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Congenital tubular aggregates myopathy associated with central nervous system involvement: description of a case

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Tubular aggregate myopathy is a rare neuromuscular condition associated with the presence of myofibers protein accumulations, in the form of dense tubular aggregates. Clinically it is characterized by proximal muscular weakness, exercise-induced cramps, myalgias, and ocular features such as ophthalmoplegia and pupillary abnormalities. The involvement of the central nervous system is rare and not completely elucidated. Variants in *STIM1*, *ORAI1*, *CASQ1* genes are frequently associated with tubular aggregate myopathy. Here we describe a 35-year-old man who presented neonatal hypotonia, motor delay, seizures, and sensorineural hearing loss. During a SARS-CoV-2 infection at the age of 35, he developed myoclonus, encephalopathy, and marked muscular weakness. A deltoid muscle biopsy revealed the presence of tubular aggregates. Genetic analyses including a Whole Genome sequencing failed to reveal a genetic cause. In conclusion, we enlarge the clinical spectrum of tubular aggregate myopathy associated with central nervous system involvement.

Key words: tubular aggregates, myopathy, myoclonus, epilepsy, sensorineural deafness

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Introduction

Tubular aggregates (TA) are clusters of protein aggregates found in muscle fibres in the form of membrane tubules, with a typical appearance in electron microscopy [1]. TA are not pathognomonic of a specific disease, they can be found in various neuromuscular disorders such as periodic paralysis, paramyotonia, alcoholic myopathy, metabolic myopathies, muscular dystrophies, and congenital myasthenic syndromes. The pathophysiological mechanisms leading to their formation and accumulation are not fully elucidated [2,3]. Tubular aggregates myopathy (TAM) has been associated with variants in the *STIM1, ORAI1, CASQ1,* and more rarely in other genes [4]. The clinical phenotype is variable, from cramps and myalgias induced by exercise to progressive muscle weakness, as well as ophthalmoparesis and miosis. A central nervous system involvement has been reported in few cases, in form of seizures, or sensorineural hearing loss, in both genetically confirmed and unsolved cases [5,6]. In other patients a severe congenital muscle weakness and epileptic encephalopathy have been described associated with the presence of cylindrical spirals (CSs), protein aggregates that share morphological similarities with tubular aggregates. For this reason, a common origin of TA and CSs has been proposed [7].

Here we describe the clinical, laboratory, imaging and myopathologic features of a man presenting with hypotonia at birth, childhood onset reduced exercise tolerance, scoliosis, seizures, hearing loss and abundant TA in muscle biopsy.

Case report

P1 is a 35-year-old man born to healthy non-consanguineous parents from Cameron, without family history of neuromuscular disorders. He has a 5-years-old son suffering from autism spectrum disorder but with normal motor development.

Clinical history of P1 started at birth with muscular hypotonia, followed by delayed motor milestones. During his childhood he presented episodes of generalized tonic-clonic seizures that spontaneously disappeared at the age of 14 years. Two years later a sensorineural deafness was diagnosed and treated with prothesis. Along his infancy he started to present cramps and myalgias induced by exercise associated to an abnormal gait with hyperlordosis, and progressive scoliosis. A spinal fusion was performed at 22 years. At 35 years he contracted a SARS-CoV-2, manifesting with fever and myalgias. Seven days later, he developed proximo-distal muscle weakness, with difficulty getting up from the lying position, myoclonus of the right arm, and dysphagia. At ten days, he showed dyspnoea and reduced oxygen saturation, requiring hospitalization. Chest CT-SCAN confirmed the presence of SARS-CoV-2 pneumopathy that rapidly improved with non-invasive ventilation (NIV) and oxygen therapy. During his stay in ICU he had generalized tonic-clonic seizures, successfully treated with Levetiracetam at 1500 mg/daily.

Clinical examination upon arrival in the Neurology department revealed mild delirium, generalized asynchronous positive and negative myoclonic jerks, prominent in the right upper limb, intention tremor, dysphagia, dysarthria. He had decreased deep tendon reflexes and *hypopallesthesia* in lower limbs. Four days after admission, the patient's clinical condition improved dramatically.

Physical examination in our neuromuscular center showed, high-arched palate, asymmetrical amyotrophy of the *pectoralis* muscles, asymmetrical scapular winging, hyperlordosis, bilateral atrophy of *tibialis anterior* muscles and *valgus* feet (Fig. 1). Manual muscle testing revealed a mild proximal and asymmetric muscular weakness with deficit in arm elevation, and first interosseous muscular weakness quoting 4/5 MRC on left side. He also showed mild axial involvement with hyperlordosis and prominent abdomen. CNS involvement remained stable with the persistence of mild myoclonus in upper limbs; no other episodes of seizure were noticed during three years of follow-up under therapy with Levetiracetam 1000 mg daily.

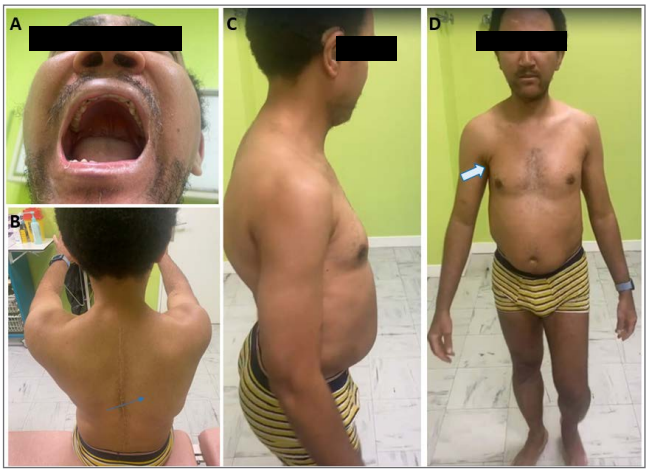

Figure 1. Clinical feature. A) High palate. B) Asymmetric *scapula alata* (thin arrow) and scar secondary to arthrodesis. C) Prominent abdomen and lumbar hyperlordosis. D) Asymmetric appearance of the pectoral muscles (thick arrow).

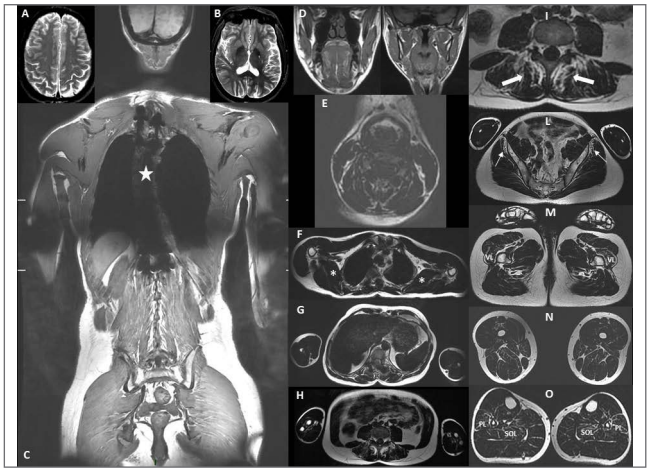

Figure 2. Whole body MRI. Whole body MRI T2 ideal 1, images on frontal (C,D) and axial (A,B,E-O) planes. Absence of pathological areas of hypersignal in brain axial images (A,B). C) Frontal plane, showing thoracic arthrodesis between T2 and T12 (star). D,E) Absence of involvement in cranio-cervical muscles. F) Normal appearance of *subscapularis* (*). G-I) *erector spinae* muscles showing moderate fatty infiltration at lumbar level (thick arrow). L) bilateral involvement of *gluteus minimus* (thin arrow) at pelvic girdle. M-O) Lower limb muscle MRI reveals mild grey striations more evident at *vastus lateralis* (VL), *soleus* (SOL) and *peroneus longus* (PL) without any specific pattern.

Laboratory work-up revealed elevates serum Creatin Kinases at 620 UI/L (normal values: < 250), increased lactates 2,55 mmol/l (normal values: 0.5-2.2 mmol/L) and pyruvate at 2,95 mg/dl (normal values: 0;3-0.9 mg/dl) with a lactates-pyruvate ratio at 16 (normal values: 6-14). EEG was normal. EMG showed a neurogenic pattern compatible with L4-L5 radicular involvement. Brain MRI was unremarkable (Fig. 2). Whole body muscle MRI showed moderate bilateral fatty infiltration in the *erector spinae* muscles at lumbar level and in *gluteus minimus* with mild grey striations of lower limb muscles without any specific pattern (Fig. 2). Cardiac and respiratory assessment were normal. A deltoid muscle biopsy was performed at 35 years. With haematoxylin and eosin (H&E) there were well delimited cytoplasmic and subsarcolemmal eosinophilic areas the stained intensively with the modified Gömöri trichrome (mGT). These aggregates were composed of rounded subunits and reacted strongly with the NADH-TR (Fig. 3C), while appeared devoid of oxidative reaction with the SDH (Fig. 3D) histoenzymatic reaction, thus confirming their sarco-tubular origin. Electron microscopy showed the presence of variably oriented

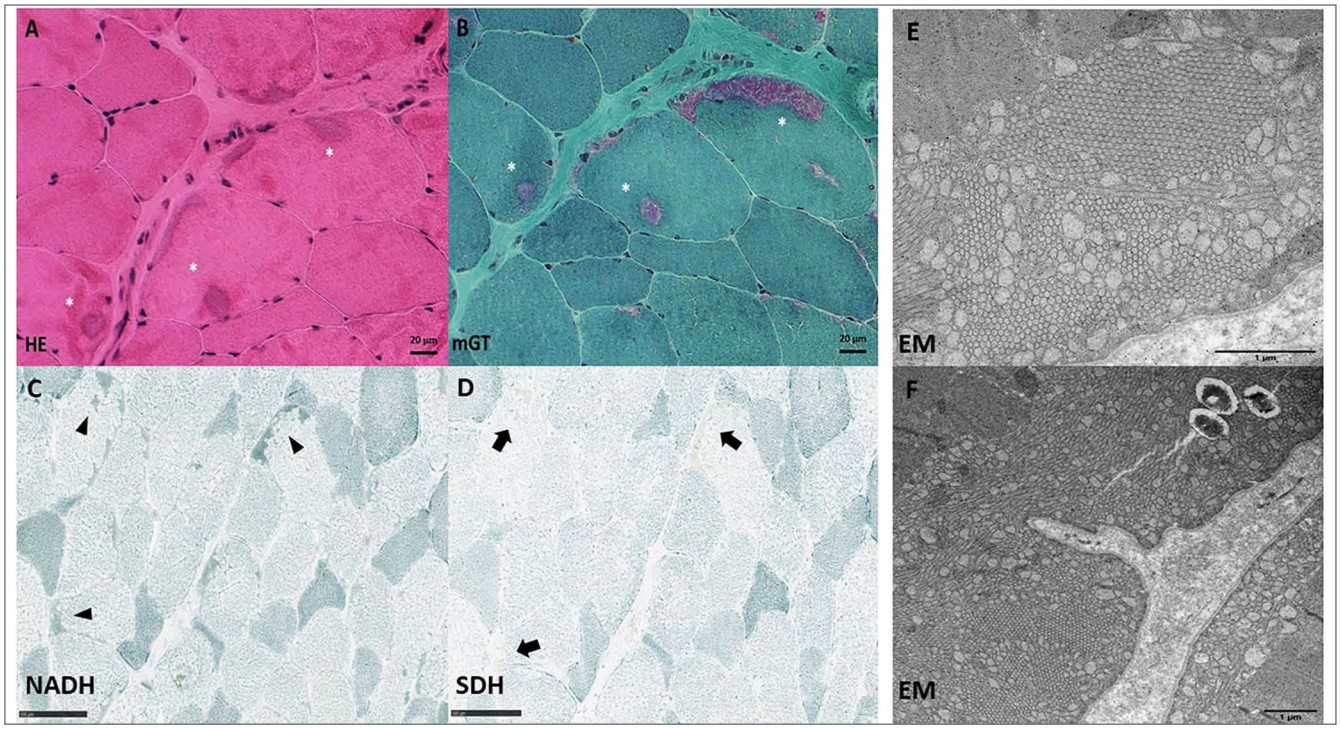

Figure 3. Muscle biopsy. A) HE shows some myocytes (*) with subsarcolemmal basophilic aggregates, which correspond to reddish granular aggregates in mGT B). These aggregates are blue-stained (arrowhead) in NADH (C) and remain unstained (arrow) with SDH (D). Electron microscopy displays the presence of subsarcolemmal tubular aggregates parallel oriented near the myofibers (E) and with the typical appearance densely organized in cross section (F).

and tightly packed tubules with a coaxial hyperintense density corresponding to tubular aggregates (Fig. 3E,3F).

P1 underwent various genetic studies after giving informed consent. Genetic analysis for SCA 1, 2, 3, 6, 7, 17, 19, Friedreich Ataxia, and Niemann-Pick disease, *EFB3*, and a panel of 500 genes linked to intellectual impairment were negative. A panel of 234 genes associated with neuromuscular disease [8], including *STIM1*, *ORAI1 and CASQ1* returned negative, as well as a panel including mitochondrial DNA and 38 nuclear genes associated with mitochondrial diseases. Eventually, a whole genome sequencing performed together with the DNA of P1's healthy mother, failed to reveal genetic hits potentially responsible for his condition.

Discussion

TAM present a large phenotypic spectrum from asymptomatic patients to progressive muscle weakness [4], with the presence of TA in muscle fibres as the hallmark of the disease. TA represent abnormal accumulations of densely packed tubules found preferentially in type II skeletal muscle fibres [9]. They contain proteins involved in calcium (Ca2+) uptake, storage and release, such as calsequestrin, sarcalumenin, triadin, STIM1, SERCA1, and RYR1; they originate from the sarcoplasmic reticulum, but the pathophysiological mechanism is still unknown. The histochemical characteristics are more constant. Tubular aggregates are subsarcolemmal deposits that stain bright red with modified Gömöri trichrome (mGT), and blue with nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR). In contrast they do not react with succinate dehydrogenase (SDH) or cytochrome *C* oxidase (COX) [1].

Their appearance on electron microscopy is variable, with different shapes, sizes, and orientation of the tubules with respect to the muscle fibres. TA displace the myofibrils [1].

Genetically determined TAM is often linked to heterozygous mutations of *STIM1* and *ORAI1* among the most frequent genes [10,11]. *STIM1* gene encodes STIM1, a calcium sensor located in the sarcoplasmic reticulum, which activates the ORAI1 calcium channel causing the entry of extracellular calcium by a store-operated calcium entry (SOCE) mechanism; mutations in these genes cause SOCE hyperactivity, due to an alteration in the activation of STIM1 or in the permeability of ORAI1, which would generate an excessive entry of calcium, with impairment of calcium homeostasis [12]. TAM have autosomal dominant and recessive inheritance, and recently have been associated to other variants in *CASQ1, RYR1, PGAM2, SCN4A* and *ALG14* genes [13]. TA in muscle can be associated with other paraclinical features such as the presence of thrombocytopenia, mild bleeding tendency and functional or congenital asplenism. In *STIM1* gain of function related TAM, the thrombocytopenia is probably linked to excessive platelet activation and consumption [14].

However, in some cases the underlying genetic cause of TAM remain unsolved as in our patient.

P1's muscular phenotype is characterized by exercise intolerance with appearance of myalgias and cramps and it is consistent with phenotypic variability of TAM ranging from myalgias, cramps, progressive proximal muscle weakness and myasthenic features, to asymptomatic patients [4].

P1 revealed a sensorineural deafness in young age as reported in other rare cases of pathogenic variants in *STIM1* suggesting that hearing loss may be due to altered calcium homeostasis in the organ of Corti [6]. History of seizure in TAM is reported in only few cases [5] and is not totally understood but probably linked to the key role of calcium in the transmission of excitatory signals in central nervous system; brain-specific *ORAI1* and *STIM1* knockout (KO) mice are described to present stronger and higher chemoconvulsant-induced mortality compared with wild type [15]. Nevertheless, we failed to find pathogenic *STIM1* and *ORAI1* variants. SARS-CoV-2 infection could probably play a key-role as a trigger in the worsening of muscular symptoms and the occurrence of seizures is probably facilitated by the hypoxia induced by the SARS-CoV-2 pneumonia. Muscle MRI in TAM usually shows fibro-fatty replacement of *subscapularis* with sparing of *trapezius* in the upper limb. In lower limb greater involvement of the *semimembranosus*, *semitendinosus*, medial and lateral *gastrocnemius* and long head of the *biceps femoris* muscles, while the anterior compartment is usually preserved [16]. In our patient we found a mild bilateral fibro-fatty replacement of *gluteus minimus* and the *erector spinae* muscles at lumbar level (Fig. 2).
Here we report the case of a patient with a mild myopathy with a long history of childhood onset seizures. He developed epileptic myoclonus following a SARS-CoV-2 infection, and a muscle biopsy revealed the presence of TA. Extensive studies failed to determine the genetic origin of this condition. In conclusion we enlarge the phenotypic spectrum of TA myopathy with central nervous system involvement.

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Conflict of interest statement

The Authors declare no conflict of interest

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Author contributions

GB, GS: collected clinical data and drafted the manuscript; CV, RYC: collected genetic and muscle imaging data; ED: planned the study, revised and submitted the manuscript

Ethical consideration

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by local Ethics Committee (DC-2012-1535 and AC-2012-1536). Informed consent was obtained from the patient.

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