly with the white patch surrounding it.” (28, p1)

In 1887, unaware of Tay’s reports, American physician Bernard Sachs wrote an article entitled “On arrested brain development, with special reference to its cortical pathology”, which was based on a document he had submitted to the American Neurological Association in July 1887. (27) It described the clinical manifestations and pathological features of what would later be known as Tay-Sachs disease. (27)

### Epidemiology

TSD is rarely found in the general population, with an estimated prevalence of 1 per 220,000-320,000 individuals, while the carrier frequency in the general population is approximately 1:300. (9,12,29-31)

Parental consanguinity is a risk factor for the manifestation of this autosomal recessive genetic disease (29), which explains why there are population groups that may show mutations in the HexA gene at higher allelic frequencies, such as the Ashkenazi Jews, whose frequency of carrier is estimated at 1:30. (12,29,32-34) It is also high among Pennsylvania Dutch, Canadians from eastern Quebec, Cajuns, Irish and Italians. (7,29) Three common mutations account for more than 99% of all mutations in the Ashkenazi Jewish community. (9)

Because the TSD rate is higher among Jews, it is important to clarify that this community is not only found in Israel, where 44% of the population is of this ethnicity, since the remaining 56% is distributed in different countries such as the United States (39.3%), France (3.1%), Canada (2.7%) and United Kingdom (2.0%). (35) In America, the total Jewish population is 6,470,600; the United States, Canada, Argentina, Mexico, Brazil and Uruguay have the highest figures. (35)

### Etiology

By 2014, 134 mutations in the HexA gene (15q23-q24) encoding for subunit α of β-hexosaminidase A had been reported (13); some of these mutations are characteristic or common in some ethnic groups and geographic locations. (25,36,37) Jamali et al. (38) established that in Ashkenazi Jewish patients, there were three prevalent mutations: an insertion of four-base duplications in exon 11 of the HexA gene (c.1274_1277dupFATC, 81%), a splicing mutation (c.1421 + 1G4C IVS12 + 1G4C, 15%) and a delayed mutation (c.805G4A, 2%). Those mutations are also commonly found in populations other than the Ashkenazi Jewish along with the mutation of the intron 9 splicing site (c.1073 + 1GNA), French-Canadian

### Table 1. Characterization of significant documents for the study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Language</th>
<th>Key findings</th>
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</thead>
<tbody>
<tr>
<td>Dersh et al.</td>
<td>USA</td>
<td>English</td>
<td>Modulation of endoplasmic reticulum quality control systems may be a potential therapeutic route to improve some forms of TSD.</td>
</tr>
<tr>
<td>Okada &amp; O’Brien et al.</td>
<td>USA</td>
<td>English</td>
<td>Hexosaminidase A enzyme deficiency, discovered.</td>
</tr>
<tr>
<td>Curd et al.</td>
<td>Australia</td>
<td>English</td>
<td>The results of this study support the TSD detection proposal in schools.</td>
</tr>
<tr>
<td>Karumuthil et al.</td>
<td>USA</td>
<td>English</td>
<td>Using a vector that encodes for HexA, intravenous adenovirus gene therapy was injected into mice, obtaining a slight increase in serum HexA activity.</td>
</tr>
<tr>
<td>Duarte et al.</td>
<td>Portugal</td>
<td>English</td>
<td>Detection of carriers in target populations can provide the grounds for more effective approaches to TSD.</td>
</tr>
<tr>
<td>Lew et al.</td>
<td>Australia</td>
<td>English</td>
<td>Results have been used to propose a pre-conception model for universal Ashkenazi Jewish population and prenatal screening in the context of primary prevention.</td>
</tr>
<tr>
<td>Scott et al.</td>
<td>USA</td>
<td>English</td>
<td>This study describes the first comprehensive carrier frequencies and residual risks of a large Ashkenazi Jewish cohort analyzed for 16 diseases prevalent in that population.</td>
</tr>
<tr>
<td>Hall et al.</td>
<td>USA</td>
<td>English</td>
<td>TSD diagnosis is based on decreased hexosaminidase activity and a change in the percentage of activity among isoforms.</td>
</tr>
<tr>
<td>Arjunan et al.</td>
<td>USA</td>
<td>English</td>
<td>Development of next-generation sequencing allows obtaining higher detection rates regardless of ethnicity.</td>
</tr>
<tr>
<td>Feldman et al.</td>
<td>USA</td>
<td>English</td>
<td>These results showed high analytical sensitivity and specificity along with good interpretation performance, confirming the genetics community impression that laboratories provide accurate test results in both diagnostic and screening environments.</td>
</tr>
<tr>
<td>Utz et al.</td>
<td>USA</td>
<td>English</td>
<td>Five biomarker candidates were distinguished by persistent elevation in the cerebrospinal fluid of patients with severe infantile phenotype: ENA-78, MCP-1, MIP-10, MIP-10 and TNFR2.</td>
</tr>
<tr>
<td>Kitakaze et al.</td>
<td>Japan</td>
<td>English</td>
<td>Study results indicate that mod28 has potential as intracerebrospinal fluid enzyme replacement therapy and should be further explored as a gene therapy for GM2 gangliosidoses.</td>
</tr>
<tr>
<td>Sinici et al.</td>
<td>Canada</td>
<td>English</td>
<td>A hybrid of the two subunits of hexoxaminidase A was recently constructed, reporting its ability to form homodimers that can perform this enzymatic reaction in vivo.</td>
</tr>
<tr>
<td>Gray-Edwards et al.</td>
<td>USA</td>
<td>English</td>
<td>After gene therapy, proliferation and microglial activation in TSD sheep increased; this demonstrates the therapeutic efficacy in the brain of the sheep, which is on the same order of magnitude as a child’s brain.</td>
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</tbody>
</table>

TSD: Tay-Sachs disease.
Source: Own elaboration.
Gangliosides are complex glycolipids containing ceramide linked to a variable number of monosaccharides and sialic acid residues, which confer a net negative charge on the molecule. (37) They are usually classified based on the Svennerholm nomenclature as follows: G for 'ganglioside', the following letter is the number of sialic acid residues (A: zero, M: one, D: two, T: three) and the final digit is the number of monosaccharides residues (1:4, 2:3, 3:2). (37) Gangliosides are found in all plasma membranes, but are most abundant in neurons, where they represent 5-10% of the total lipid mass. (37,39)

Gangliosides suffer catabolism through the lysosomal degradation pathway, where they are sequentially degraded by a series of hydrolytic enzymes assisted by lipid-binding proteins. (39)

Research on molecular pathogenesis and the development of possible treatments for TSD based on the pathophysiological mechanism are limited due to the fact that endogenous accumulation of GM2 is not observed in the peripheral cells of the patients. (30) Although murine models are available, they are not suitable to carry out these studies since the degradation pathway of GM2 gangliosides in mice (known as sialidase pathway) limits the clarification of pathogenic pathways in humans. (11,30,40)

Under normal physiological conditions, lysosomal degradation enzymes are known to be composed of the following dimers: hexosaminidase A (heterodimer HexA, composed of a subunit α and a subunit β), hexosaminidase B (HexB, homodimer composed of two subunits β) and hexosaminidase S (HexS; homodimer composed of two subunits α). (3)

TSD is caused by mutations in the subunit α of the heterodimeric enzyme β-hexosaminidase A (HexA), whose function is to catalyze the hydrolysis of N-acetylglucosamine residues from an oligosaccharide chain of the glycosphingolipid ganglioside GM2. (11,29,41) In short, this disease is the result of the lysosomal accumulation of GM2 gangliosides in the central nervous system. (42,43) The pathophysiological mechanism of GM2 gangliosidosis involves the storage of lipids in neurons with neuronal loss and dendritic changes, indicating an alteration of synaptic function and altered brain microconnectivity. (44)

The subunits α and β of HexA are encoded by the HexA (15q23-q24) and HexB (15q13) genes, respectively. (4,24,29) They are 60% identical at the amino acid level and are synthesized in the endoplasmic reticulum, where they form intramolecular disulfide bonds and are glycosylated and dimerized. (4) Lesions in the HexA, HexB and GM2A genes may cause TSD, SD or GM2 gangliosidosis AB variant, respectively. (4,29) SD is caused by mutations in the HexA subunit β. (11,15) The HexA enzyme requires a substrate-specific cofactor called GM2-activating protein (GM2AP) to degrade GM2 efficiently; mutations in the gene encoding GM2AP lead to the AB variant. (11) Gangliosidosis GM2 can have infantile, juvenile and late-onset phenotypes. (29,45)

Clinical manifestations

As TSD is an autosomal recessive disorder, heterozygous genetic carriers are phenotypically normal, but if both members of a couple are carriers, 25% of pregnancies will have the disease. (13) Under this condition, the central nervous system undergoes a progressive degeneration, usually in the first years of life, that is characterized by neurodevelopmental regression, hypotonia, hyperacusis, cherry-red spots in the macula, among others. (3,42,46)

TSD has three forms (47) —infantile, juvenile and adult onset—as a consequence of the difference in the progressive accumulation of GM2 ganglioside rate, which allows for such classification and a variable clinical phenotype. (30)

Classic infantile TSD occurs in children under 1 year of age, usually appears between 4 and 8 months and presents early symptomatology and rapid progression. (15,44,47) This form is characterized by neurological deterioration and evidence of sensory abnormalities, epilepsy, loss of motor skills and muscle weakness; bilateral spots in the macula of the retina and blindness; and macrocephaly after 2 years of age. (3,25,29,32,44,47-49) Children born with this disease have irreversible deterioration and usually die before age 5. (50)

The juvenile form is rare and has a slower course. It is considered a subacute form and is characterized by spinocerebellar degeneration, intellectual impairment, gait abnormality, progressive dystonia, cerebellar ataxia, dementia, hyperacusis and spinal muscular atrophy. (3,47,48).

The late-onset adult form, like the juvenile form, is rare; it presents with progressive mental and motor impairment, proximal and distal weakness, upper and lower motor neuron disease and psychiatric disorders. (25,44,47) The last two groups are less severe and more variable due to the presence of residual enzymatic activities. (38)

Increased Moro reflex is considered one of the first clinical signs of TSD. The study by Nakamura et al. (46), which sought to establish the evolution of this reflex and compare the temporal relationship between it and brainstem evoked potentials, evaluated the results obtained from the clinical and electrophysiological data of three patients with TSD, revealing that increased Moro reflex appeared between 3 and 17 months, and disappeared between 4 and 6 years of age. In addition, a patient with an increased Moro reflex also showed a blink reflex with significantly large amplitude. (46)

Discussion

The findings regarding diagnosis and management of the pathology are discussed below, focusing on the importance of prenatal screening and its impact on reducing incidence, as well as confirmatory tests once the disease has been developed. Advances in the use of potential biomarkers are also discussed.

This section also highlights that there is currently no approved effective treatment for TSD; however, several experimental methods that seek to restore enzyme function are presented, but are still under research and validation.

Diagnosis

Currently, guidelines established by the American College of Medical Genetics and Genomics and the American College of Obstetricians...
and Gynecologists recommend screening for 4-9 conditions in individuals of Ashkenazi Jewish descent. (16) The most advanced genetic testing technologies comprise a greater number of disorders than the previous recommendations, with an approximate number of 19, including TSD. (16)

Prenatal screening for TSD was introduced in 1971 in the U.S. and throughout history its application has been directed only at Ashkenazi Jewish populations. (9,13,17) Between 2006 and early 2011, the median number of tests per month was 2,900, with an annual rate of 35,000; the analytical sensitivity and specificity for U.S. participants were 97.2% and 99.8%, respectively. (17) This screening has been associated with a >90% reduction in the incidence of the disease in populations that have been intervened, mainly in the USA, Israel and Canada. (9,50)

At present, TSD carrier detection assays are designed to exclusively search for the most common mutations in a gene; carrier status can be determined by molecular analysis that detects genetic mutations in the hexosaminidase A sub-unit α. (51,52)

Enzymatic assays, instead of a DNA-based test, are another alternative, taking into account the wide range of HexA variants that have been found in non-Jewish heterozygous carriers. (13)

The analysis of hexosaminidase A activity allows detecting 98% of carriers of all ethnic groups with TSD. The enzymatic activity of non-carriers is above 60%, while carriers have a percentage less than 52%. (13) The leukocyte enzyme assay measures HexA and HexB using the thermolabile nature of HexA, so that both enzymes can be measured in a single assay. Affected patients present a deficient activity of the enzyme β-hexosaminidase A in leukocytes/plasma or fibroblasts. (15)

Diagnosis should be suspected from the onset of the first symptoms and the earliest clinical manifestations of the disease, which include excessive responses to sound and progressive loss of motor skills that had previously been acquired until the onset of psychomotor retardation. (53) This can be confirmed by evaluating the activity of hexosaminidase A, which may show low levels or none at all (normal range: >50.0%). (28,52) Molecular genetic analysis is also indicated; this is done by sequencing genes to identify a genetic mutation in HexA. (29,32) The age of onset, disease progression, and age of death will determine whether it is a child, juvenile, or adult form. (18)

The search for biomarkers potentially associated with the disease has been the subject of research: Utz et al. (18) quantified 188 analytes with serial measurements in the cerebrospinal fluid (CSF) of human patients and found that 13 factors associated with inflammation increased in the CSF of patients with the infantile form and to a lesser extent in the juvenile form. (18) Five of the identified biomarkers were characterized by persistent elevation in the CSF of patients with the infantile form: epithelial cell-derived neutrophil-activating protein-78 (ENA-78), monocyte chemotactant protein 1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), macrophage inflammatory protein-1 β (MIP-1 β), and tumor necrosis factor receptor 2 (TNFR2). (18)

The abnormal elevation of these biomarkers associated with other variables of the disease, such as the severity of the clinical phenotype and the absence of other neurodegenerative lysosomal diseases, allows the identification of analytes as biomarkers of gangliosidoses and their specific neuropathology. (18)

Also, several articles have reported magnetic resonance imaging findings, where the thalamus shows a low intensity signal on T2 and high intensity on T1, compared to the brain’s white matter that had a high intensity signal on T2. (26,48) A high intensity signal on T2 and low intensity signal on T1 is observed in the globus pallidus, caudate nucleus and putamen. (26) As the disease progresses, a symmetrical high-intensity signal is observed in the cerebellum, cortex, white matter and finally a diffuse high intensity signal on the white matter and cerebral atrophy. (26)

Treatment

Even though several alleles associated with the disease have been identified, there is no approved effective treatment for TSD or a way to stop its progression. (4,18,19,52,54)

Death usually occurs before age 5 and is often associated with aspiration pneumonia and bronchoaspiration; however, various methods have been explored to restore the function of β-hexosaminidase A. (19,52)

Elements of both subunits of hexosaminidase A (α and β) are needed to interact productively with the GM2-GM2AP ganglioside complex in the lysosome. (20) A complementary DNA encoding a hybrid subunit of hexosaminidase with the ability to dimerize and hydrolyze GM2 gangliosides could be incorporated into a single vector, whereas if both subunits of HexA are packaged into vectors such as adenoviruses, size restrictions would not allow it and would not be practical. (20) A hybrid was constructed consisting of a modified subunit β that can form a homodimer but act as a heterodimer of a α/β subunit of HexA, capable of hydrolyzing GM2, although no significant result was found. (20)

TSD also occurs in sheep, this being the only experimental model that shows clinical signs. (21) Intracranial gene therapy is tested using monoconstronic AAV/rh8 vectors, which encode the α subunit of Hex (TSD α) or a mixture of the vectors encoding the α and β subunits separately (TSD α + β) injected at a high dose (1.3 x 1013 vector genomes) or a low dose (4.2 x 1012 vector genomes). (21)

In all the sheep that were treated with associated adenoviruses, there was a delay in the onset of the symptoms or a reduction of the existing ones. (21) In the post-mortem assessment, a superior HexA genome distribution and the TSD α + β vector were observed in the brain of the treated sheep compared to a sheep with TSD α, but the distribution in the spinal cord was low in all groups. (21) The analysis of isoenzymes showed a greater formation of HexA after treatment with both vectors (TSD α + β); in TSD α + β sheep that were treated with high doses, the clearance of gangliosides was more widespread. (21) After gene therapy, proliferation and microglial activation in TSD sheep increased, proving the therapeutic efficacy in the brain of the sheep, which is on the same magnitude as a child’s brain. (21)

A murine model for TSD showed several of the neuropathological characteristics of the disease, mainly the accumulation of GM2 gangliosides. (2) However, it did not present its clinical signs because of the presence of a lysosomal sialidase able to hydrolyze GM2 in GA2, which is its asialo neurito derivative that interacts with HexB to degrade until it reaches glucosylceramide. (11)

On the other hand, mice with TSD keep the accumulation of GM2 below a toxic level thanks to this alternate metabolic pathway and avoid the onset of clinical symptoms. (11) Gene therapy with adenovirus using a vector coding only for HexA was injected intravenously into mice with the disease and produced a slight increase in serum HexA activity, while a simultaneous injection of vectors encoding for HexA and HexB increased HexA activity by 42%. (11) In this case, unlike sheep experiments, the difference in brain size makes it difficult to take this approach to humans, in addition to the limited diffusion of AAV vectors from the injection site. (11)

In other murine experiments, a modified human hexosaminidase subunit β, called mod2B, was produced, which was composed of homodimeric subunits β containing amino acid sequences from the subunit α that degraded GM2 gangliosides and conferred resistance.
to proteases. (19) Intracerebroventricular administration of mod2B reduced the accumulation of GM2 in the cerebellum, hippocampus and hypothalamus; moreover, a significant improvement in motor function and a longer useful life was observed. (19) The results of this study indicated that mod2B may be an effective therapeutic measure for enzyme replacement with cerebrospinal fluid, but requires further studies to explore an effective therapy in GM2 gangliosidoses. (19)

Substrate reduction therapy and the production of GM2 gangliosides did not show a response in the prevention of neurodegeneration. It could also affect the cells compromising cellular metabolism. (4)

Gene therapies to restore enzymes in patients could cure such diseases, but time, vector type and kinetics in enzyme production require extensive optimization. (4) Previous research and experimental therapies have not yet shown conclusive and indisputable results in humans.

Conclusions

TSD is an autosomal recessive neurodegenerative disorder caused by the deficiency of the lysosomal enzyme β-hexosaminidase A (HexA), which result in the accumulation of GM2 gangliosides mainly in neurons. It has an estimated prevalence of 1 per 220,000 individuals and patients usually die before 5 years of age.

There is no effective treatment approved to treat TSD nor to stop its progression; however, various methods have been explored to restore the function of β-hexosaminidase A. Gene therapies to restore enzymes in patients could offer treatment for these diseases but more studies and research are needed as they currently have multiple limitations. Gathering existing information on the pathology allows emphasizing the importance of conducting research on this disease in order to provide timely treatment and achieve good prognosis for patients.

Conflicts of interest

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