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Review article

Clinical features of spinal muscular atrophy (SMA) type 3 (Kugelberg-Welander disease)

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A B S T R A C T

Spinal muscular atrophy type 3 (SMA3), also called Kugelberg-Welander SMA, typically presents with muscle fatigue, slowly progressive weakness and atrophy of lower limbs once they have already acquired independent ambulation. Visceral involvement frequent in type 1 and 2 subtypes is rare in SMA3. Hypotonia, hyperlaxity and absent osteo-tendinous reflexes are typical features. By definition, standing or walking without support is achieved but the vast majority of SMA3 patients lose ambulation with time. Lifespan is normal. In some classifications, an additional subtype is included in the mild end of the spectrum, namely spinal muscular atrophy type 4 (SMA4). In this rare subtype, symptoms begin in adulthood; patients remain ambulatory at least until the fifth decade and have a normal respiratory function. Molecular genetic testing is the gold standard tool for diagnosis of SMA. However, diagnosis in a child affected with SMA3 is often challenging because clinical presentation mimics a muscular dystrophy. Electrodiagnostic studies and muscle biopsy are useful tools for demonstrating the presence of denervation but sometimes may not show meaningful differences to help distinguish between SMA and myopathy. Recent specific therapies show promising results before severe neuronal degeneration and motor dysfunction is installed. Therefore, high suspicion should be maintained and genetic analysis performed early in the diagnostic process when facing patients with symmetric and prominent proximal weakness, especially if they present progressive motor impairment.

1. Introduction

Spinal muscular atrophy type 3 is also called Kugelberg-Welander SMA, due to its description by these authors in 1956. They reported a "pseudomyopathic" form of spinal muscular atrophy with onset between 2 and 17 years [1], which several decades later was genetically related to the 5q proximal SMA and confirmed to be the end of the spectrum of this disease in the pediatric age. More recently, the term 'walkers' has been proposed because patients present their first symptoms once they have already acquired independent ambulation [2]. Course is slow but, as in the other more severe forms, continuous progression is observed [3,4]. SMA3 is less frequent than earlier forms (<15%) [5].

In the continuum of type 1, type 2 and type 3, an additional subtype included in current classifications, among the pediatric age, is type 4 SMA. This subtype represents < 5% of individuals with SMA and is the mildest form of the disease [6]. Patients remain ambulatory at least until the fifth decade and have a normal respiratory function, lacking bulbar and visceral common complications of the pediatric forms [7,8]. SMA 4 was initially defined by age at onset

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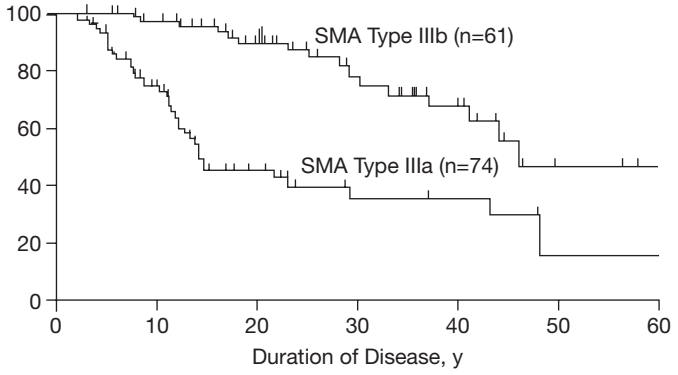

Fig. 1. Interval between disease onset and loss of ambulation in SMA3a (lower line) and SMA3b (upper line). Kaplan–Meier distribution in 74 SMA3a patients and 61 SMA3b shows that SMA3a lose ambulation earlier than 3b. Note that more than 60% SMA3a lost ambulation in the first 15 years of disease. To find this proportion in SMA3b patients, disease duration had to be more than forty years (from Zerres et al. 1995) [10].

over 30 years [7,9]. More recently, literature defines its onset after the age of 18 years (adulthood) [10,11].

2. Presenting symptoms

SMA3 typically manifests after 18 months of age, although initial symptoms may be insidious. In a recent systematic literature search, mean age of onset was estimated to be 39 months (± 32) and confirmed genetic diagnosis was 50 months (± 12), with a diagnostic delay of 43 months [12]. As in other forms of SMA, muscle fatigue, weakness and atrophy starts in lower limbs, has proximal predominance and spreads later in life to upper limbs and the trunk in an ascending manner. Children first show difficulties running, climbing stairs, getting up from the floor or jumping. Distal limbs may be also affected, showing *pes cavus* deformity in the feet (Fig. 2B), hand tremors and brisk and short movements of fingers in the hands, which are due to weakness and fasciculations of the forearm muscles. As the disease evolves, pelvic muscle involvement leads to waddling gait and children complain of fatigability and reduce walking distances. Falls are increasingly frequent and body changes during puberty, such as rapid growth or significant weight gain, may contribute to loss of ambulation. In contrast to SMA1 and SMA2, tongue fasciculations are not frequent until later stages of the disease. Adults show similar progressive symptoms of muscle weakness and often complain of fatigue, which can adversely affect quality of life and function. Atypical presentations with disease onset in upper limbs, asymmetric weakness, or upper motor neuron signs have been reported but are rare [13,14]. Children with SMA3 have usually little to no symptoms of respiratory muscle weakness [15,16]. Visceral complaints (constipation, gastro-esophageal reflux, urinary incontinence) and bulbar symptoms frequent in SMA1 and SMA2 are rare in SMA3, even at adult age [17]. No cardiac involvement is observed. SMA3 children do not show learning disabilities provided that the school has an adapted environment and, when required, personal assistance is available. Interestingly, no significant behavioral problems are observed in the children but their non-affected siblings show a two- to threefold higher rate than the normative population) [18].

3. Natural History

In contrast to earlier SMA forms, life expectancy in SMA3 is not reduced [7]. Concerning ambulation, most children with SMA3 treated only with supportive care make gains in their motor function until the age of 6 years and then experience a slow decline in function until puberty. A growth spurt may be associated with a rapid decline in motor abilities, slowing down again during a variable period at adulthood [19]. The vast majority of SMA3 patients will lose ambulation with time. Natural history studies have shown different motor prognosis in patients presenting before and after 3 years (Fig. 1). Those with onset before this age (SMA3a) are prone to lose ambulation in the following 20 years [10,20]. In contrast, those presenting later (SMA3b) often remain ambulant until the fourth decade of life [8]. In an ancillary study, the probabilities of being ambulatory at 10, 20, and 40 years were estimated to be 73%, 44%, and 34%, respectively, in patients with SMA3a, while they were much higher in patients with SMA3b (97%, 89%, and 67%) [10]. Due to the arrival of new innovative therapies, a number of studies have been performed worldwide in the last years [3,21-25]. Concerning respiratory function, while SMA3b and 4 show normal values throughout life, forced vital capacity (FVC) declines slowly in 3a individuals, although to a lesser degree than in SMA2 (−0.67% per year vs −1.35%) [16].

Quality of life and burden of disease studies are emerging and show that domains such as self-care and mobility assistance are better preserved for longer in SMA3b compared to SMA3a. Stair management seems a major obstacle for independence in achieving mobility, and bathing and dressing the upper and lower body often require help or supervision. Cognition is well preserved, although a significant proportion of SMA3a requires assistance or supervision in problem solving, while this is not detected in most SMA3b [25].

4. Clinical examination

The most striking sign (that is shared with types 1 and 2) when examining a child with SMA3 is the wasting of proximal and limb girdle muscles (Fig. 2A). Muscle bulk is markedly reduced when comparing with more distal regions (forearm, calf). Weakness is localized in the same distribution as muscle wasting. Hypotonia, hyperlaxity and absent osteo-tendinous reflexes are typical features. In addition to weakness, a certain degree of muscle fatigability is observed, as in all forms of SMA, but in SMA3 it is mostly restricted to the limbs. Triceps, deltoid, iliopsoas and quadriceps are the most affected muscle groups. The strength of the flexors and extensors of the hand and fingers, biceps and hamstrings are relatively preserved in the majority of patients in the first decade [26]. Face, ocular movements and tongue are usually normal during childhood. There is no bulbar or ocular involvement. Patients who remain ambulant outdoors do not show joint contractures or spinal stiffness, although minor feet deformities such as flat or high arched foot (*pes cavus*) are frequent (Fig. 2B). Getting up from the floor becomes progressively more difficult requiring support (Gowers' sign) and will become impossible overtime. When ambulation is limited to indoor spaces, hip joint contractures and feet deformities develop (equinovarus) and may be asymmetric.

Progressive axial weakness and hypotonia increases the risk of scoliosis in the period of loss of ambulation and may evolve rapidly with severe motor and respiratory functional consequences (Fig. 2B-D). With the progression of the disease, upper limbs become weak and fingers show a suggestive tremor, making it difficult to distinguish clinically non ambulant SMA3 from SMA2.

Adults with SMA3 present a similar distribution of muscle weakness and atrophy as children, mimicking a limb girdle-like pattern, reduced or absent reflexes, and tremor [14]. In SMA 4, there may only be a loss of patellar reflexes, with sparing of the deep tendon reflexes in the upper extremities and Achilles. Findings are similar to but less severe than those described for SMA3, and if loss of ambulation occurs, it is rare before the fifth decade [27].

5. Diagnosis

Diagnosis in a child affected by SMA3 is difficult based solely on clinical grounds, because, as Kugelberg and Welander remarked

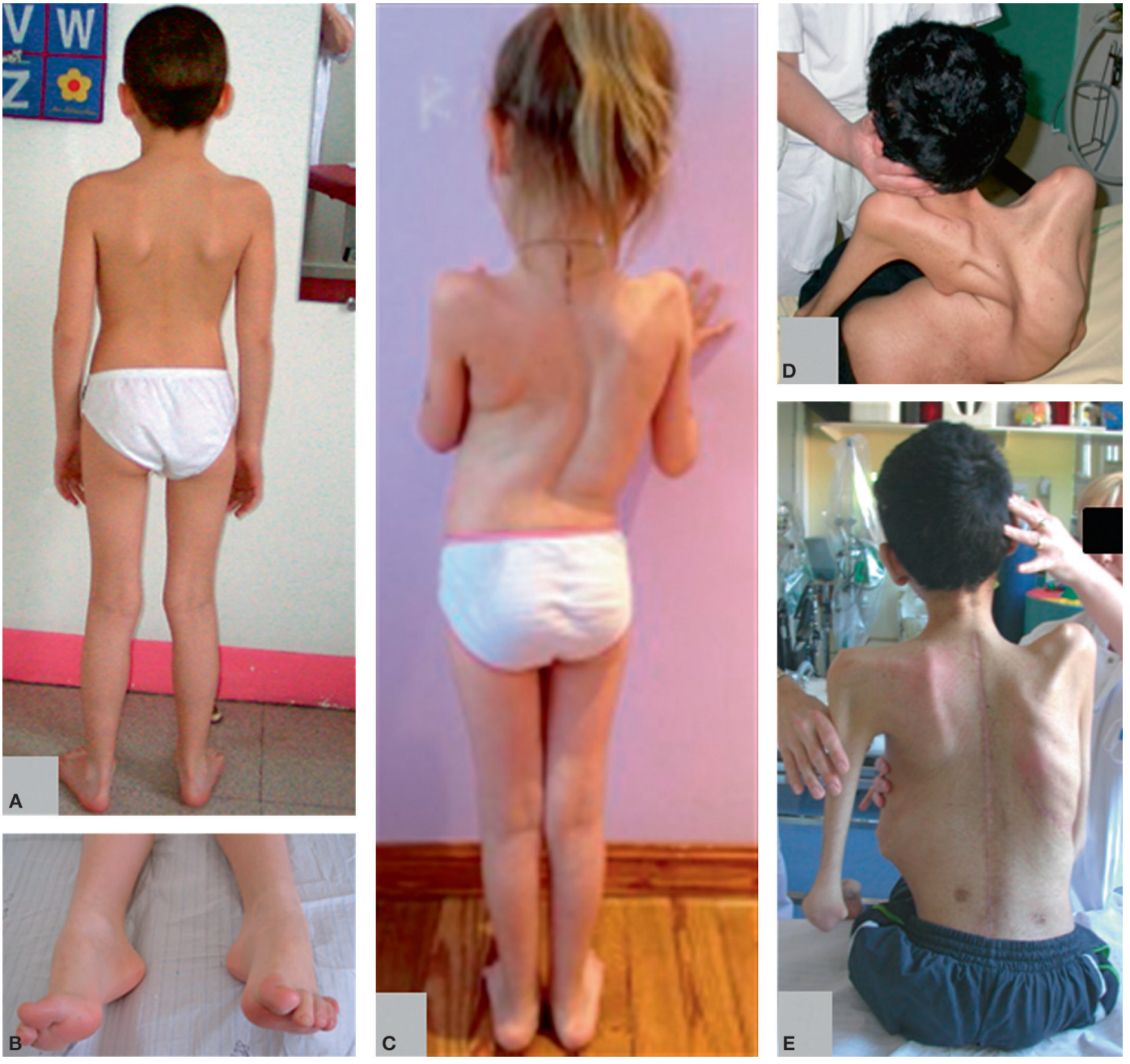

Fig. 2. Clinical features in SMA3 children:
2A) Ambulant SMA3 patient showing typical wasting of girdle and proximal limb muscles, and scapular winging; B) Pes cavus in the same patient; C) SMA3a patient standing with support showing thoracic scoliosis and valgus feet; D) SMA young man with untreated severe scoliosis; E) Same patient in after a 6 months orthopedic program (stretching, casts and cephalic halo-traction series) followed of surgical arthrodesis.

in the title of their original article, patients mimic muscular dystrophy [1]. Limb girdle progressive muscle weakness in a toddler or an older child is much more often due to a myopathy. Therefore, complementary tests play a more important role in the diagnosis of SMA3 than in earlier forms. However, especially in children, they may not give clear-cut results. CK levels are often slightly increased as in myopathies, and muscle biopsy and electroneuromyography (ENMG) may be misleading [28, 29]. In recent years, muscle imaging seems to provide further clues to suspected SMA3 in a 'pseudo-myopathic patient', in particular when there is marked motor progression and no abnormalities are found in the genetic studies for muscle diseases [30].

5.1. Electroneuromyography (ENMG)

ENMG is useful for performing differential diagnosis with muscular dystrophies, especially in patients with atypical and/or later-onset phenotypes. Electrodiagnostic studies in weak and atrophic territories show variable features of motor neuron/axon loss [31, 32]. Nerve conduction studies show normal sensory nerve action potentials (SNAP) and reduced amplitudes of compound muscle action potentials (CMAP) with relatively preserved conduction velocities. Needle electromyography (EMG) demonstrates abnormal spontaneous activity in the form of positive waves and fibrillation potentials (denoting active denervation), and very

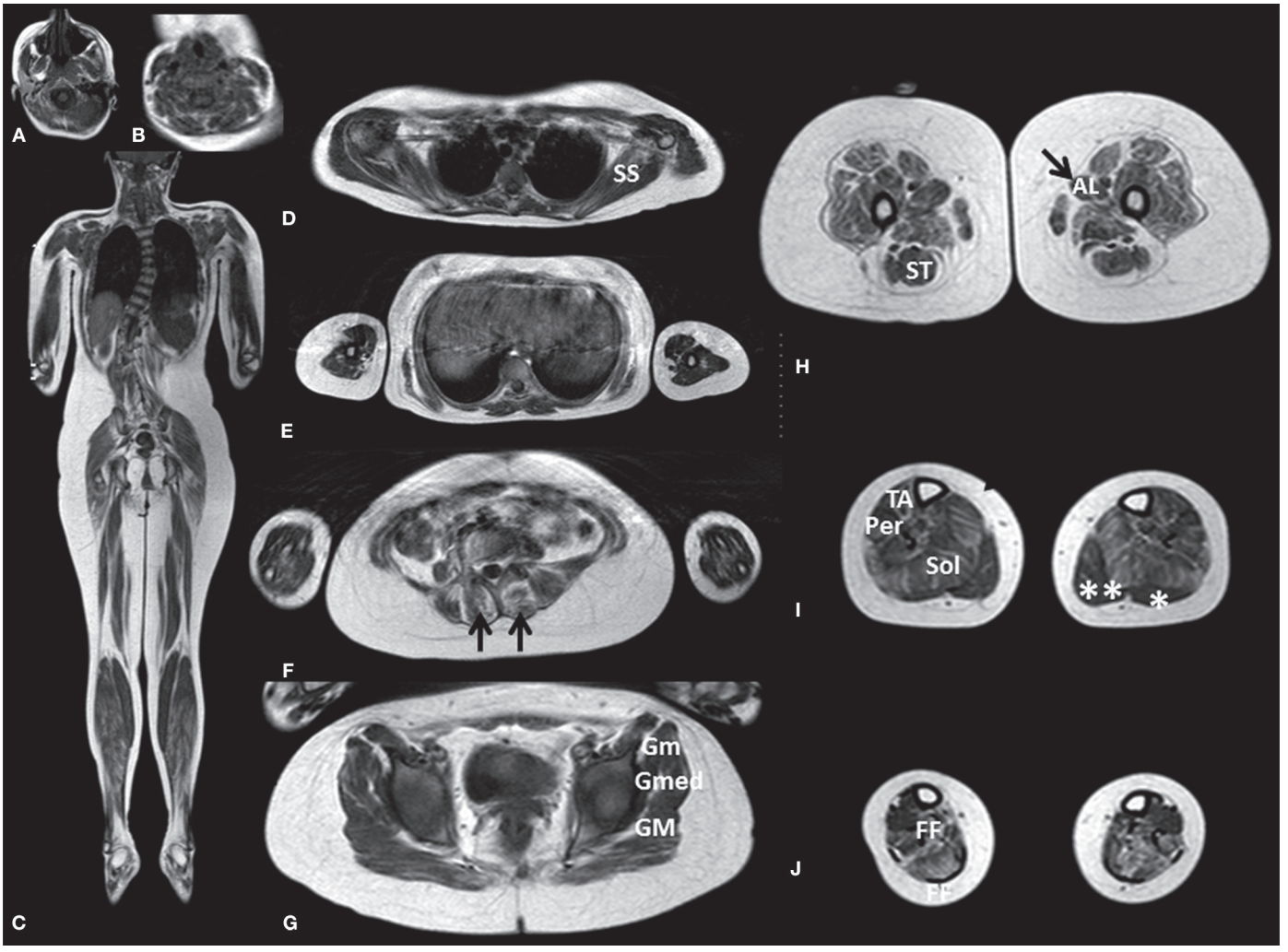

Fig. 3. T1 weighted Whole-Body Magnetic Resonance Imaging (WB-MRI) findings in an ambulant 13-year-old SMA3b girl. Frontal (C) and coronal views (A-B, D-J)
Regional analysis: Fibroadipous replacement (hyperintense signal) is more predominant in lower limbs (H-J), pelvic girdle (G), thigh (H) and lumbar paraspinals (black arrows in E).
Muscle analysis: Shoulder, trunk and upper limb muscles are relatively spared. In the thigh, the most severe involvement is observed in quadriceps, abductor magnus and semimembranosus muscles. Muscles selectively spared are: semitendinosus (ST), sartorius gracilis and adductor longus (AL). This last muscle is strikingly enlarged (black arrow in H). In the leg, soleus is the most affected muscle and tibialis anterior (TA), peroneus (Per) and gastrocnemius muscles (white stars) are relatively spared (I). (*Modified from: Neuromuscular Imaging. Motor Neuron Diseases. Quijano-Roy S, Avila-Smirnow D &Carlier RY. Ed Mike P. Wattjes, Dirk Fischer. Springer Science and Bussiness Media (2013) [43].*

enlarged motor unit action potentials (MUAPs), along with reduced recruitment [32]. Sometimes, in severely affected patients, when end-stage individual muscles are explored, tracing may mimic a myopathy because the extreme atrophy of muscle fibers leads to MUAPs with markedly reduced amplitude and duration.

CMAP amplitudes are well correlated with age, disease progression and clinical severity [33,34]. In milder forms of the disease, or at early ages, CMAP amplitudes may be in the normal range. Impairment of the maturation of the neuromuscular junction (NMJ) has been reported in animal models as well in postmortem histopathological studies [35,36]. It is unclear whether these changes are primary defects of the NMJ transmission or rather secondary to instability of the NMJ consequence of denervation and reinnervation processes. Interestingly, repetitive nerve stimulation studies in SMA patients showed decremental responses [37] and some authors have found signs of fatigability in time-tests such as 6MWT that can help identify SMA3 patients with NMJ dysfunction [38].

Motor unit number index (MUNIX) is a recent, non- invasive electrophysiology technique which relies on surface EMG and provides an estimation of the number of functional motor units in a given muscle [39]. Recent studies have shown that MUNIX values in hand muscles are decreased in SMA3 and SMA4 compared to healthy controls, and the pattern differs from amyotrophic lateral sclerosis [40]. Moreover, the MUNIX profile of SMA patients correlates with muscle strength and disability so that it seems useful in follow-up studies [41].

5.2. Muscle Imaging

Muscle MRI shows a relatively homogeneous pattern, with atrophy of proximal muscles and predominance of fibroadipous replacement in lower extremities and lumbar paraspinal muscles. In the legs, quadriceps femoris and soleus muscles are the most abnormal muscles, which may resemble a RYR1 related-myopathy MRI pattern. However, several features are different: in the arms, triceps are more severely impacted than biceps (which is rare in myopathies); in the pelvic girdle, iliopsoas is atrophic and more affected than the gluteus maximus. Interestingly, despite the wasted thigh muscles, the adductor longus looks markedly enlarged (Fig. 3). Other preserved muscles are deltoid, semitendinous, gracilis and sartorius. A positive correlation between MRI changes and disease duration has been observed in gluteus maximus and triceps brachii in a large number of 3b patients suggesting that these muscles may be used in follow-up studies [42,43]

5.3. Muscle biopsy

Since molecular diagnosis is readily available and efficient, in most SMA3, a muscle biopsy is no longer required. In atypical cases, ENMG is often sufficient for suggesting the diagnosis. Histopathology in SMA3 is variable, ranging from minimal changes to a small or large group of uniformly atrophic fibers between groups of non-atrophic muscle fibers [31,32]. Both the atrophic and non-atrophic groups may either be of type 1 or 2 muscle fibers. The non-atrophic fibers are arranged in large groups of 30–200 fibers of a single type and are most commonly composed of type 1 rather than type 2 fibers (Fig. 4). A variable degree of fatty infiltration may be observed. In some patients, a pseudomyopathic pattern is noted. Histopathological features are similar in SMA4 [44]. Muscle biopsy is useful in atypical cases in order to rule out differential diagnosis.

5.4. Autopsy studies

Postmortem features of SMA1 have been well described but relatively few autopsy cases of SMA3 have been reported so far [45]. The main pathological findings are a marked neuronal loss in the anterior horns along the length of the spinal cord and prominent chronic changes such as fibrillary gliosis. The anterior spinal roots are atrophic, and there is a loss of myelinated fibers with abundant glial bundles. There are no abnormalities in the thalamus and pyramidal tract, as seen respectively in SMA1 and 2.

5.5. Differential diagnosis

Clinical overlap with SMA3 is mainly observed in hereditary myopathies: muscular dystrophies (dystrophinopathies, limb-girdle muscular dystrophies), which are often associated with higher CK levels and muscle hypertrophy, and metabolic myopathies (mitochondrial neuromyopathies, TK2-myopathy). Neurogenic disorders mimicking SMA3 include other motor neuron disorders (non-5q form of SMA, late-onset hexosaminidase A deficiency, Fazio-Londe syndrome due to defects of the riboflavin transporter) and axonal motor neuropathies. Pes cavus and neurogenic needle EMG tracing with conserved conduction velocities may evoke Charcot-Marie-Tooth disease, but preserved sensory responses and proximal atrophy and a much more progressive weakness makes it possible to distinguish between the two diseases. An insidious onset of slowly progressive and symmetrical weakness over many years with a prominent distal involvement is suggestive of distal hereditary motor neuropathies (dHMN) whereas the pattern of muscle involvement in SMA is predominantly proximal [46]. A selective or prominent weakness in upper limbs may point to a dHMN with a mutation in GARS or BSCL2. Monomelic amyotrophy (Hirayama disease) may be suspected in rare cases with onset in upper extremities before a more diffuse involvement is observed. SMA4 can sometimes be difficult to distinguish from other motor-neuron late-onset disorders, such as amyotrophic lateral sclerosis and Kennedy disease (X-linked spinobulbar muscular atrophy), although these diseases usually show a different topography (asymmetric, bulbar, upper limbs).

6. Pregnancy and SMA

In two large studies performed between 1992 and 2012 by Zerre's group among women affected with SMA who have had at least one child and who are under 35 years of age, the two most important results were the occurrence of preterm deliveries (one third of SMA gestations), prolonged labor and delayed postpartum recovery [47,48]. The number of miscarriages and hypertensive diseases in pregnancy was not increased. Patients delivered more frequently by vaginal operations. Neonatal outcome was favorable in all [46]. Exacerbation of muscle weakness after the second trimester of pregnancy was experienced by one third of the mothers, followed by a persistent deterioration in some of them or improvement during the puerperium.

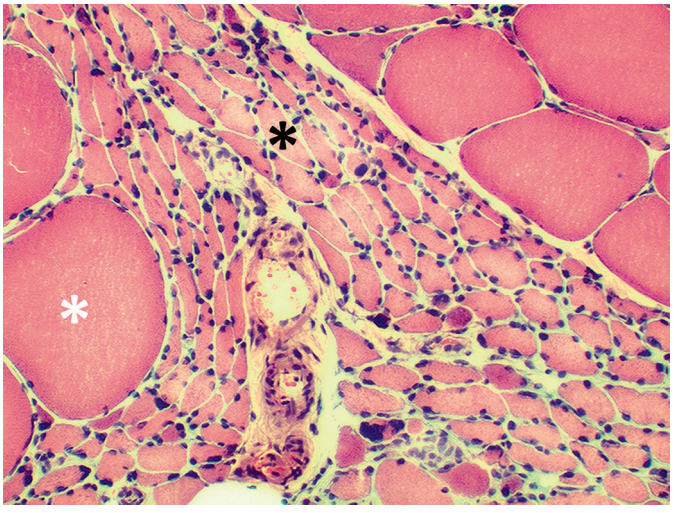

Fig. 4. Morphological findings in SMA
Typical neurogenic pattern with groups of atrophic muscle fibres (black star) in the proximity of groups of normal fibres (white star) *(Courtesy Norma B Romero).*

7. Conclusion

SMA3 (and the adult form SMA 4) are the less severe forms of SMA. However, diagnosis is more difficult on clinical grounds than in earlier forms due to overlapping features with more frequent myopathies. Complementary tests are useful for showing denervation and neurogenic abnormalities or a specific pattern of muscle involvement. The arrival of new emerging therapies for this motor neuron disease requires an early diagnosis and therefore a high suspicion should be maintained and SMN genetic analysis should be performed in any patients with symmetric and proximal weakness, if possible at early stages of the disease.

Disclosure of interest

E. Salort-Campana has received fees for consultancy services to Biogen and Roche.

S. Quijano-Roy has received fees for scientific advisory boards and consultancy services to AveXis, Biogen, Roche.

Authorship

All authors have made substantial contributions by: (1) drafting the article; (2) revising it critically for important intellectual content.

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