

Severe progressive respiratory involvement requiring ventilator support in autosomal recessive Bethlem myopathy. A case report

Anna Annunziata, Gerardo Langella, Rosa Cauteruccio, Luigi Fiorentino, Giuseppe Fiorentino

Unit of "Malattie, Fisiopatologia e Riabilitazione dell'Apparato Respiratorio", V. Monaldi Hospital, Naples, Italy

Bethlem myopathy (BM) was first described in 1976 by Bethlem and van Wijngaarden in patients who presented a myopathy characterized by slowly progressive muscle weakness and typical flexion contractures of the long finger flexors, wrists, elbows, pectoralis muscles and ankles. Patients with Bethlem myopathy usually become symptomatic during the first or second decade of life. The condition is in most cases slowly progressive and more than two thirds of patients over 50 years of age may require aids for ambulation. Inheritance is usually autosomal dominant. However, patients with autosomal recessive (AR) BM have been recently reported in Literature. Cardiac involvement is usually absent. Respiratory muscle involvement necessitating nocturnal respiratory support is rarely reported in association with severe weakness later in life. We describe a further case of ARBM in a 52-year-old man who presented a slowly progressive myopathy but developed a severe progressive respiratory involvement requiring ventilatory support.

Key words: Bethlem Myopathy, autosomal recessive, respiratory involvement, non invasive ventilation

Received: October 2 2024
Accepted: December 12, 2024

Correspondence

Anna Annunziata
E-mail: anna.annunziata@gmail.com

How to cite this article: Annunziata A, Langella G, Cauteruccio R, et al. Severe progressive respiratory involvement requiring ventilator support in autosomal recessive Bethlem myopathy. A case report Acta Myol 2024;43:149-152. <https://doi.org/10.36185/2532-1900-654>

© Gaetano Conte Academy - Mediterranean Society of Myology



OPEN ACCESS

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>

Introduction

Bethlem myopathy (BM) was first described in 1976 by Bethlem and van Wijngaarden in twenty-eight patients from three Dutch families, who presented a myopathy characterized by slowly progressive muscle weakness and typical flexion contractures of the long finger flexors, wrists, elbows, pectoralis muscles and ankles, as well as of the spine ¹.

Patients with Bethlem myopathy usually become symptomatic during the first or second decade of life although hypotonia in infancy can also be seen ^{1,2}. The condition is in most cases slowly progressive and more than two thirds of patients over 50 years of age may require aids for ambulation, especially outdoors.

BM represents the initial form of the wide spectrum of collagen VI-associated myopathies. In majority of patients, the phenotype is caused by mutations in one of the three genes coding for collagen type VI, located on chromosome 21 (COL6A1 and COL6A2) as well as on chromosome 2 (COL6A3) ². The pattern of inheritance is usually autosomal dominant ^{2,3}. However, recently cases of patients with autosomal recessive (AR) inheritance have been reported in Literature ^{4,5}.

Cardiac involvement is usually absent⁶, as well as respiratory muscles and especially diaphragmatic involvement necessitating nocturnal respiratory support is rarely reported in association with severe weakness later in life ^{6,7}.

We describe a case of autosomal recessive Bethlem myopathy in a 52-year-old Italian man born to consanguineous parents, who presented a slowly progressive myopathy but developed a severe progressive respiratory involvement requiring ventilatory support.

Case description

A 52-year-old patient, born to consanguineous parents first-degree related, who is affected by autosomal recessive Bethlem myopathy (BM), with onset of the disease at 12 years of age.

At the first examination at the Cardiology and Genetics Service of the Luigi Vanvitelli University Hospital in Naples - October 1988 - his mother reported having noticed slight difficulties in walking, defined as awkward and with a tendency to stumble, since the age of six. Due to the worsening of the symptoms he had to stop sporting activity shortly after. At the time, he complained of difficulty climbing stairs and weakness of the right upper limb, cramps and myalgia after exercise and the appearance of fasciculations. The physical examination showed evidence of Gowers' sign when rising from the floor, difficulty in adduction of the upper limbs, a tendency to wing scapula, and elbow contractures. CK values were 2.78 time the up-

per normal limits. Heart and respiratory apparatus were normal. The Forced Ventilatory Capacity (FVC) was 2200 ml.

In August of the same year, the patient had been admitted to the San Raffaele Hospital in Milan, where he underwent a needle biopsy that showed a muscle picture compatible with muscular dystrophy. CreatinKinase (CK) values were four time the upper normal limits. He was discharged with a diagnosis of Emery-Dreifuss Muscular Dystrophy. The diagnosis of Bethlem Myopathy was achieved many years later by the Next Generation Sequencing (NGS) analysis which identified the homozygous variant c.2060T > C (p.Phe687Ser) in exon 26 of the COL6A2 gene, inherited from both parents.

Clinical assessments, including cardiac and pulmonary follow-up were performed once a year. Cardiac parameters were always within the normal limits. The trend of FVC, both in percentage and in absolute values, recorded during the period of the long follow-up is shown in Figure 1.

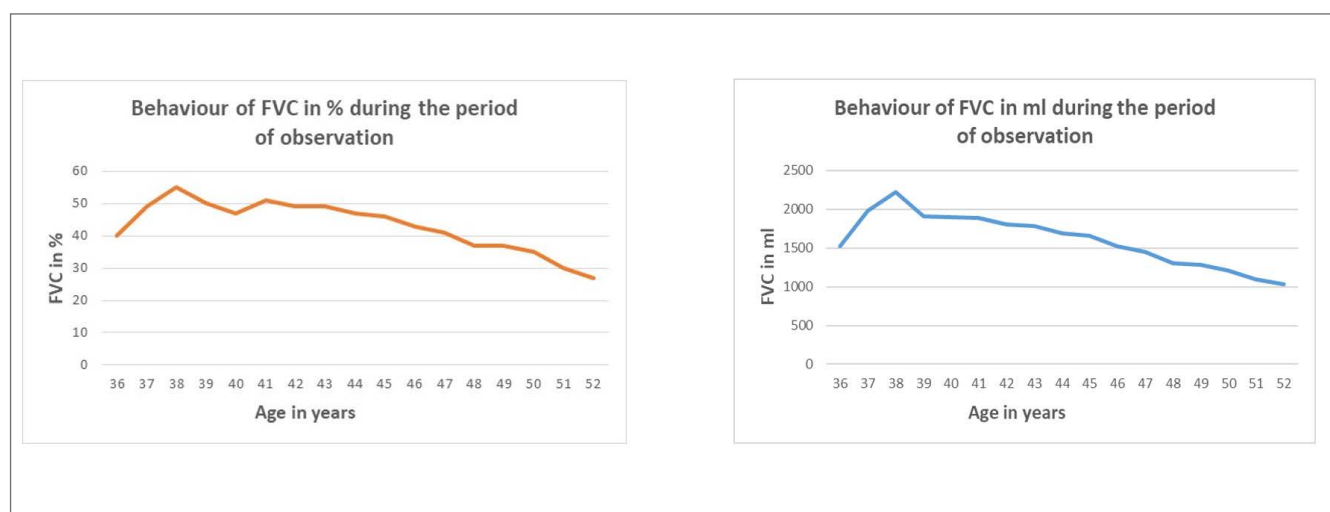


Figure 1. Behaviour of respiratory function in the sixteen years of follow-up. Left: FVC in percentage; Right: FVC in ml.

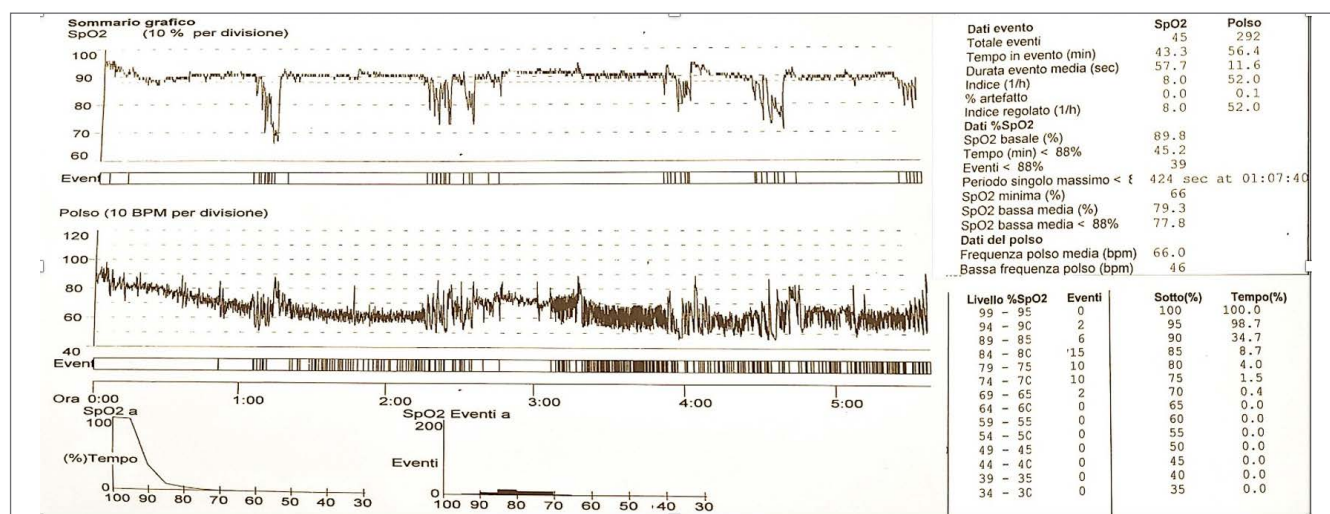


Figure 2. Nighttime oximetry monitoring

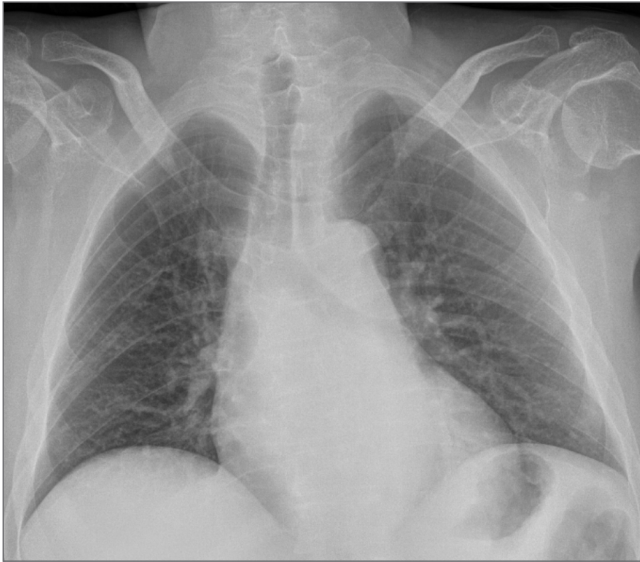


Figure 3. Chest X-ray showed normal-expanded costophrenic sinuses.

Daytime functional assessment showed FVC 1030 ml (30%), FEV1 750 ml (27%), PEF 1170 ml (27%). Arterial blood gas analysis documented compensated respiratory acidosis with pH 7.38, pCO₂ 47 mmHg, pO₂ 66 mmHg, HCO₃ 29 mmol. Nocturnal oximetry monitoring documented the presence of phasic and tonic desaturations with an increase in CO₂ upon awakening (56 mmHg) and respiratory acidosis (Fig. 2). Subsequent cardiorespiratory monitoring confirmed nocturnal hypoventilation.

Cardiological evaluation confirmed the normal function of the heart. DDimer (283 ng/mL; n.v. < 500) and proBnp (15 pg/mL; n.v. 0-125) were within the normal limits as well as the blood chemistry tests.

Chest X-ray showed no lesions of thickening of the lung parenchyma, normal-expanded costo-phrenic sinuses, hemi-diaphragms within the normal limits.

Abdomen CT documented severe atrophy with adipose involution of the muscles of the anterior abdominal wall, psoas and gluteus, which were included in the study volume.

The patient underwent several attempts at non-invasive mechanical ventilation initially during the day and then at night, monitoring the normalization of the nocturnal saturation, the blood gas parameters upon awakening, and the symptoms.

Discussion

Clinical manifestations of BM are quite variable, ranging from a very mild and slowly progressive myopathy to a severe phenotype with contractures at birth including torticollis, neonatal hypotonia, or slightly delayed motor milestones. Although many children exhibit neuromuscular features in the first 2 years of life, most patients do not become fully symptomatic until they are 5 years old². Contractures during childhood are dynamic in nature and worsen slightly in terms of weakness, often leading to relative recovery during puberty. Except for contractures, many patients are almost asymptomatic during early adult life. From middle age onwards, slow deterioration

becomes evident to a certain level which is sufficient to justify various aids, facilities and wheelchairs in most elderly patients².

Walking is usually possible until adulthood; however, two-thirds of patients require walking aid by age 60^{2,3}. Pulmonary function decline is variable and does not occur until adulthood^{6,7}. In Bethlem myopathy, respiratory muscle involvement is thought to be uncommon^{6,7}. Haq et al.⁸ in 1999 first reported a patient with autosomal dominant Bethlem myopathy who demonstrated childhood onset, slowly progressive limb-girdle muscle weakness, contractures, and progressive respiratory compromise. Chest x-ray, pulmonary function tests, and electrophysiologic studies suggested respiratory muscle involvement. Luisa Panades-de Oliveira et al.⁹ described only two patients out of 16 with Bethlem myopathy in treatment with non-invasive mechanical ventilation. These patients had their first symptoms at birth with a clinical presentation of "floppy infant".

In the group of 28 Brazilian patients with collagen VI-related dystrophies, described by Zanoteli et al.¹⁰, seven (25%) had the BM phenotype, and presented neonatal manifestations; however, all of them had normal motor development and normal pulmonary function.

Seven (16%) out of 43 patients with BM reported by Van der Kooi et al.⁶ had a forced vital capacity less than 70% of the predicted value. One of two patients with a forced vital capacity less than 50% was also receiving respiratory support. All patients with compromised respiratory function were still ambulatory, and there was no significant correlation between the severity of arm weakness and the severity of respiratory muscle involvement. They concluded that pulmonary involvement, although rare, is part of the clinical spectrum of BM, especially in patients with severe muscle impairment and nocturnal respiratory disorders.

In the group of 145 patients with Collagen VI – related myopathies reported by Foley et al.⁷, only those categorized as "intermediate", unable to hop or run, showed a cumulative decline of FVC of 2.3% per year.

The natural history of lung capacity in our patient with autosomal recessive BM can be assimilated to Foley's "intermediate" group one. In fact, his respiratory function has undergone a constant and progressive decline starting from the age of 43, while the weakness of the girdle muscles has slowly progressed, being able to still walk independently even if with compensatory manoeuvres. At the time of re-evaluation for the onset of respiratory symptoms, he presented a FVC 1030 mL (30%), FEV1 750 mL (27%) indicating a severe restrictive syndrome, associated with nocturnal hypoventilation together with phasic desaturations and hypercapnia upon awakening. However, the beginning of respiratory support allowed the restoration of the normal gas analysis values and the normalization of the nocturnal respiratory profile.

According to our knowledge, this is the first report of respiratory dysfunction in a patient with autosomal recessive Bethlem Myopathy, supporting the occurrence of respiratory dysfunction in patients with Collagen VI-related myopathies.

We suggest that a regular monitoring of respiratory parameters and sleep studies should be recommended in these patients, even if they are still ambulant. In our opinion, respiratory involvement, although described in a low percentage of cases of BM, should be carefully evaluated because it can affect the quality of life and the prognosis of the patient.

Acknowledgements

We thank Professor Luisa Politano for her support and above all for her dedication to patients suffering from neuromuscular disorders.

Conflict of interest statement

The Authors declare no conflict of interest.

Funding

None.

Authors' contributions

A.A.: conceptualization, data collection, data analysis, writing, revision; G.L.: data collection, conceptualization, revision; L.F.: data collection; R.C.: writing, revision; G.F.: data analysis, revision. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

The authors obtained consensus to publish data and photo

References

- 1 Bethlem J, Wijngaarden GK. Benign myopathy, with autosomal dominant inheritance. A report on three pedigrees. *Brain*. 1976 Mar; 99(1):91-100. <https://doi.org/10.1093/brain/99.1.91>.
- 2 Jöbsis GJ, Boers JM, Barth PG, et al. Bethlem myopathy: a slowly progressive congenital muscular dystrophy with contractures. *Brain* 1999;122:649–655. <https://doi.org/10.1093/brain/122.4.649>
- 3 Kwong AK, Zhang Y, Ho RS, et al. Collagen VI-related myopathies: clinical variability, phenotype-genotype correlation and exploratory transcriptome study. *Neuromuscul Disord*. 2023 May;33(5):371-381. <https://doi.org/10.1016/j.nmd.2023.03.003>.
- 4 Foley AR, Hu Y, Zou Y, et al. Autosomal recessive inheritance of classic Bethlem myopathy. *Neuromuscul Disord*. 2009 Dec;19(12):813-817. <https://doi.org/10.1016/j.nmd.2009.09.010>.
- 5 Caria F, Cescon M, Gualandi F, et al. Autosomal recessive Bethlem myopathy: A clinical, genetic and functional study. *Neuromuscul Disord*. 2019 Sep; 29(9):657-663. <https://doi.org/10.1016/j.nmd.2019.07.007>.
- 6 van der Kooi AJ, de Voogt WG, Bertini E, et al. Cardiac and pulmonary investigations in Bethlem myopathy. *Arch Neurol*. 2006; 63(11):1617-1621. <https://doi.org/10.1001/archneur.63.11.1617>
- 7 Foley AR, Quijano-Roy S, Collins J, et al. Natural history of pulmonary function in Collagen VI-related myopathies. *Brain* 2013;136:3625-33. <https://doi.org/10.1093/brain/awt284>.
- 8 Haq RU, Speer MC, Chu ML, et al. Respiratory muscle involvement in Bethlem myopathy. *Neurology*. 1999;52(1):174-176. <https://doi.org/10.1212/wnl.52.1.174>
- 9 Panadés-de Oliveira L, Rodríguez-López C, Cantero Montenegro D, et al. Bethlem myopathy: a series of 16 patients and description of seven new associated mutations. *J Neurol*. 2019; 266(4): 934-941. <https://doi.org/10.1007/s00415-019-09217-z>
- 10 Zanoteli E, Soares PS, Silva AMSD, et al. Clinical features of collagen VI-related dystrophies: A large Brazilian cohort. *Clin Neurol Neurosurg*. 2020; 192:105734. <https://doi.org/10.1016/j.clineuro.2020.105734>