

The Schwartz-Jampel Syndrome. A Minireview

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Abstract

The Schwartz-Jampel Syndrome (SJS) is a very rare condition characterised by Constant findings such as typical facial appearance, muscle hypertrophy and continuous muscle activity. Other findings are more or less frequently associated, especially skeletal abnormalities, including dwarfism or anyway short stature.

The Authors review the literature about this condition analysing the clinical picture, the recent genetical findings, the electrophysiological and histopathological studies and the different pathogenetical hypothesis.

Key words: Schwartz-Jampel Syndrome, chondrodystrophic myotonia, myotonic disorders, channelopathies.

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The Schwartz-Jampel Syndrome (SJS), or Chondrodystrophic Myotonia, was described for the first time in 1951 by Catel et al. [9] and was then better defined in 1962 by Schwartz and Jampel [33]. It is a very rare disease (only about 50 cases have been described so far); it's usually transmitted as autosomal recessive although autosomal dominant cases have also been reported [13].

The clinical picture of SJS has been widely described, while the genetical and pathogenetical aspects are still under debate. Recent reports about some patients treated successfully with Carbamazepine suggest new therapeutic possibilities [39, 41].

We are going to review the literature about SJS concerning the clinical findings, advances in molecular genetics, pathogenetical hypothesis and therapeutic trials.

From a clinical point of view, SJS is characterised by some Constant features and other more or less frequently associated conditions. Constant findings can be considered the typical facial appearance, muscle hypertrophy and continuous muscle activity (myotonia?) [1, 2, 3, 6, 16, 19, 28, 30, 31, 32, 33, 42, 43]. Very often also skeletal deformities are associated, but some cases without skeletal abnormalities have been described. Typical facial appearance, with convex profile, short palpebral fixures, telecanthus, dimpling or quivering of the chin, prominent eyebrows, low hairline, low-set ears, flat base of the nose, micrognathia, microstomia, sometimes high-arched palate muscular hypertrophy and myotonia is diffuse, but more prominent in proximal and facial muscles. The continuous myotonia is probably responsible for both muscular hypertrophy and peculiar facial appearance and can also cause a high-

pitched voice or speech defect. Skeletal muscles are stiff even at rest and during sleep, and are resistant to passive range of motion. Limited range of movements of the major joints is reported to be progressive, involving mainly the knees, hips, shoulders and elbows. Tendon reflexes are generally depressed.

Skeletal deformities: these may include dwarfism or anyway short stature, short neck, various vertebral deformities, lumbar hyperlordosis, with scoliosis, hip dysplasia/luxation, joint contractures and metaphyseal deformities, similar to those described in Morquio's disease, even if no abnormalities in mucopolysaccharides have been described so far in SJS.

Additional findings, reported in some cases, are: diffuse hypertrichosis, myopia, strabismus, intellectual impairment of various degree, that, according to a recent study, consists of a developmental language disorder rather than mental retardation [27, 43]. There have been also isolated reports of associated diseases: Von Willebrand's disease [22], recurrent chest infections [21], malignant hyperthermia [34], hydrocephalus, carpal tunnel syndrome [10], and compressive myelopathy [36]. The last two associations are probably due to the skeletal abnormalities.

Onset is generally by the third year of age, but also neonatal cases have been described, for which presuming onset had occurred *in utero* and could be demonstrated by ultrasound performed during pregnancy [12, 18].

In newborns feeding and respiratory problems, due to severe myotonia, can dominate the clinical picture [12, 18]. The intake of cold drinks at any age can cause even severe respiratory problems and, generally, the coldness

worsens the muscle condition. There can be a slight delay in achieving motor milestones, due to muscular stiffness.

The course of the disease seems to be slightly progressive, reaching the maximum of contractures and of motion impairment in adolescence, after which it tends to remain stable. Also more severe courses have been described. Life expectancy is normal [6, 11, 14, 16, 28, 32, 43].

As far as described so far, the clinical picture is quite heterogeneous in the same kinship and it is possible that SJS comprises a group of different diseases, which share some clinical features, or that the phenotype is the result of the combination of genetic and external factors.

Recent Genetical Findings

In 1995, a group of researchers constituted by Nicole, Ben Hamida, Viljoen, Fardeau et al. has mapped SJS locus on chromosome 1 (1p34-p36.1) in a 8 cM interval [25]. The authors analysed families from Tunisia and South Africa, which all showed a linkage to that locus. The disease shows some similarities with other conditions due to some abnormalities in ion channels, therefore the candidate genes could have been the ones for ion channels or proteins regulating the ion channel function. Nevertheless, none of such genes has been mapped in 1p34-p36.1 region. A further study performed by Fontaine et al. [15] confirmed the linkage to chromosome 1p and reduced the SJS locus to a 3 cM interval, but the gene has not been mapped yet. Thinking of the skeletal abnormalities, also the trophic factors and the genes implicated in development have been searched, unsuccessfully, in that region. Finally, murine chromosome 4 has a homologous region to human 1p, but no murine disease similar to SJS has been described so far [25].

So, even though the recent genetic advances are surely important, it has not been possible to conclude anything about the causes of SJS so far. The following questions are still unanswered:

- 1) Is there any correlation between the skeletal and systematic abnormalities and the muscular problems?
- 2) What is the cause of myotonia, or of the continuous muscular activity?

As to the first problem, it must be probably distinguished between the skeletal and the other abnormalities. In fact, the skeletal abnormalities could be the consequence of the muscular problem: continuous muscular contractions could cause both the muscular hypertrophy (as already shown in other disorders characterised by continuous muscle contractions) and the impaired stature growth (mainly because of the early onset of SJS) and the bone deformities. To demonstrate this hypothesis is the remarkable improvement regarding both the stature growth and the skeletal deformities that has been obtained by Topaloglu et al. who treated very early and successfully with CBZ a patient affected by SJS [41]. Because the skeletal deformities resemble those in Morquio's syndrome, muchopolysaccharide analysis have been performed, but no abnormalities have been reported. Fowler et al. [16] speculated on a

possible abnormal response of muscle membrane to neural influence during fetal development, which would result in abnormal regulation of membrane ion conductance. There is only one report of abnormal urine excretion of acidic glycosaminoglycans, that is not enough, to suppose any true role of chondroitin-4-sulfate (or acidic glycosaminoglycans) in the pathogenesis of SJS [26].

The associations with Von Willebrand's disease [22] and IgA deficiency [21] seem instead to be casual.

The pathogenesis of SJS is still unknown: we'll describe the results of the histopathological, ultrastructural, electrophysiological and physiological studies trying to focus the arising hypothesis.

Light microscopy studies of muscle have never revealed any specific feature: myopathic, neurogenic and even almost normal muscle biopsies have been described [6, 8, 16, 19, 20, 31, 37]. Different Authors found increased variability in fibre size, internal nuclei, type 1 fibre predominance, type grouping. Histological studies of peripheral nerve have not shown abnormalities.

Immunohistochemistry of contractile and cytoskeletal proteins showed abnormal atrophic fibres, with abnormal accumulation of desmin, vimentin and titin, in addition to the coexpression of fast, slow, foetal and embryonic MHC isoforms, suggesting that these are regenerating fibres. Moreover, predominance of type 1 fibres and fibre type grouping suggests reinnervation [38].

More homogeneous appear the ultrastructural features, characterised by dilated mitochondria, with rare cristae. However, no specific alterations of mitochondrial enzymes have been described so far, and the mitochondrial features reported above are not particular to any disease. Moreover, no ragged-red fibres have been found. A constant finding in electron microscopic studies in SJS are the interruptions in the sarcomeres, including Z disks, together with focal disarray of myofibrils. Also these findings are aspecific. Endplate did not reveal specific changes in morphology.

Electrophysiological Studies

Nerve conductions are usually normal. Only recently has been reported the evidence of central conduction impairment, documented by somatosensory evoked potentials [35]. Clear abnormalities have been found instead at needle examination and a matter of debate is whether the abnormal activity registered on EMG is myotonia or not and where it comes from.

Myotonic syndromes in childhood differ one from another for clinical, genetical and EMG findings.

From the EMG point of view, myotonic discharges are not the same in the various myotonic syndromes, because they differ in incidence, mean duration and amplitude frequency pattern. The spontaneous EMG activity in SJS has been described variously in different patients. Some authors like Aberfeld in 1970 [1] and Pavone in 1978 [30], found typical myotonic discharges in patients affected by SJS. Others, instead, like Huttenlocker in 1969 [17],

Brown in 1975 [6], Cao in 1978 [8], and Ferranini in 1982 [13], found continuous muscle activity at rest, with high frequency discharges and low voltage potentials and high-frequency, spontaneous repetitive potentials and also discharges similar to the myotonic ones, but which did not wax and wane. The high-frequency discharges have been observed at rest, during sleep and in general anaesthesia. Finally, other authors found a combination of both kinds of activity.

The regular, spontaneous activity has been described in different ways and, more recently, as complex repetitive discharges (CRDs) [23]. This definition is important from a pathogenetic point of view, because CRDs consist of muscle fibre potentials which are closely timed-locked as a result of ephaptic impulse transmission between the fibres and are mainly encountered in chronic neurogenic disorders, but also in muscular dystrophies, metabolic myopathies and polymyositis.

Pathophysiology

Explanations of the pathophysiology underlying this electrical hyperexcitability and stiffness are conflicting. Several authors [7, 16, 40] suggested that the origin of the involuntary activity may be neural because curare decreases it *in vivo*. Other authors [6, 8, 37] found that curare had no effect and concluded that it was due to a defect of the muscle fibre itself. Moreover, other authors suggested the possibility that ephapses are responsible for the muscle hyperactivity [20]. The *in vitro* study performed by Lehmann-Horn et al. in 1990 showed that the skeletal muscle in SJS is affected by several different defects [23], such as abnormal Na^+ channels gating, reduced Cl^- conductance and altered regulation of myoplasmic free Ca^{++} .

The Na^+ channels were activated with a delay that was variable, yet often the openings of the Na^+ channels were synchronised. Moreover, gating of the Na^+ channels was observed even after repolarisation of the membrane patch. On the other hand, in this study it was demonstrated that Na^+ channels were inactivated within a few milliseconds, in a potential-dependent manner, like in normal muscle. Tocainide suppressed the hyperexcitability, presumably by blocking the synchronised opening of the sodium channels. The behaviour of Na^+ channel in SJS was different from the one observed in Myotonic Dystrophy, in which late openings of the Na^+ channel were always preceded by an early activation of Na^+ channels. Lehmann-Horn et al. in this study hypothesised that the synchronised late openings could be the result of a structural defect of the Na^+ channel itself, an alteration in the surrounding lipid membrane, or an altered intracellular control of the Na^+ channel gating, but concluded that a defect of the channel protein itself was not very probable [23].

The good results obtained treating some patients with CBZ could be related to the mechanism of action of CBZ and to the hypothesis of a defect in Na^+ channels as pathogenetic basis for SJS. CBZ appears to affect sodium channels. The effect is likely to involve the inactivation

process of sodium channels. It has been proposed [24] that CBZ binds to sodium channels only in the inactive state and produces limitation of repetitive firing only when the membrane is depolarised, so that a fraction of the channels are in the inactive state. It is also possible that CBZ produces limitation of high-frequency repetitive firing by binding to sodium channels in the inactive state and by slowing the rate of recovery of these channels from inactivation. There are also studies that show that CBZ may decrease excitatory synaptic transmission. However, these studies do not clarify whether the effect of CBZ is presynaptic or postsynaptic.

Anyway, even though only a few cases have been treated with CBZ up to now, the results showed that patients had good response to this therapy, especially if a very early diagnosis is possible, so that both the muscular problems and the skeletal abnormalities can be reduced.

Conclusions

SJS is a very rare disease.

It must be included in differential diagnosis in both dysmorphic syndromes with joint contractures, like for instance Freeman-Sheldon Syndrome and the Myotonic Syndromes of childhood.

The diagnosis relies on both clinical and EMG findings and sometimes can be even prenatal, by ultrasound evaluation. Even though the EMG and also the clinical picture of SJS differs from myotonic dystrophy, a recent study about somatosensory evoked potentials suggests some similarities in the CNS involvement. This aspect must be better studied.

Other questions are still unanswered in SJS, about genetics and pathogenesis.

It's worthwhile trying therapy with CBZ.

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