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Review article

Spinal muscular atrophy (SMA) type I (Werdnig-Hoffmann disease)

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ABSTRACT

Spinal muscular atrophy type I, also called Werdnig-Hoffmann disease, is the most serious form. The disease appears before the age of 6 months and is characterized by major global hypotonia and abolition of tendon reflexes, with children never being able to sit unaided. Cognitive development is normal and the expressive gaze of these children contrasts with the paralytic attitude. Respiratory involvement predominates in the intercostal muscles, and sometimes brainstem involvement are all serious aspects of the disease. Type I spinal muscular atrophy has been subdivided into 3 groups: – type IA, the clinical signs of which set in between birth and 15 days of life with sudden severe motor impairment, sucking-swallowing disorders attesting to bulbar involvement, respiratory distress. – type IB with onset of symptoms before the age of 3 months, which implies no head control – type IC starting between 3 and 6 months with the possibility of checking head control, often referred to as "I bis" by French practitioners.
The development and use of innovative therapies in recent years does actually change the natural course of this disease. But we do not know for sure what the long-term evolution of infants who received these new therapies will be.
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This form is also called Werdnig-Hoffmann disease. It was first described by Werdnig in 1891, when he observed two infant brothers with the onset of progressive proximal leg weakness at 10 months of age [1]. Hoffman, between 1893 and 1900, described an additional seven patients from three families [2-4].

SMA are all recognized by a progressive and symmetric weakness involving the proximal extremities, axial muscles and intercostal muscles, with prominent sparing of the diaphragm, and abolition of tendons reflex. This spectrum of phenotypes was formally classified in 1991, based on the age of clinical onset and maximum motor function achieved [5].

1. Clinical signs and classification

The International Consortium on SMA has classified as type I (severe) SMA children with onset before 6 months who have never achieved the ability to sit unaided. [5]

Infants with type I SMA have muscle damage characterized by major global hypotonia and abolition of tendons reflexes: it associates poor control of head hold, predominantly proximal symmetrical flaccid quadriparesis preferentially affecting the lower limbs (therefore leaving the roots of the limbs on the plane and especially allowing movements of the hands and forearms, feet or toes). In a supine position, these children have a characteristic spontaneous "in batrachian" attitude. Fasciculations of the fingers are visible in a third of cases. Sitting without support is never a given and there is an important hypotonia of the trunk. Respiratory involvement predominates in the intercostal muscles while initially respecting the diaphragm, thus creating paradoxical abdominal breathing, leading to a bell-shaped thoracic deformity. Often delayed facial involvement manifests as hypomimia. On the other hand, lingual fasciculations are early and constant. Cognitive development is normal and the expressive gaze of these children contrasts with the paralytic attitude.

There is a prenatal form called type 0 SMA. At birth, a majority have profound hypotonia, severe muscle weakness, severe respiratory distress and cranial nerve involvement (inability to suck or swallow, facial muscle weakness). They show characteristics of fetal akinesia deformation sequence and congenital heart defects. Recurrent episodes of bradycardia were observed. Death occurred within the first month. At prenatal stage,

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decreased fetal movements were frequently reported, mostly only by mothers and in late stages of pregnancy. Congenital heart defects, abnormal amniotic fluid volume or joint contractures can be warning signs.

Type I spinal muscular atrophy has been subdivided into 3 groups:

- type IA, the clinical signs of which set in between birth and 15 days of life by sudden severe motor impairment, sucking-swallowing disorders attesting to bulbar involvement, respiratory distress.
- type IB with onset of symptoms before the age of 3 months, which implies a no head control.
- type IC starting between 3 and 6 months with the possibility of checking the head control, often called "I bis" by French practitioners.

In the SMA Type 1, hypotonia is global:

- preservation of the liveliness of the gaze which excludes a central neurological origin.
- presence of lingual fasciculations and a tremor in the extremities.
- thoraco-abdominal swing for type 1 testifying to the involvement of the intercostal muscles and respect of the diaphragm.

Early types I (IA and IB) are characterized by the severity and progression of respiratory failure and by the impairment of trunk functions leading to the death of the child [6]. The involvement of the brainstem is manifested by swallowing disorders (with pharyngeal stasis, coughing during meals and difficulty eating), dysphonia, nasal voice, fasciculations and atrophy of the tongue, facial involvement, and vasomotor disturbances. Certain morphological parameters, such as a limitation of the maximum opening of the mouth (defined by an interincisor distance of less than 35mm), testify to bulbar involvement. We can compare micro-retrognathia and a hyper-ogival palate frequently encountered in type I patients. Dysautonomic disorders, frequently encountered in type I patients, are also the expression of the involvement of the brainstem: attacks of severe and symptomatic bradycardia, fluctuations in arterial pressure, marked vasomotor disorders during thermal variations. Dysautonomic impairment can also be the cause of acute gastric dilation: it manifests itself by intense abdominal pain, repeated vomiting associated with severe dehydration, correlated with metabolic acidosis and hypoglycemia. This complication occurs regardless of the child's age and trophicity and requires urgent venous rehydration.

Congenital heart defects have now been reported in patients with SMA type I [7]: for example hypoplastic left heart, atrial or ventricular defects. Homozygous SMN1 deletion may play a role in the development of congenital heart defects when it occurs in the presence of mutations or polymorphisms in other genes that are important for cardiac development.

2. Differential diagnosis

- Spinal Muscular Atrophy and Respiratory Distress 1 (SMARD 1 linked to a mutation in the IGHMBP2 gene): the motor deficit here is predominantly distal and, especially in the upper limbs, there is early respiratory failure linked to diaphragmatic paralysis between 6 weeks and 6 months of life. There is an elevation of the diaphragmatic dome on the chest X-ray and on the EMG there is an absence of sensory impairment.
- Congenital myopathy, Congenital muscular dystrophy: the hypotonia is global but, here again, the absence of lingual fasciculations, a tremor in the extremities and the preservation of diaphragmatic involvement correct the diagnosis. In certain congenital muscular dystrophies, there is cerebral and ocular damage, and biologically marked elevation of CPKs in early forms due to merosine deficiency.
- Prader-Willi syndrome: hypotonia is deep early on but is associated with a characteristic facial dysmorphia (high and narrow forehead, bitemporal retraction, almond-shaped eyes, mouth in a policeman's hat) and absence of lingual fasciculations.
- Congenital Steinert's disease: in this case there is predominantly axial hypotonia and severe damage to the face with hypomimia and fall of the jaw.
- Pompe disease: the hypotonia is global but the chest X-ray reveals cardiomegaly and laboratory results show an increase in CKs.

3. Evolution and natural course

Spinal muscular atrophy type 1 with early onset has a severe course developing generalized progressive muscle weakness and atrophy. Associated with this generalized paralysis, children develop chronic respiratory failure and bulbar dysfunction (sucking and swallowing difficulties, phonation trouble) leading to death before 2 years of age.

There are different **prognosis factors** influencing the course of the disease:

- The age of onset and the severity of paralysis: Early onset is associated with a greater severity of the disease and with a premature evolution to death.
- The number of copies of SMN2: The number of copies of SMN2 is not completely correlated to the severity of the disease but most patients with early onset of SMA have 2 copies of SMN2 (73% of patients with SMA1 have 2 copies of SMN2) and one study has shown that infants with early onset SMA and 2 copies of SMN2 have a median survival time of 8 months [8].
- Thoracic circumference: The TC/HC (Thoracic Circumference on Head Circumference) ratio decreases over time in all infants with SMA1 and, in one study, those with a TC/HC ratio <0.85 died within 3 months [9].

Different studies have reported **the natural course** of this disease with early onset:

One retrospective multicentric French study reported the development of 222 SMA type 1 patients over a 20-year period [10]: The mean age of onset of clinical signs was 2.1 months and mean age at diagnosis was 3.95 months. The median age of death was 6.64 months. In this study, there were 10% of sudden deaths, probably consecutive to brutal bulbar dysfunction. Also, causes of death are multiple: acute pulmonary infection, airway obstruction, respiratory exhaustion or sudden bradycardic arrest.

Another French prospective multicentric study precisely reported clinical features in 37 infants [11]: Most parents (93%) reported difficulties in feeding their child at a median age of 4.7 months of age. 63% of the parents also reported prolonged meal duration, eating-induced fatigue for 78%, restriction intake for 70%, and food refusal for 44%. Gastro-oesophageal reflux was reported in 30% and food being swallowed in the wrong way in 52% of cases. Constipation was present for 81% of cases.

4. Care modalities

There are technical possibilities for maintaining life among these infants, for example artificial ventilation with tracheostomy. In our mind, it is very important to consider the whole life of these children and their families and, at the diagnosis with the parents, to discuss what life can mean with such a major disability and what kind of technical assistance should be chosen and accepted. That is why we believe that care should be essentially supportive and palliative with an objective of comfort and quality of life for the babies. This also requires experienced practitioners.

Respiratory management associates respiratory tract drainage, treatment of respiratory infection and technical support for ventilation. For respiratory tract drainage, physiotherapy is performed, in most cases, by a physiotherapist during short sessions, and most patients require a suction aspiration system at home. Oxygenotherapy can be given to avoid hypoxemia, with a very low flow of oxygen. Hully et al. reported using oxygen at home starting at a median age of 5 months [11]. Respiratory infections can be treated by adjusted antibiotherapy. Vaccinations must be done carefully (also for influenza, haemophilus and pneumococcus) and the use of palivizumab in the prevention of RSV infection should be discussed.

Non-invasive ventilatory (NIV) support is not useful for severe types and may even not be well tolerated for infants presenting bulbar signs. NIV should be discussed in some cases to pass a critical stage. In the French cohort, NIV was used in 7%. Invasive ventilatory support in chronic use is not indicated in these cases because of the extreme paralysis and the progressive course of the other functions (facial mobility and phonation for example).

Nutritional and digestive management: It is important to track and prevent deglutition trouble and to check that the baby can consume enough energy intakes. Enteral nutrition is frequently used (43% among the historical French cohort and 92% among the prospective cohort at a median age of 5 months, reported by Hully et al. [11]. Enteral nutrition is usually administered through a nasogastric tube. The use of a gastrostomy is frequent in some countries and rare in others: In France, it is used for very few patients (3%).

Installation and motor physiotherapy are essential for the comfort of babies: in most of them, the prone position is not comfortable and they seem to be more comfortable in side decubitus. A comfortable installation can be performed by a specialist practitioner (physiotherapist or occupational therapist) and will be evaluated according to the age of the child and his respiratory insufficiency: in very advanced deterioration babies no longer support the seated position and prefer being in decubitus to improve diaphragm strength.

Sometimes medicines are used to improve comfort. Hully et al. have reported that paracetamol was used in 61% at a median age of 5.2 months, grade 3 analgesics in 34% (mostly oral morphine), Benzodiazepines in 26%, and amitriptyline in 31%. [11]

5. New therapies

The development and use of innovative therapies in recent years does actually change the natural course of this disease [12]. However, we do not yet have a treatment that will cure; although some infants may be improved with these treatments, they will still have a major disability. We also need to be modest because we do not know for sure what the long-term evolution of infants who received these new therapies will be.

Disclosure of interest

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

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