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Review article

Clinical features of spinal muscular atrophy (SMA) type 2

C. Cancès[a,*], C. Richelme[b], C. Barnerias[c], C. Espil[d]

[a] AOC (Atlantique-Occitanie-Caraïbe) Reference Centre for Neuromuscular Disorders, Neuropaediatric Department, Toulouse University Hospital, Toulouse, France
[b] CMR Neuromusculaire PACARARE, Hôpitaux Pédiatriques de Nice CHU – Lenval, Nice, France
[c] CMR Neuromusculaire NEIDF, AP-HP, Paris, France
[d] CMR Neuromusculaire AOC, Hôpital des Enfants CHU Bordeaux, Bordeaux, France

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A B S T R A C T

Infantile spinal muscular atrophy (SMA) type 2 is sometimes called intermediate SMA to indicate the disease severity. Generally, psychomotor development is normal until the age of 6 to 8 months, with the acquisition of a stable sitting position. The early signs are muscle weakness, mostly affecting the lower limbs, generalized hypotonia and areflexia.

The consequences of motor neuron degeneration are functional and orthopaedic, respiratory, nutritional, socio-professional, and psychological. The implementation of standardized care (i.e., standard of care recommendations) has improved the quality of life and survival outcome of patients. The emergence of innovative therapies, some of which are now available, should further improve the clinical evolution of this disease.

1. Introduction

Spinal muscular atrophy type 2 is a disease of intermediate severity on the clinical-genetic continuum of infantile spinal amyotrophies, and it affects approximately one third of patients [1]. It was first described in 1893 by Thompson and Bruce [2], but the designation type 2 was introduced in the first classification of Byers and Banker in 1961 [3].

Psychomotor development is considered normal in affected children up to the age of 6-8 months, with the acquisition of a stable sitting position without support. Two subtypes have been distinguished: 2a, referring to children who are able to remain seated without support but are unable to stand or walk even with assistance, and 2b, referring to children who, in addition to acquiring the sitting posture without support, can stand with help and even take a few steps [4].

2. Diagnostic signs

The early signs are present before the age of 18 months, appearing as a lag or delay in motor and postural skills and associated with axial and segmental hypotonia, which is often underestimated. The child acquires the ability to maintain a sitting position at an appropriate age but is unable to achieve this position on his/her own. Moreover, dorsolumbar kyphosis with excessive curvature is observed early on [5]. The ability to grasp objects, mainly for playful activities, is not initially impaired, in contrast to lower limb weakness and the inability to perform a dorso-ventral rollover, get into a crawling position, or stand with support. The acquisition of a standing position, or taking a few steps with support is rarely observed. Independent walking – that is, more than ten steps – is a criterion for SMA type 3 classification.

The peripheral origin of hypotonia is suggested by its global, axial and segmental character, although it may be asymmetric, associated with osteotendinous areflexia and excellent arousal and interaction capacities that reflect the integrity of the central nervous system. Twitching of the tongue and fingers, with or without associated vasomotor disorders, is a minor sign of the denervation process. Salivary stasis, which is rather rare, is indicative of bulbar muscle dysfunction.

The regression of certain motor skills may also be an initial reason for consultation, such as losses in the ability to sit stably,

* Corresponding author.
E-mail address: cances.c@chu-toulouse.fr (C. Cancès).

use the lower limbs to support a standing position, or get into the position for crawling.

Initially, muscle weakness rarely affects the chest region and therefore the respiratory tract is spared. Yet, thoracic dystrophy is sometimes observed early on in the form of a bell-shaped or asymmetric chest.

3. Diagnostic confirmation

The clinical signs and symptoms are sufficient to suggest the diagnosis of SMA type 2, but the next step is to look for a homozygous deletion of exon 7 of the *SMN1* gene by quantitative polymerase chain reaction (qPCR). Normal or moderately elevated CK levels are not a good indicator. An electrophysiological study to identify neurogenic damage is unnecessary, except when the findings of the molecular study of the *SMN1* gene are negative [6].

4. Clinical changes

Disease progression varies from one patient to another and even within the same patient. Motor functions may appear stable over a brief period of 6 to 12 months, but the patients are in fact undergoing a slow functional decline [7–9]. Retrospective and natural history studies of SMA type 2 patients have confirmed this orthopaedic and functional, as well as respiratory, progression of the disease [10–12]. Developmental scales – the Bayley Motor Scales, Hammersmith Infant Neurological Examination Section 2 (HINE 2), Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Functional Motor Scale Expanded (HFMSE), Motor Function Measure (MFM 20 or 32), and Revised Upper Limb Module (RULM) for nonambulatory patients – can be useful for objectively monitoring the motor performances of patients, both children and adults [10,13–15].

4.1. Functional and orthopaedic changes

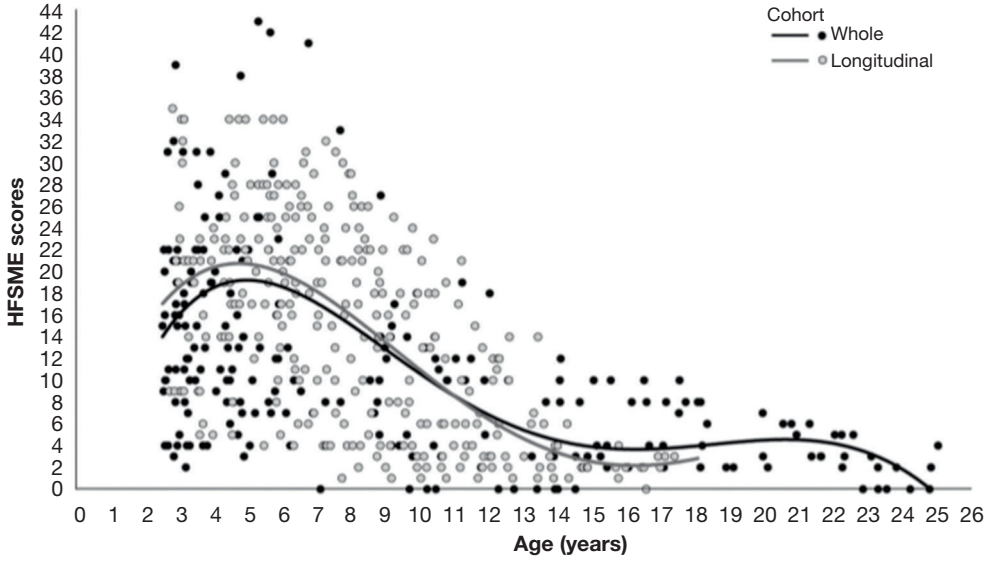
Patients with SMA type 2 may acquire new motor and functional skills in the first years of life, presumably due to an attenuation of the underlying motor neuron damage, although all natural history studies show a loss of capacity over time [9,16,17]. The decline is not significant in the first 12 months [8], but beyond this, the average annual loss in motor skills is at least 1 point on the Medical Research Council score and 0.5 points on the HFMSE score in both children and adults [17]. Mercuri et al. [16] performed a retrospective analysis of a series of 73 patients with SMA types 2 and 3 and reported an initial gain in function up to the age of 5 years, followed by a fairly rapid decline up to 13 years, and then a stabilization or slower decline thereafter (Fig. 1). Almost 20% of patients may lose the sitting function [18].

The weakness results in the progressive appearance of joint contractures, with frequencies that differ between the children, due to hypomobility, with a reduced range of motion and prolonged static positioning: progressive equinus foot deformity, most commonly associated with flexum of the knees and hips. Instability followed by dislocation of the hip joint is common and is at times transiently painful with the spontaneous « batracoid » or froglike position: ulnar tilt of the wrists, limited supination, and loss of amplitude in elbow extension. These contractures seem to progress more slowly in adult patients.

Muscle atrophy is often masked by rather loose fatty tissue.

Sixty to ninety percent of SMA type 2 patients develop early and progressive hypotonic scoliosis, noticeable from the age of 3 years and often preceded by thoracic kyphosis [19,20]. This can be aggravated by an oblique pelvis, initially induced by asymmetric weakness and contractures of the pelvic-trochanteric and spinal muscles, which increases the risk of a dislocated hip. Systematic inspection of the spine is important to detect scoliosis, and radiological assessment can confirm it. Thereafter, monitoring every six months is recommended, particularly by means of the objective measurement of the Cobb angle. An oblique pelvis, aggravated by scoliosis, can sometimes cause impingement by the lowest rib against the iliac crest before any surgical correction of the scoliosis is performed [21]. Insufficient ribcage muscles can cause a deformity of the ribs, which appear thin with progressive verticalization (similar to the closing of an umbrella). This process can be aggravated by the scoliosis, but the ribcage can also be flattened in the anteroposterior direction [21].

A pain syndrome can be induced by massaging and stretching the joint flexum over the course of patient care. At a later point in time, the pain syndrome may be secondary to one or more « spontaneous » fractures or to prolonged immobility, which indicates an induced osteoporosis with very disabling repercussions, particularly for quality of life [22].



Hammersmith Functional Motor Scale-Expanded (HFMSE) score distribution of the whole cohort (black circle) and longitudinal cohort (gray circle). Interpolation line represents the HFMSE progression subdivided by whole cohort (black line) and longitudinal cohort (gray line).

Fig. 1. Distribution of HFSME scores for two cohorts: Whole cohort, including all patients; longitudinal cohort, including all patients seen before the age of 5 years, and long-short follow-up. Reproduced with permission from Mercuri et al., 2019 [16].

4.2. Respiratory changes

Impaired respiratory capacity is the second clinical component that needs to be taken into account: impairment is characterized by a progressive decline, especially in forced vital capacity (FVC) and notably during infancy, which may then be followed by a certain stability in adulthood (Fig. 2) [23]. This results in a restrictive syndrome secondary to the weakness of the intercostal, abdominal and spinal muscles and the restriction of thoracic-pulmonary and alveolar growth. Respiratory failure may occur, initially characterized by repeated pulmonary infections and then by progressive alveolar hypoventilation, which is a late clinical sign. Respiratory failure often begins silently (which is why early and systematic screening is vital), expressed fairly early on by progressive rib deformity with « progressive verticalization » or funnel chest [5,24], features that are accentuated by the presence and aggravation of a hypotonic scoliosis. This is the direct result of the weakness and progressive fatigability of the respiratory muscles, particularly the intercostal (inspiratory) and abdominal (expiratory) muscles, and accentuated by a lack of cough strength, swallowing disorders and frequent gastro-oesophageal reflux [18,25].

4.3. Feeding and nutritional changes

20% to 30% of patients with SMA type 2 present chewing disorders or swallowing difficulties in close correlation with motor capacities; the increased risk of aspiration increases the risk of pneumonia and/or malnutrition in these children [26]. Bulbar dysfunction may explain the impaired swallowing and motor functions, and additional explanations for feeding and swallowing difficulties include age, respiratory status, the current state of motor functions and, especially, the control of head posture while eating [26]. Mouth opening may also become progressively limited (30%), secondary to the paralysis of the facial muscles and the contracture of the masseters. This also contributes to feeding problems, in addition to limiting access for oral care and rendering emergency respiratory procedures very difficult. Finally, difficulties in feeding may be complicated by a hypoplasia of the middle and lower facial mass, especially if the patient has received early non-invasive ventilation support [27].

A potentially life-threatening situation can arise if it is not recognized and treated appropriately: acute gastric dilation, a complication found in a quarter of the patients with SMA type 2 [28]. The sequence of clinical signs is abdominal pain, vomiting, dyspnoea and epigastric bloating. Signs of dehydration may rapidly occur, accompanied by metabolic acidosis. Treatment consists of placing the patient in the prone position to stop the vomiting and electrolyte rehydration if the vomiting persists for more than one hour [21]. The investigation should systematically look for constipation, a "false" diarrhoea following constipation, and signs of gastro-oesophageal reflux or gastroparesis with delayed gastric emptying. Recurrent vomiting should suggest either a gastrointestinal motor disorder, even extreme symptoms of chronic intestinal pseudo-obstruction, or vomiting of metabolic origin.

Despite the absence of growth curves specific to SMA, the profile of weight change, and to a lesser extent a change in length or height, can identify the emergence of underweight (37% of SMA type 2 with weight <-2DS) or obesity (5% of SMA type 2 with weight >+2DS). It should be noted that the risk of overweight and obesity is higher in SMA type 2 patients with good motor functions and seems to be associated with an increased risk of hyperinsulinism with insulin resistance and disruption of carbohydrate metabolism [29].

4.4. Changes in urethral sphincter function

Malfunctioning of the urethral sphincter has been rarely reported and is probably underestimated. In adolescents and adults, urinary lithiasis, feeling of incomplete bladder emptying, and urinary incontinence have been described [34].

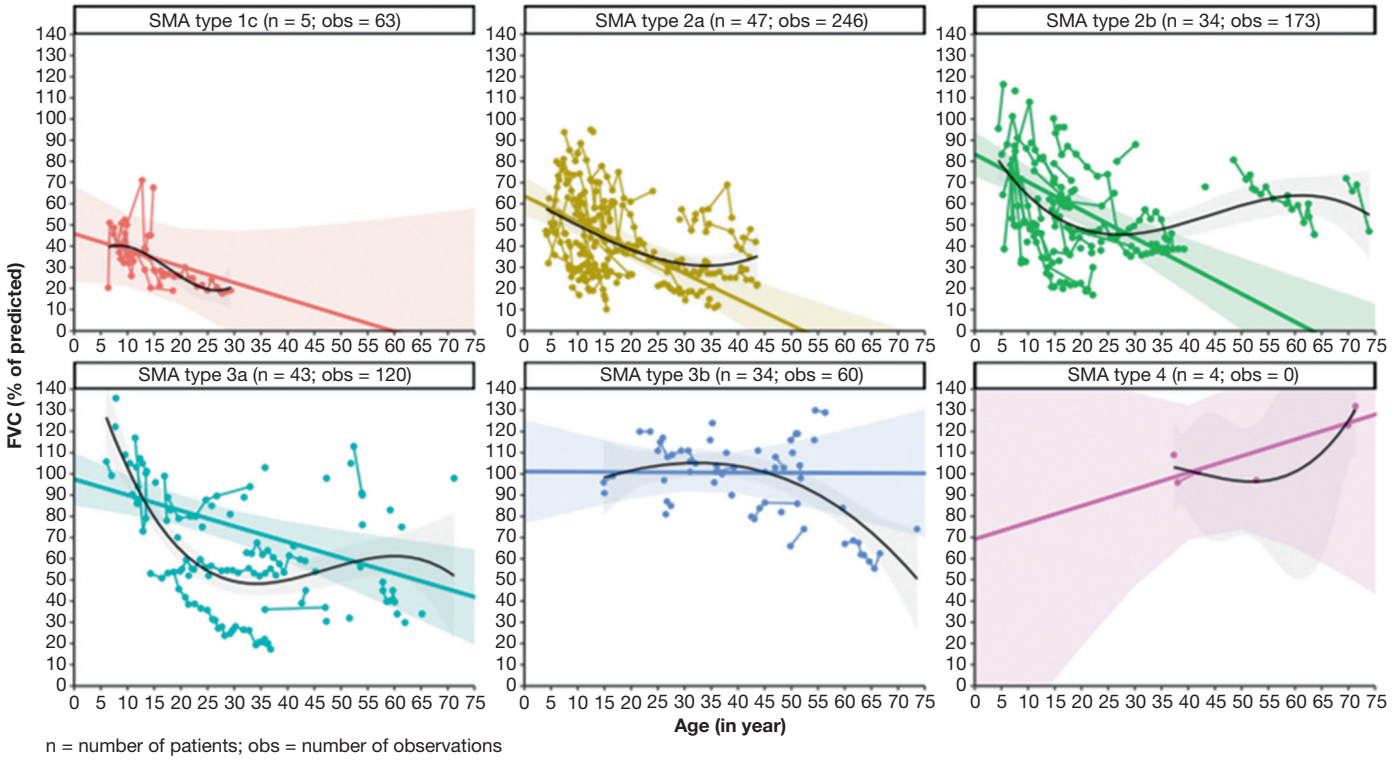


Fig 2. CVF evolution of all types SMA patients, especially type SMA 2a and SMA2b patients (Figure extracted from Wijngaarde et al., 2020 [23]).

4.5. Cognitive assessments

Various studies have evaluated the cognitive functions of patients with SMA, often with all types combined and more rarely according to subtype. A recent review of the literature investigated nine studies [30]: cognitive difficulties were more frequent in SMA type 1 patients, although no difference was noted when cognitive scores using the Wechsler Intelligence Scale were compared, with normal and identical scores for types 1 to 3 [31]. However, impaired executive functions were noted in 22% of SMA type 2 patients, whereas only 10% of the type 3 patients presented similar difficulties [32]. No language acquisition disorders, either expressive or receptive, were found in SMA type 2 patients compared to a control group [33]. With appropriate support, most patients can obtain a conventional education and possibly even continue on to university studies.

4.6. Survival

We have little recent quantitative data on the median survival of patients with SMA type 2. In 1995, Zerres et al. [18] described a median survival of 100%, 100%, 98% and 77%, respectively, at 2, 4, 10 and 20 years. More recently, estimated endpoint-free survival is 74.2% and 61.5%, respectively, at 40 and 60 years for patients with SMA type 2a taken from literature reviews and their own cohort [35]. The endpoint-free survival of SMA types 2b, 3 and 4 is relatively normal, at least for the first 60 years of life. This data has undoubtedly changed for the better with the generalization of supportive care, particularly spinal management with arthrodesis and respiratory management with non-invasive ventilation. Medians of survival are likely to continue to change with treatments that modulate *SMN2* gene splicing or gene therapy. Such information may soon be accessible in current databases, particularly within the network of French reference centres for neuromuscular diseases: FILNEMUS.

5. Clinical changes with the new innovative therapies

The quality of life and survival of SMA patients of all types have improved considerably since the implementation of standard care recommendations, which take into account all aspects of the disease and its expression. The following articles in this supplement address the full scope of the issues concerning the "specific, general, and ethical management of these diseases".

On the other hand, as underlined in the article on pathogenesis and therapeutic targets in SMA by Lefebvre and Sarret in this supplement, we address the new clinical features of patients treated with the molecules known collectively as innovative therapies to the extent that they are understood at the present time.

The first available data presents the results of molecules that modulate the splicing of the *SMN2* gene in SMA type 1 patients, and in SMA types 2 and 3 patients.

The first results come from the CHERISH study, which compared 84 SMA patients with types 2 and 3 who were treated with a molecule that modulates *SMN2* gene splicing, and 42 SMA patients with types 2 and 3 who served as controls. The treated patients showed significant improvement in motor function compared with those in the sham "control" procedure, but no patient had been able to reach a new motor milestone 15 months later, probably too short to identify a long-term effect [6,36]. These patients were followed up in the medium term, however, and it was possible to confirm improvements in motor functions or a stabilization of the disease [37].

In 2020, Audic et al. [38] presented the results of the first 12 months of treatment with this drug, which was the first to obtain marketing authorization. The French cohort was composed of 123 patients, including 89 SMA type 2 patients. Overall, this treatment was found to be even more effective when it was started early, in line with the findings of other studies. Gains in function were seen in patients between 2 and 5 years old on the D2 and D3 dimensions of the MFM-20 – that is, those testing axial, proximal and distal motor skills – and in patients between 6 and 17 years old on the D3 dimension – testing distal motor functions. Hagenacker et al. [39] presented the results at 6, 10 and 14 months for 124 patients between 16 and 65 years treated with the same molecule: the mean HFMSE scores increased significantly compared to the baseline values at 6 months (mean difference 1.73 [95% CI 1.05-2.41], p<0-0001) and 14 months (3.12 [2.06-4.19], p<0-0001). Clinically significant improvements (≥3-point increase) in the HFMSE scores were observed in 35 (28%) of 124 patients at 6 months, 33 (35%) of 92 patients at 10 months, and 23 (40%) of 57 patients at 14 months, indicating a slow but steady benefit in more than a third of the patients. Various studies have reported similar findings, especially in adult patients with SMA type 2 or 3 followed for 10 to 14 months, and notably identified stable functional scores [40,41].

The main side effects in the studies have been related to the intrathecal injection procedure [36–39,42].

A second molecule that modulates *SMN2* gene splicing is currently in therapeutic trials, with marketing authorization being sought for patients with SMA types 1 and 2. The first efficacy data appears favourable but has not yet been published.

Finally, gene therapy, which began in 2019 for SMA type 1 patients and more recently for type 2 patients, is a major therapeutic advance. However, we have no data on efficacy for patients with SMA type 2, although partial results have just been published [43].

In the coming years, we should be able to refine the precise indications for each of these innovative drug therapies and better define first-line therapies and their protocols.

6. Conclusions

Diagnosing infantile SMA type 2 requires a good knowledge of the early clinical signs and symptoms, especially since the early initiation of advanced therapy drugs is a determining factor for their effectiveness.

Disclosures of interest

In the past 5 years, C. Cancès has received honoraria or funding for participation in congresses, educational activities and expert groups from Biogen, Avexis and Roche.

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