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ORIGINAL ARTICLE

# The FHL1 myopathy spectrum revisited: a literature review and report of two new patients

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**Objectives. Mutations in the FHL1 gene have been associated with a diverse spectrum of X-linked diseases affecting skeletal and cardiac muscle. Six clinically distinct human myopathies can be recognized, including reducing body myopathy (RBM), X-linked dominant scapuloperoneal myopathy (SPM), X-linked myopathy with postural muscle atrophy (XMPMA), rigid spine syndrome (RSS), hypertrophic cardiomyopathy (HCM) and type 6 Emery- Dreifuss muscular dystrophy (EDMD). The core features of all described FHL1opathies are mostly scapuloperoneal muscle weakness, rigid spine, cardiac involvement, and cytoplasmic bodies in the muscle biopsy.**
**Methods. We systematically reviewed the medical literature between the years 2000 and 2024 regarding the phenotype and genotype description of FHL1-associated myopathies.**
**Results. Here, we report two novel patients presenting with an X-linked myopathy with postural muscle atrophy (XMPMA) caused by the c.672 C > G FHL1 gene mutation.**
**Conclusion. When encountering these features in a patient, one may consider screening for an FHL1 mutation. The course ranges from a severe fatal course with early onset to very mild features with late onset. Once a dystrophinopathy has been excluded, increased CK values in male subjects with possible X-linked inheritance should always trigger FHL1 gene screening.**

**Keywords: X-linked** myopathy, FHL1, X-linked myopathy with postural muscle atrophy

## Background

Mutations in the FHL1 gene have been associated with diverse X-linked diseases affecting skeletal and, more rarely, cardiac muscle. Six clinically distinct human myopathies can be recognized (Tab. I) [1], including reducing body myopathy (RBM), X-linked dominant scapuloperoneal myopathy (SPM), X-linked myopathy with postural muscle atrophy (XMPMA), rigid spine syndrome (RSS), hypertrophic cardiomyopathy (HCM) and type 6 Emery-Dreifuss muscular dystrophy (EDMD). These myopathies present with a wide clinical variability and age at presentation, which ranges from early childhood to adulthood. In FHL1opathies, rigid spine syndrome is a core feature [2].
The molecular basis of how FHL1 mutations cause this broad spectrum of partly overlapping clinical phenotypes of myopathies remains unclear, and there are currently no therapies [1]. About 30 different FHL1 mutations have been identified [3].

### *Methods*

Clinical, histological and molecular data from the probands were integrated into our literature review of FHL1 patients carrying different variants (Tab. II suppl.). As far as the literature review is concerned, the following terms were searched through PubMed encompassing the years 2000 to 2024 using the following keywords, filtering for human studies, abstract and full-text availability in English: "((FHL1) AND (myopathy)) OR (X-linked myopathy with postural muscle atrophy)." We included publications reporting patients of any age and providing clinical, instrumental, and molecular characterization.

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**Table I**. Clinical features of FHL1-associated myopathies.

| | Reducing body myopathy | Scapuloperoneal myopathy | X-linked myopathy with postural muscle atrophy | Rigid spine syndrome | Emery Dreifuss muscular dystrophy | Contractures and Hypertrophic Cardiomyopathy |
|---|---|---|---|---|---|---|
| **Onset** | Childhood and adult | Adult | Childhood and adult | Adolescence | Childhood and adult | Childhood and adult |
| **Clinical presentation** | Progressive muscle loss. Rigid spine. Scapular winging. Contractures. scoliosis | Footdrop. Rigid spine. Scapular winging. Contractures. | Bent spine. Rigid spine. Scapular winging. Contractures. | Rigid spine. Scapular winging. Contractures. | Progressive muscle loss. Rigid spine. Contractures. Scoliosis. | Diaphragm weakness Rigid spine. Contractures. |
| **Muscle affected** | Proximal | Shoulder girdle, peroneal | Atrophy of postural muscles. Hypertrophy of proximal upper limb muscles | Pelvic girdle, thigh, neck, back | Scapula-peroneal, proximal | Pelvic girdle, thigh |
| **Cardiac involvement** | rarely | yes | yes | yes | yes | yes |
| **Respiratory involvement** | yes | no | yes | yes | yes | yes |

## Results

It has been suggested to classify FHL1-related disorders into two main groups: the reducing body (RB) subgroup, including RBM, X-linked dominant scapuloperoneal myopathy and rigid spine syndrome, all characterized by RB at the histological examination, and a second subgroup, including the XMPMA and EDMD patients, characterized by later onset and absence of RB [4]. The morphology of FHL1opathies overlaps with myofibrillar myopathies. However, cytoplasmic or reducing bodies, possibly pathognomic for FHL1opathies, seem not to be core features of any other myofibrillar myopathies yet [2].

The causative gene, FHL1, was identified in 2008 on chromosome Xq26 and is composed of eight exons, of which exons 1 and 2 are noncoding, and exons 3 to 8 are alternatively spliced, giving rise to three major transcribed isoforms: FHL1A, FHL1B, and FHL1C. Striated muscles mainly express the isoform FHL1A. FHL1 proteins belong to a family of four LIM domains preceded by an N-terminal zinc finger/half LIM domain, which are highly conserved sequences constituted by two zinc fingers in combination, involved in several interactions [5]. FHL proteins, in general, appear to be involved in cytoskeletal scaffolding and in the regulation of transcription factors [6].

### *Reduced body myopathy - RBM*

Reducing body myopathy (RBM) is a rare disorder of muscle, which was first described more than 35 years ago in 2 children who presented with an early-onset and rapidly progressive myopathy in the context of a floppy infant syndrome, leading them to death in early childhood (Brooke and Neville, 1972) [6]. The first adult-onset patient was reported in 1999 [7]. RBM is the most severe myopathy caused by a mutation in the FHL1 gene and presents a dominant inheritance or sporadic. It´s characterized by progressive muscle loss with weakness, primarily involving scapuloperoneal and neck muscles, contractures, rigid spine, scoliosis and scapular winging. With the progression of the disease, swallowing difficulties were present.

Sometimes, it manifests with severe infantile and childhood-onset with rapid progression and cardiac/respiratory failure [8]. Cardiac involvement may also be present. In all family reports, the male patients were more significantly affected than the females, who can be asymptomatic or suffer from mild proximal muscle weakness [4].

RBM is a rare muscle disorder characterized histopathologically by nitroblue tetrazolium (NBT)-reactive accumulations in the cytoplasm of muscle fibres, called “reducing bodies’, which contain mutated FHL1 protein [9].

### *Scapuloperoneal myopathy - SPM*

X-linked scapuloperoneal myopathy (XSM) presents a progressive weakness in the shoulder girdle and peroneal muscles, scapular winging, a rigid spine, and foot drop without cardiac involvement. The age of onset in patients with X-SM is between 20 and 40.

Menadione–NBT–positive reducing bodies on muscle biopsy were reported. It is considered a milder form of RBM with an onset in adults [10].

### *X-linked myopathy with postural muscle atrophy (XMPMA)*

This phenotype is characterized by an initially pseudoathletic appearance with early-onset neck rigidity and Achilles tendon shortening in adolescence, followed by the formation of a scapula-axio-peroneal syndrome with postural muscle atrophy, scapular winging, and proximal weakness in a limb-girdle distribution pattern, gait difficulties. In sporadic patients at older age, respiratory insufficiency can occur. Cardiac involvement is also reported. In some biopsies, rimmed autophagic vacuoles, increased fiber size variation, and fiber hypertrophy were reported, and reducing bodies have not been detected [11].

### *Rigid spine syndrome - RSS*

This rare condition has an early clinical onset, with muscle atrophy and weakness mainly involving the proximal lower limbs, pelvic girdle, sternomastoid, trapezius, and paravertebral muscles combined with winging of scapulae and Gowers's sign, with associated joint contractures.
The histopathology evidence of reducing bodies suggests that RSS is a milder form of an FHL1opathy, most likely RBM [12].

### *Emery-Dreifuss muscular dystrophy – EDMD type 6*

EDMD presents with early joint contractures, rigid spine, childhood onset of muscle wasting, and weakness, mainly with a scapuloperoneal distribution pattern. Cardiac involvement is the most severe symptom in EDMD patients, which can precede significant muscle weakness and lead to death resulting from sudden cardiac failure. Muscle histology reveals biopsies that show nonspecific myopathic changes or dystrophic patterns [5].

### *Contractures and Hypertrophic Cardiomyopathy - HCM*

The reported patients presented with contractures and rigid spine syndrome. The clinical onset ranges from childhood to the third decade of life. Muscle weakness was once reported, but muscle atrophy is not shared. Patients show hypertrophic cardiomyopathies and cardiac fibrosis. Histopathology showed cytoplasmic bodies [13;4].

## Patient reports

### *Patient 1*

An 11-year-old German boy presented with a familiar history of FHL-1 gene mutation detected in his mother (Fig.1A), who underwent a diagnostic work-up due to repeatedly elevated CK levels. A genetic test was not performed on the father. The patient presented with slight symptoms; in particular, he noticed a decreased range of motion at his shoulders and knees without complaining of any functional limitation. He regularly plays sports. On neurological examination at age 11, tendon contractures were noticed in the shoulders, knees and neck flexors. Paravertebral muscle hypertrophy was evident, with an athletic appearance (Fig. 2C), scapular winging and axial muscular atrophy of postural muscles.
Additionally, neck rigidity, limiting neck (and spine) flexion, is present (Fig. 2 A, B). Neither motor nor sensory impairment was detected. Minimal scapula alata was present, more pronounced on the right.
Muscle ultrasound showed hyperechogenicity of paraspinal muscles (Fig. 2D). Serum creatine kinase (CK) was mildly elevated at 413 U/L (the upper limit of normal 152 U/L), and electromyography (EMG) showed myopathic changes without spontaneous activity. Cardiovascular evaluation showed normal results.
A targeted muscle gene panel, including 29 muscle genes, explored by Next Generation Sequencing revealed (see File A as supplemental) the same mutation already detected in the mother, c.672 C > G (p.C224W) in the FHL1 gene, with an X-linked hemizygous transmission pattern.
The patient doesn´t complain about worsening his clinical status on regular follow-ups. At the last clinical evaluation, at age 16, a slightly bent spine was noticed. Our clinical findings are consistent with other cases of X-linked myopathy with postural muscle atrophy (XMPMA), characterized by a pseudo-athletic appearance with early-onset neck rigidity and scapular winging. Our patient did not present Achilles tendon contractures.

### *Patient 2*

A 91-year-old German woman presented with a 6-year history of instability of the gait, complaining of a collapse of the right hip during walking, without pain. Her weakness progressed slowly over the years, requiring her to use a stock at age 89.
On family history, her father, around age 70, and her son, in his early 50s (Fig.1B), presented a slowly progressive gait impairment. A

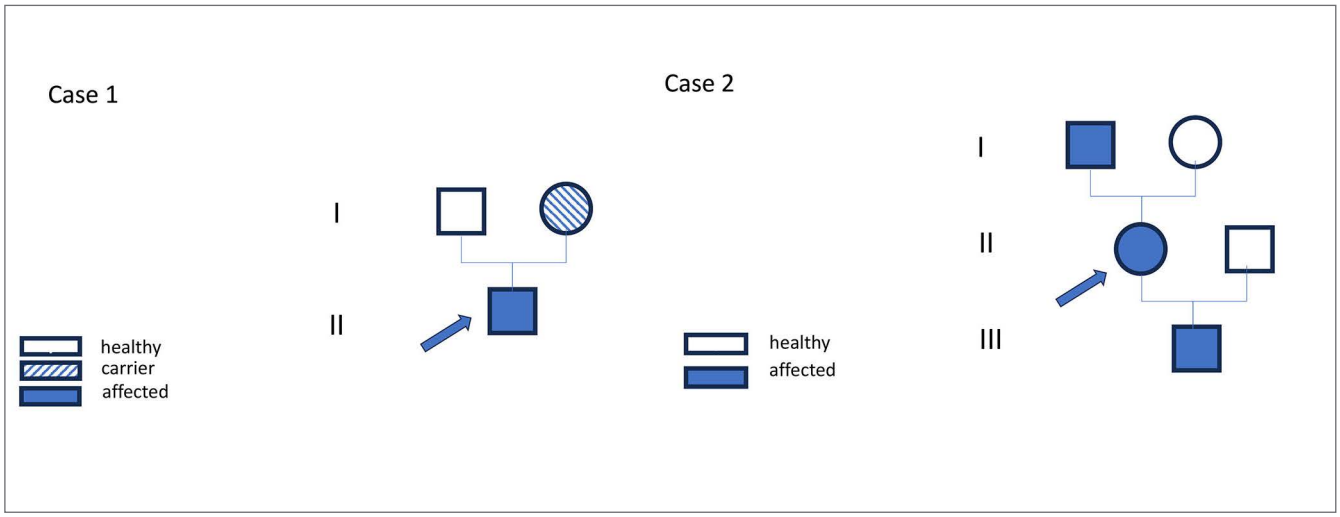


**Figure 1.** (A) Proband's pedigree (indicated by an arrow). The filled blue symbols indicate individuals affected by the disease. The striped symbol indicates the proband's mother, presenting with hyper CKemia. (B) Proband's pedigree (indicated by an arrow). The filled symbols indicate individuals affected by the disease.

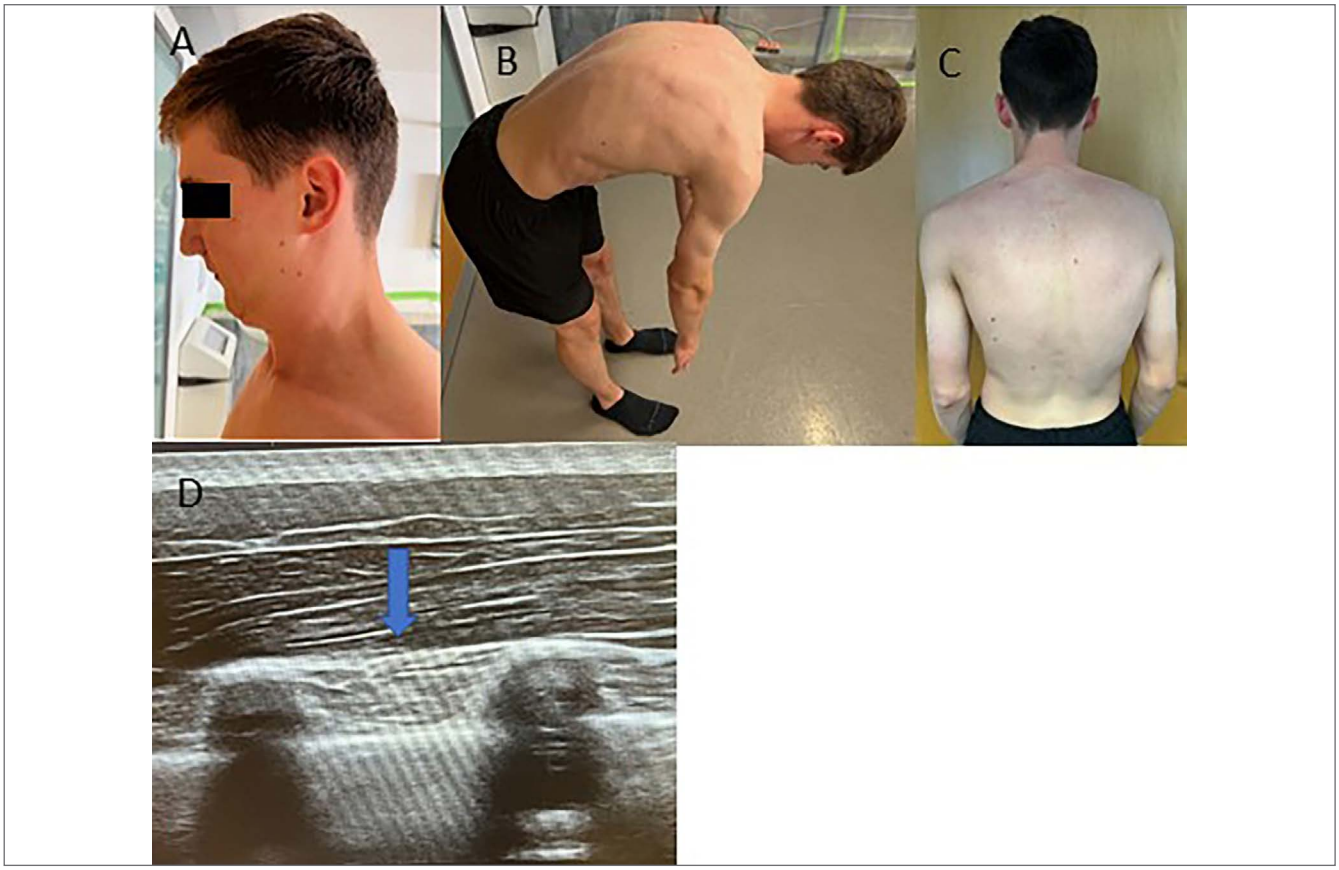


**Figure 2.** The clinical phenotype at age 16 presents an athletic appearance (C). scapular winging and axial muscular atrophy of postural muscles are found in this patient. Additionally, neck rigidity with limiting of the neck (and spine) flexion is present (A, B). Ultrasound image showing hyperecogenicity of paraspinalmuscles (Heckmatt grade 3) (D), (blue arrow).

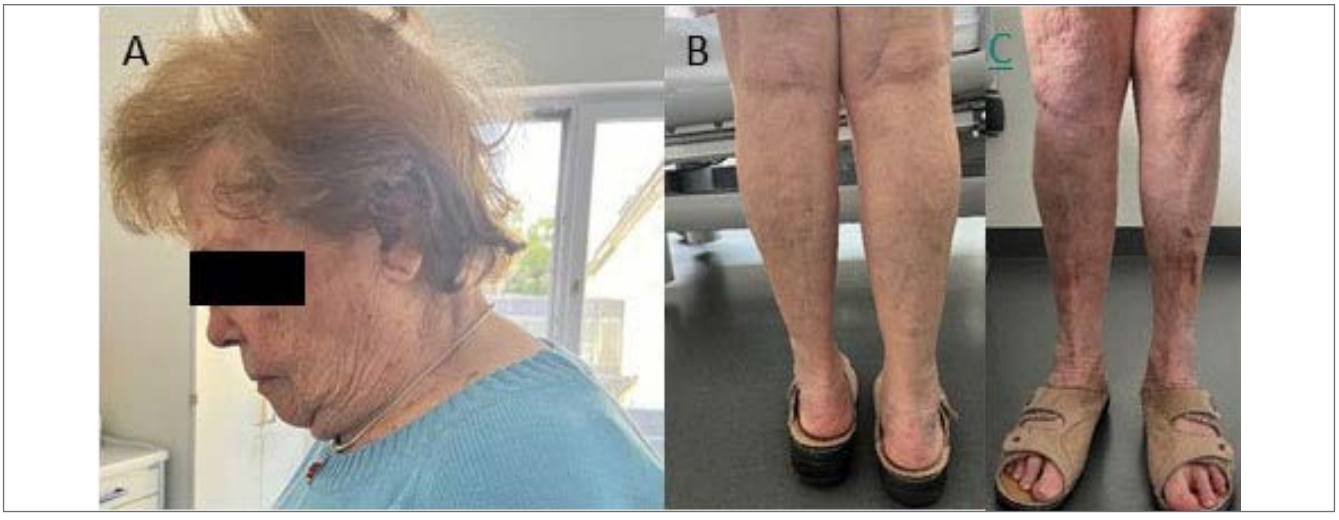


**Figure 3.** The clinical phenotype of a 91-year-old FHL1 conductor here reported presents neck rigidity with limitation of neck (and spine) flexion (A), together with medial calf hypotrophy (B, C).

genetic test was not performed on the mother. A targeted multigene panel including 29 muscle genes explored by Next Generation Sequencing detected the known c.672 C > G (p.C224W) variant in the FHL1 gene.

On neurological examination, the 91-year-old woman presented a waddling gait with a Trendelenburg sign on the left. Neck rigidity with neck

(limitations was observed (Fig. 3 A). Mild muscle weakness was present in the hip flexors, leg abductors, and medial calf hypotrophy (Fig. 3 B, C). Slight distal hypoesthesia in lower limbs was also detected.
ENG showed an axonal sensor-motor polyneuropathy prevalent in the lower limbs, and EMG showed a mixed neurogenic and myopathic pattern, especially in the gluteal region.
A hip MRI showed bilateral gluteal muscle atrophy, and a lumbar MRI showed mild neuroforamen stenosis from L4 to S1 with associated degenerative alterations. Cardiovascular evaluation showed normal results. Serum creatine kinase (CK) was at upper limits. Our clinical findings are consistent with other cases of X-linked myopathy with postural muscle atrophy (XMPMA).

## Discussion

Here, we provide the clinical picture of two patients presenting with an FHL1-associated myopathy, reporting the molecular variant c.672 C > G. Our clinical findings are consistent with other reported cases of the clinical phenotype of XMPMA. According to the literature, our patients present with a rigid spine, a frequent feature in FHL1–mutation–associated phenotypes.
Our patients reported two different clinical presentations regarding the onset age and the symptoms' nature and severity. The male patient presented an early-onset and very mild form of the disease, complaining only of a slightly decreased range of motion at his shoulders and knees without complaining of any functional limitation; conversely, our female patient reported first symptoms in her 80s, complaining of severe gait disturbance. The course is slowly progressing; our patients are still ambulant.
Our male patient had an earlier disease onset than our female patient, whose son also had an earlier disease onset, indeed in his 50s. Schessl et al., in 2008 [15], asserted that mutations in this X-linked disease act in a dominant way; however, a female patient with a given mutation would be less affected compared to a male patient with the same mutation as lyonization results in a mix of mutant and wild-type nuclear domains in female muscle.
A literature review shows that different mutations in FHL1 are associated with a broad phenotypic heterogeneity. Table II (see supplements) summarizes FHL1 gene mutations and their associated phenotypes [2-7,10-14,16,19-33].
Most patients complained about proximal upper or lower limb weakness, with contractures limiting the range of articular motion. Physical examination also revealed scapuloperoneal muscle weakness, scoliosis, contractures, a rigid spine, and a pseudo-athletic appearance. This classic XMPMA phenotype was present in our two patients and six other cases reporting the same variant, as described by Schoser and Windpassinger et al. [2,11].
Depending on the clinical phenotype, cardiac and respiratory involvement have been described. CK values range from normal to x40 of normal.
Electromyography usually shows myopathic pattern, often with an association of neurogenic signs. MRI shows hypotrophy and fatty infiltration predominantly of posterior leg muscles and the soleus muscle of the calf, with hypotrophy or hypertrophy of paraspinal muscles depending on the clinical phenotype. Histology displayed myopathic changes with FHL1 inclusions, with menadione NBT positive inclusion and cytoplasmic bodies in the cases of RBM. In addition to specific inclusions and protein aggregation, the histopathology of RBM and XMPMA, encompasses the spectrum of myofibrillar myopathies (MFM) [16].
LIM domains are cysteine-rich, double-zinc binding structures. The C224W mutation replaces a highly conserved cysteine within the fourth LIM domain of FHL1, which plays a significant role for the central binding of a Zn2+ ion [11].
The C224W mutation affects FHL1 isoforms A and B but not C. C224W probably impair the Zn2+-binding properties of FHL1A. In contrast, in FHL1B, the mutation disrupts the first nuclear localization sequence (NLS1) and thus might result in impaired FHL1B shuttling between the nucleus and cytoplasm [17]. FHL1 is considered a regulator of the family of proteins that determine muscle fiber composition in skeletal muscles (MYBPC, SRF and ERK2) [18]. Impairment in the interaction of these proteins might lead to myopathies affecting postural muscles. As a result of the different protein-binding properties of the different LIM domains in FHL1, mutations within the other domains might have different phenotypic consequences [11].
The course ranges from a severe fatal course with early onset to very mild features with late-onset [4], as in the case of our female patient. The age at which patients become wheelchair-bound is variable. The course in some early-onset patients is slow, and they remained ambulant after more than 20 years of disease [19].
The principal differential diagnosis for FHL1-associated muscle diseases includes other contractural myopathies, such as Bethlem myopathy, Emery-Dreifuss myopathies, and other rare myofibrillar myopathies. After ruling out dystrophinopathy, FHL1 gene screening should be considered for elevated CK values in males with possible X-linked inheritance [3].

## Conclusion

In summary, we describe the broad clinical phenotype and follow-up of two novel patients with XMPMA with a c.672 C > G (p.C224W) mutation in the FHL1 gene. Furthermore, by performing a literature review that shows a wide range of phenotypes associated with mutations in FHL1, we aim to help clinicians become aware of the different clinical pictures of this clinical spectrum disorder.

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### *Conflict of interest statement*

The authors declare no conflict of interest. The funders had no role in the study's design, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

### *Author contribution*

MC and BS reviewed the literature and collected the data together. Both developed and wrote the manuscript.

## *Ethical consideration*

This study was performed under the LMU Munich Ethic Board approval no. 224-0242.

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