Dear Editor,

A missense mutation in the laminin α-5 subunit (LAMA5) gene (c.9418G>A p.V3140M) has recently been identified on chromosome 20q13.2-q13.3 in a three-generation Italian family (Sampaolo et al., 2017). Laminins are structural components of the basal membrane that play a central role in the complex interaction with cell surface constituents (Kierszenbaum et al., 2012). Gene mutations in different laminin chains might have severe negative effects, even incompatible with survival, such as Alport syndrome, epidermolysis bullosa, and muscular dystrophies (Guldager Kring Rasmussen and Karsdal, 2016).

However, to the best of our knowledge, there is still no evidence of muscle weakness, impaired balance and gait, or bone health involvement in patients with mutations in the laminin α gene (LAMA), except for those with a merosin deficiency (Helbling-Leclerc et al., 1995).

We therefore investigated musculoskeletal impairment and functional limitations in a 59-year-old woman affected by a multisystem syndrome due to a missense mutation in LAMA5 (c.9418G>A p.V3140M) on chromosome 20q13.2-q13.3, referred to our rehabilitation unit for patients affected by musculoskeletal and neuromuscular diseases. The patient, with a personal history of sensorimotor polyneuropathy, coagulopathy, degenerative retinopathy, thyroiditis and small airways obstruction syndrome, reported diffuse myalgia, joint pain, and impaired balance and gait performance, which had worsened in the last six months.

We assessed the patient, according to a specific protocol, comprising three sections: ‘Section A – Muscle impairments’ included the following outcomes: 1A) passive range of motion (pROM), to evaluate joint mobility; 2A) Manual Muscle Testing (MMT), to assess muscle strength; 3A) Tinetti Performance Oriented Mobility Assessment (POMA), to evaluate balance and gait performance, and the risk of falls; ‘Section B – Functional limitations’: 1B) Functional Ambulation Classification (FAC), to assess ambulation ability; 2B) Functional Independence Measure (FIM), to evaluate patient disability; 3B) Fatigue Severity Scale (FSS), to measure perceived fatigue; ‘Section C – Bone health’: 1C) serum and urinary bone biomarkers; 2C) bone mineral density and Vertebral Fracture Assessment by Dual-energy X-ray Absorptiometry; 3C) bone microarchitecture, through the Trabecular Bone Score (TBS).

On physical examination of the patient, we found no limitations in pROM in any of the appendicular joints; muscle strength was slightly impaired in the shoulder rotators, elbow and wrist flexors, ankle flexors, and extensor hallucis longus (MMT=4/5), bilaterally. The patient could get out of a chair or bed and use the toilet independently. She had a high risk of falling (POMA score =11) (Raîche et al., 2000), requiring manual contact (continuous or intermittent) in ambulation (FAC=3) (Holden et al., 1986).

Moreover, her FIM score (96/126) indicated a moderate level of independence in activities of daily living (ADLs) and FSS results (54/63) showed a moderate level of perceived fatigue (Armutlu et al., 2007).

Furthermore, the results of her bone metabolism tests were: serum calcium 9.4 mg/dL, urinary calcium 143.5 mg/24h, serum parathyroid hormone 33.7 pg/mL, serum alkaline phosphatase 87 U/L, and serum 25-hydroxyvitamin D₃ [25(OH)D₃] 22.1 ng/mL, the latter a level considered to constitute vitamin D insufficiency, according to the Endocrine Society (Holick et al., 2011). The patient, already receiving alendronate, had severe osteoporosis (lumbar spine T-score = -3.1 SD) with mild wedges in the T8 and T9 and moderate wedges in the T10 and T11 vertebrae and altered bone microarchitecture (TBS = 1.119).

These data suggest worse bone health rather than muscle impairment, probably linked to pathogenic mechanisms directly related to bone damage and independent of the muscle involvement.

In particular, our multidisciplinary patient-tailored approach included physical therapy three times a week (each session lasting 60 minutes), with dynamic and isometric strengthening exercises and low-intensity aerobic training, and hydrotherapy (twice a week) that further improves proprioceptive skills.

Considering the patient’s severe osteoporosis and the poor tolerance of alendronate, we prescribed subcutaneous denosumab (60 mg/every 6 months), calcium carbonate (1000 mg/day) and cholecalciferol (800 IU/day); indeed an adequate vitamin D status is mandatory in myopathic patients, because of the relationship between vitamin D deficiency and poor muscle function (Iolascon et al., 2015; Iolascon et al., 2017 a, b).

Although it is well known that muscle weakness and low physical performance are key issues in patients affected by myopathies, the role of specific therapeutic exercise, such as the practice of eccentric exercises (Kilmer et al., 1994; Philips and Mastaglia, 2000), is still not clear.
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A recent Cochrane systematic review demonstrated the safety of moderate-intensity muscle strengthening training in progressive myopathies, although insufficient evidence supports its effectiveness in improving dynamic strength and aerobic capacity (VO2 max) (Voet et al., 2013).

Moreover, considering that physical activity could exert beneficial effects in both muscle and bone tissues, it has a key role in the management of myopathic patients.

Myopathic patients have been found to show a high risk of falling, independently of their skeletal fragility and so balance exercises are highly recommended in this population, as well as in osteoporotic patients (Armstrong et al., 2016). Mutation of LAMA5 causes a heterogeneous syndrome in which there is not only bone involvement, but also musculoskeletal impairment and functional limitations in ADLs.

In our opinion, in clinical practice a comprehensive and multidisciplinary evaluation of musculoskeletal health status and adequate pharmacological and rehabilitation treatments are mandatory in patients affected by mutation of LAMA5 in order to improve their functioning and their quality of life.

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References