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Case Report

The Interplay of Infection, Pain, and Locking Syndrome in LGMD-TNPO3 Related: Evidence from a Sporadic Slovakian Patient

Corrado Angelini [1] and Alicia A. Rodriguez [2]

[1] Neuromuscular Lab, Department of Neurosciences, University of Padova, 35122 Padova, Italy
[2] Department of Psychology, University of Deusto, 48007 Bilbao, Spain
* Correspondence: corrado.angelini@unipd.it

How To Cite: Angelini, C.; Rodriguez, A.A. The Interplay of Infection, Pain, and Locking Syndrome in LGMD-TNPO3 Related: Evidence from a Sporadic Slovakian Patient. *International Journal of Neuromuscular Diseases* **2026**, *1*(1), 2.

Received: 26 June 2025
Revised: 27 August 2025
Accepted: 10 September 2025
Published: 3 December 2025

Abstract: Limb-girdle muscular dystrophies (LGMDs) are a group of muscular diseases characterized by predominant proximal muscle weakness. Phenotypically, LGMD subtypes are highly variable in terms of age of onset, speed of disease progression, and overall severity; at a histopathological level, their common feature is progressive muscle degeneration with connective tissue substitution, CK elevated and degenerative changes found in Muscle MRI, although they do not share a common pathological mechanism. The incidence for all forms is 1:100,000, and LGMD are divided into two major subgroups: autosomal dominant forms (LGMD type D) and autosomal recessive (LGMD type R). We report a novel Slovakian patient with all these clinical features and entertain a hypothesis regarding the "locking" symptoms that LGMD1F/D2 patients experience.

Keywords: LGMD-D2; transportinopathy; TNPO3; quality of life

1. Introduction

Limb-girdle muscular dystrophy (LGMD) includes a group of muscular dystrophies that show proximal muscle weakness, elevated creatine kinase (CK) levels, and dystrophic changes on muscle biopsy [1]. LGMDs have an overall prevalence of approximately four to seven per 100,000 people, depending on the region. Prevalence varies greatly between subtypes and geographically [2,3]. These disorders are subdivided into autosomal dominant forms, which constitute 10% of the total, and autosomal recessive forms, which constitute 90% [4]. To date, more than 30 different genetic subtypes of LGMD have been identified [5] and are grouped according to inheritance pattern: dominant or recessive. Clinical phenotypes due to mutation in LGMD genes include severe childhood-onset forms, distal and proximal myopathies, pseudometabolic myopathies, eosinophilic myositis, and hyperaemia [6].

The onset of the disease can vary from infancy to adulthood with progressive muscle weakness. Specific parts of the muscles that are affected are the hip, pelvis, upper arm, and shoulder girdle, making walking difficult [7].

Currently, LGMD lacks curative treatment [8]. In most patients, physiotherapy and occupational therapy should be encouraged to prevent contracture formation and maximise limb use. Some patients with LGMD present with muscle cramps, and symptomatic treatment can be provided with baclofen, tizanidine, or gabapentin. In addition, genetic counselling may be helpful for those affected and their relatives [9].

Among the less frequent forms of LGMD, the autosomal dominant LGMD (LGMD-D) are a genetically heterogeneous group of myopathies presenting with progressive proximal weakness [9,10].

Within these forms, LGMD-D2, transportin 3 (TNPO3) related deficiency, is a very rare autosomal dominant myopathy, characterized by muscle fiber degeneration and progressive weakness [11]. Genetic investigation of DNA from affected subjects identified a heterozygous mutation in the termination codon of the *TNPO3* gene, which will be discussed later. The *TNPO3* gene encodes for transportin-3 (*TNPO3*), a protein that belongs to the

importin beta family and which is directly involved in protein translocation from the cytoplasm to the nucleus [12]. In particular, TNPO3 binds and transports proteins rich in serine/arginine domains (SR), and several of these SR proteins include essential splicing factors and proteins involved in mRNA splicing and metabolism [12].

This pathology has been recognized in the media for its relationship with HIV. The protein affected in this pathology, transportin 3, has been found to play a key role in the transport of HIV proteins. Transportin 3 knockdown significantly reduced cellular susceptibility to HIV infection. A similar effect was also observed in cells derived from LGMD-D2 patients [13].

A total of 32 affected individuals were initially reported, with later studies further extending the pedigree. The age of onset is highly variable, ranging from infancy (<1 year) to 58 years. Most patients experience juvenile onset before the age of 15, while others develop symptoms in their 20 s or 30 s. The disorder's penetrance has been estimated at 87% by a mean age of 47. However, some individuals who appear clinically unaffected may exhibit subclinical signs detectable by electromyography or MRI [10].

Clinically, initial muscle weakness primarily affected the proximal lower limbs and later progressed to the upper girdle, with notable involvement of the triceps. A distinctive feature was the presence of abnormally long fingers (arachnodactyly), along with weakness in the neck, axial, and limb muscles—more pronounced in flexors than extensors. A key clinical sign was the ability of patients to raise their arms horizontally while lying down, but not while standing, due to scapular winging. In cases with early onset, individuals typically became wheelchair-dependent by around age 30, whereas those with later and milder onset retained ambulation into their 60 s. Additional prominent features in the early-onset group included bulbar symptoms such as dysphagia and dysarthria, with variable involvement of distal and axial muscles among family members [14].

Early genetic investigations in a large Spanish family ruled out linkage to known LGMD loci and later pinpointed a region on chromosome *7q32.1–32.2* [15,16]. The underlying genetic mutation was not discovered until a decade later, when next-generation sequencing identified a single nucleotide deletion in the TNPO3 gene (*c.2771delA*). Additional frameshift mutations in the final coding exon of TNPO3 were later identified in two other families affected by LGMD-D2: a Swedish family with the *c.2757delC* variant and a Hungarian family with *c.2767delC*. Similar to *c.2771delA*, these mutations result in an extension of the transportin 3 protein by 15 amino acids [14,17,18]

Although large families and a few cases with these characteristics have been detected, sporadic cases have also emerged thanks to genome sequencing. This broadens the picture and justifies the need to identify new cases that help us to better understand the disease and its progression, psychosocial impact, and care needs [6,19,20].

Because of that, the aim of this paper is to present a new clinical case from Slovakia, affected by a sporadic form of TNPO3-related LGMD along with the impairment of their quality of life due to the pathology.

2. Case Report

This 31-year-old male patient from Slovakia was diagnosed with a sporadic form of TNPO3-related LGMD, carrying a heterozygous pathogenic variant *c.2686* in the TNPO3 gene and a heterozygous *c.23335* mutation in the WASHC5 gene, associated with spastic paraplegia type 8.

Clinically, he developed in the third decade a weakness compatible with LGMD syndrome; he had a Gowers' sign and difficulty walking. A detailed genetic analysis of the family showed that his parents did not carry the mutation and appeared healthy.

Evoked potentials showed in both upper and lower limbs with bilateral cortical stimulation, total and central latencies appeared normal, and findings are bilaterally symmetrical, and exclude spastic paraplegia.

This patent carried a pathogenic stop codon mutation of the *TNPO3* gene, in exon 21, that could result in a shorter protein of the terminal part of transportin-3 from exon 22.

An important clinical feature was that the patient's illnesses were frequent since, as a child had a lot of infections, and such unfortunate features persisted in adulthood. He often had sinusitis, sore throat, and frequent headaches; in addition, he complained of frequent sores in his feet, cold hands, and tiredness. It is likely that his immune system is pretty weak, but specific immune tests showed no specific disorders. There is low iron in the blood.

He was also affected by Lyme disease and had to be treated for two years with antibiotics to eradicate the Borelliosis. This treatment resulted in several gastrointestinal symptoms: for 8 years, he had daily diarrhea and/or stypsis. Lyme disease is one of the most stubborn, treatment-resistant infections in the world. It is also spreading rapidly in European countries. Recent research indicates that, in addition to tick bites, Lyme disease may be transmitted by sexual contact and bites from other insects.

Borrelia Burgdorferi, the elusive and dangerous bacterium responsible for Lyme disease, can mimic many seemingly unrelated diseases, leading to frequent misdiagnosis of the infection. It might be difficult to diagnose Lyme disease and successfully treat it. In many cases, standard antibiotic treatment fails and symptoms persist. When this occurs, Lyme disease becomes chronic, leading to indefinite suffering.

After Lyme disease, he started presenting joint and muscle pain; this last feature is unusual for patients with Lyme disease since this infection, caused by Borrelia Burgdorferi might be associated with multiple sclerosis-like signs, Bell's paralysis, and peripheral nerve involvement such as radiculitis. This patient's arthritis and joint pain might be explained, but not myalgia.

Indeed, muscle pain is an uncommon symptom for most LGMD patients. His muscle pain presented as a feeling like fibromyalgia, with a "burning sensation". He commented the following about the symptom: "It feels like when somebody has Influenza, and sometimes other times I feel in rest mode".

Often, when he moved presented a locking feeling in his hand muscles or moving thighs. This locking always worsens when he is ill. TNPO3 patients during INQoL testing often complained of locking in muscles [21]. The cause of this symptom was attributed to contractures, sometimes occurring in LGMD1F/D2 patients [22], but the present case suggests a different pathogenesis due to myalgia and infections. We propose, based on novel findings, that a series of molecular players are involved in the pathogenesis, and different mechanism(s) are involved in the pathophysiology.

The combination of in vitro and silico data supports the hypothesis that LGMD D2 is caused by several possible mechanisms likely involving nuclear transport and myofibrillar network [20]. The interplay with infection appears to be because transportin-3 directly participates in nuclear import in the infection of HIV-1, holding promise for research in drugs concerning both disorders. The TNPO3 mutation involved in LGMD/D2 represents a pathogenetic clue/ to both diseases, and this case demonstrates a clear link with frequent infections such as Lyme disease.

Such a locking sensation might be mistaken for spinal stenosis, but it instead appears to be related to LGMD-TNPO3 pathomechanisms, with altered immune status and pain likely contributing to this symptom.

This patient's report is supported by his scores on the INQoL scale, a scale aimed at measuring the quality of life in people affected by a neuromuscular disease. In this scale, we can observe those alterations associated with the neuromuscular disease that have the greatest impact on his daily life. In this sense, the domains most affected in this patient were muscle weakness, locking, muscle pain, and fatigue. Furthermore, the muscle symptoms also had a major impact on activities of daily living and on an emotional level. Scores on the INQoL can be seen in Table 1.

These results can be compared with other patients with the same diagnosis, the results of which can be seen in the article by Rodríguez et al. [19]. The results of this patient show that, compared to other patients affected by transportinopathies, this patient has greater muscle pain, fatigue, muscle weakness, and greater impairment of activities of daily living, emotional, and body image due to the disease. It is interesting to note that the symptom associated with "locking" is often seen in the present study and in that of Rodriguez et al. [19], occurring in a high percentage of patients affected by LGMD-D2.

On the other hand, the opinion of the mother as a caregiver about the impact of the disease on the patient's daily life was analyzed. The results can be seen in Table 2.

It can be observed that, in general, the mother scores higher in most domains of the INQoL, implying that the mother observes a greater impact of the disease on the affected person. In the aforementioned study, previously carried out by the authors of this study, the quality of life in patients with transportinopathies was also analyzed. On the other hand, the opinion of the mother as a caregiver about the impact of the disease on the patient's daily life was analyzed. The results can be seen in Table 2.

Below is a comparative table (Table 3) of the total score of 6 LGMD-D2 patients previously evaluated and their comparison with the current clinical case.

It can be observed in Table 3 that this patient has higher scores compared to six patients with the same diagnosis, but different mutation(s), in almost all domains except independence and impairment of social relationships. It is worth mentioning that the patient reports independence in his daily activities despite the impairments caused by the disease.

In sum, several possible mechanisms may be involved in the transportinopathy molecular pathophysiology. To elucidate the pathogenic effects of the here-described *TNPO3* mutation, studies clarifying how the various mutations affect the nuclear import/export dynamics will be required. In addition, the splicing of muscle genes, especially the interplay regulated by the *TNPO3* gene, with several molecules involved in immunity, might be useful.

Table 1. Responses on the domains of INQoL by the patient.

Muscle Weakness %	Locking %	Muscle Pain %	Fatigue %	Activities %	Independence %	Relationships %	Emotions %	Body Image %	INQoL Total Score %
73%	73%	94%	73.68%	66.66%	33.33%	41.66%	66.66%	50%	56.27%

Table 2. Responses on the domains of INQoL by the caregiver (his mother).

Muscle Weakness %	Locking %	Muscle Pain %	Fatigue %	Activities %	Independence %	Relationships %	Emotions %	Body Image %	INQoL Total Score %
89%	84.21%	100%	100%	86.60%	83.33%	56.66%	80.55%	61.11%	82.38

Table 3. Comparison between LGMD-D2 patients and case report.

Patient	Muscle Weakness	Locking	Muscle Pain	Fatigue	Activities	Independence	Relationships	Emotions	Body Image	INQoL Total Score
Total score of patients with LGMD-D2	60.52%	34.86%	23.02%	59.86%	59.86%	50.83%	52.77%	23.33%	29.16%	38.88%
Case report	73%	73%	94%	73.68%	66.66%	33.33%	41.66%	66.66%	50%	56.27%

3. Conclusions

LGMD-D2 is a rare autosomal dominant myopathy characterized by progressive proximal muscle weakness and muscle fiber degeneration. This case report of a Slovak patient with a sporadic TNPO3 mutation highlights the wide clinical variability of LGMD-D2, including muscle weakness, locking sensations, and significant muscle pain, which negatively impact quality of life.

The association between TNPO3 dysfunction and susceptibility to infections, such as Lyme disease, suggests an intriguing link between the nuclear transport protein's role in muscle pathology and immune system interactions. The patient's experience of frequent infections and persistent muscle symptoms underscores the complex interplay between genetic mutations, immune response, and disease progression.

Costa et al. [11] observed that by morphology *TNPO3* patients' muscles appeared weaker and poorly organized, with sporadic cytoplasmic aggregates positive for TNPO3; both SRSF1 and sarcomeric alpha actinin showed different expression. Careful observation of transportin 3 and related proteins in LGMD-D2 muscle biopsies suggests a possible interference in the morphology and function of the myofibrillar network by mutated TNPO3. These findings are supported by the *in silico* identification of genes involved in muscle contraction that could help to explain the pathogenic mechanisms of LGMD D2.

Quality of life assessments reveal a higher burden of symptoms in this patient compared to others with LGMD-D2, particularly in muscle pain and fatigue, emphasizing the need for personalized management strategies. Further research is necessary to elucidate the molecular mechanisms by which TNPO3 mutations disrupt nuclear import and muscle gene splicing, as well as to explore therapeutic options that address both muscle pathology and immune dysfunction in LGMD-D2.

Author Contributions

Both authors performed some of the statistical analysis, created and promoted the participant assessment tools, and wrote and approved the final manuscript.

Funding

This research received no external funding

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Deusto (Ref: ETK-39/18-19).

Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement

The datasets generated and/or analysed during the current study are not publicly available because they belong to the University of Deusto, but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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