SCHWARTZ-JAMPEL SYNDROME (SJS) A RARE ENTITY: CASE REPORT

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ABSTRACT: PURPOSE: Systemic and ocular evaluation of a rare case of Schwartz-Jampel syndrome. **METHODS:** A case of Schwartz-Jampel syndrome was identified and evaluated during eye checkup as patient attended eye OPD of a tertiary eye care centre in central India. **CONCLUSION:** Schwartz-Jampel syndrome (SJS) is Characterized by myotonia and osteoarticular abnormalities.¹ Causative gene for SJS, HSPG2 (1p36), encodes perlecan, a major component of the Cellular matrix.² **KEYWORDS:** EMG, multi system SJS, blephrophemosis.

INTRODUCTION: In 1962, Oscar Schwartz and Robert Jampel jointly described a rare autosomal recessive disorder in a pair of siblings.^{3,4} the children had short stature, myotonia with paucity of facial expression, blepharophimosis, pectus carinatum, and contractures.⁵ This disorder was also designated osteo-chondro-muscular dystrophy or chondrodystrophic myotonia,⁶ and it was initially thought to be neurogenic in etiology. Recently, mutations in the gene Perlecan (HSPG2) encoding the protein heparan sulfate proteoglycan 2, have been found to be responsible for this condition. Perlecan resides in 1p34-p35.1. Its attendant defect leads to abnormal cartilage development and anomalous neuromuscular activity, resulting in skeletal dysplasia and electrophysiological signs of myotonia as seen in chondrodystrophic myotonia or Schwartz-Jampel syndrome (SJS).⁷

BACKGROUND: Schwartz-Jampel syndrome (SJS) is a term now applied to 2 different inherited, autosomal recessive conditions, sometimes termed SJS type I and SJS type II. Both are very rare. SJS type I has two recognized subtypes, IA and IB, which are similar except that type IB manifests earlier and with greater severity. The first described cases of SJS were reported in 1962 by Oscar Schwartz and Robert S. Jampel in the Archives of Ophthalmology in an article titled "Congenital blephar-ophimosis associated with a unique generalized myopathy."

SJS Type I: The clinical features of muscle stiffness in SJS type I⁸ somewhat resemble those seen in myotonic disorders, stiff person syndrome, and Isaacs's syndrome. The stiffness does not disappear with sleep or benzodiazepine treatment (As in stiff person syndrome), and it is not abolished reliably with curare (As in Isaacs syndrome).

Neurophysiologic examination typically shows continuous electrical activity (Similar to myotonic discharges). However, the electrical activity often lacks the waxing and waning quality of true electrical myotonia and might be better described as complex, repetitive discharges. At other times, the pattern resembles neuromyotonia (i.e, extremely rapid, repetitive discharges that wane from an initially high amplitude). In other cases, a combination of these and other electrical patterns are seen. Perhaps a unique Schwartz-Jampel pattern exists that has not yet been fully defined. In affected patients with type I, problems with motor development frequently become evident during the first year of life.

Usually, the characteristic dysmorphic features lead to an early diagnosis, no later than age 3 years. SJS types IA and IB derive from mutations of the same gene, the HSPG2 gene, which codes for perlecan, a heparin sulfate proteoglycan.

Type IA: The most commonly recognized and described form of SJS is type IA, which exhibits muscle stiffness, mild and largely nonprogressive muscle weakness, and a number of minor morphologic abnormalities. Type IA is the classic type described by Schwartz and Jampel. It becomes apparent later in childhood and is less severe than type IB. (See Presentation.)

Type IB: Type IB is apparent immediately at birth and is clinically more severe, although it is typically compatible with life and even long-term survival.

SJS Type II: SJS type II,⁸ like type IB, is apparent immediately at birth. The patients look similar to those with type IB. However, it has been known for many years that type II does not map to the same chromosome as types IA and IB. It is now known that type II relates to a mutation in a different gene, the gene for the leukemia inhibitory factor receptor (LIFR). This is the same disease as Stuve-Wiedemann syndrome, which has been known separately, mainly in the rheumatologic and orthopedic literature, rather than the neurologic literature. The cardinal features of type II are joint contractures, bone dysplasia, and small stature. Infants with type II have severe respiratory difficulties and feeding problems. Hypotonia (Rather than stiffness) is prominent. Frequent bouts of hyperthermia have been described possibly related to mitochondrial dysfunction.

A high infant mortality rate is associated with this condition. Long-term survivors are rare but do exist, including 2 survivors, ages 3 and 12 years, reported on by Di Rocco et al in 2003. In addition to problems with bone dysplasia, these 2 children manifested dysautonomic and neuropathic features, including reduced patellar reflexes, lack of corneal reflexes, and paradoxical perspiration at low temperatures. Their tongues lacked fungiform papillae (In addition to showing ulcerations). Reither et al reported on a survivor aged 16 years with SJS type II.

Genetics of SJS Type I: A multinational⁹ collaboration of scientists localized the gene defect for type I SJS to the 1p34-p36 region of chromosome 1. Further research showed that the specific gene affected was the gene for perlecan, which is a heparin sulfate proteoglycan, the major proteoglycan of basement membranes. It is also involved in cartilage. The gene encoding for perlecan is called HSPG2. Nicole et al described 3 families with a mutation in the HSPG2 gene. Although SJS types IA and IB both involve a mutation of the perlecan gene, type IB is a more severe condition and, therefore, is usually diagnosed earlier than type IA. One factor that has impeded the further understanding of SJS type I is that until the early 21st century, very few patients had been studied genetically. Through 2005, only 8 patients from 6 families had been reported in molecular genetic studies.

Stum et al made a major addition to this literature with a molecular mutations were private. Thus, no existence of a founder effect was suggested, whereby genetic study of 35 patients in 23 families, finding 22 new mutations. Most all (or a large percentage) of mutations could be presumed to derive from a single original case. The mutations included insertions and deletions and splice-site, missense, and nonsense mutations. Most of the mutations allowed for some level of functional protein production.

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Often, a given patient has 2 different types of mutations, 1 of which allows a greater production of functional perlecan protein than the other. Based on the cases studied molecularly thus far, some level of functional perlecan protein production always seems apparent. Indeed, through alternative splicing, the normal protein may actually be produced, albeit at a lower level than normal. In other cases, a functional, but somewhat abnormal, protein may be produced. Alternatively, a combination of different variants of perlecan could be produced, although at lower levels of functional protein than normal. Thus, a significant amount of molecular heterogeneity exists, genomically and proteomically, within SJS type I.

One would like to think that the molecular heterogeneity could explain the clinical heterogeneity, especially the existence of types IA and IB. In other words, it might be plausible that in type IA, more normal, or at least more functional, protein is available than in type IB. So far, however, that has not been shown.

In addition, no correlation has yet been found between the specific mutations found and the specific features of a given case. However, the findings by Stum et al should be important tools to help find correlations among genetic variants, perlecan forms and levels, and clinical subtypes. Of course, other facts yet unknown also may influence the severity and the specific characteristics of the disease.

A study by Rodgers et al questioned the concept that the C1532 mutation is the sole causative factor in SJS. The investigators developed perlecan knock-in mice to model SJS. The authors suggested that the transcriptional changes leading to perlecan reduction may represent the disease mechanism for SJS.

A study by Stum et al concluded that partial endplate acetylcholinesterase (AChE) deficiency may contribute to muscle stiffness. However, this deficiency was not associated with spontaneous activity at rest on EMG in the diaphragm, suggesting that there are additional factors that are required to generate the activity seen in SJS.

Dyssegmental dysplasia of the Silverman-Handmaker type.

An additional point of interest related to perlecan is that another disease, called dyssegmental dysplasia of the Silverman-Handmaker type (DDSH), is also caused by a recessive mutation of the perlecan gene. This disease is even rarer than SJS or Stuve-Wiedemann syndrome, and even fewer cases have been studied molecularly.

In the few patients who have been studied, mutations that totally eliminate the ability to produce any functional protein product (i.e, functionally null mutations) have been discovered. Therefore, whereas in SJS types IA and IB some level of functional (and often even normal) perlecan protein is always produced, in DDSH, none is produced.

Conceptually, one could argue that DDSH is a third form of SJS type I (e.g, type IC)-the worst type. However, it is considered a separate disease for several reasons.

Genetics of SJS Type II: SJS type II is not caused by the same genetic abnormality as SJS type I. The diseased gene in type II has been mapped to band 5p13.1, at locus D5S418. By studying the genetic material of 19 patients who had been diagnosed with either Stuve-Wiedemann syndrome or SJS type II, investigators found that all patients had null mutations in their LIFR gene at the above-mentioned locus. This impaired the function of the JAK/STAT3 signaling pathway. Although the exact mutation was not identical in all 19 patients, the fact that the mutations all appeared to have the same

molecular biologic and biochemical effect led to the conclusion that Stuve-Wiedemann syndrome and SJS type II should be considered a single, homogeneous disease.

Prognosis: Except for the patients with Stuve-Wiedemann syndrome, which is fundamentally a different disease from SJS type I, most patients with SJS have a good prognosis. Muscle stiffness, muscle weakness, and skeletal abnormalities may worsen gradually or remain essentially stable.

MORBIDITY AND MORTALITY: SJS type IA does not significantly shorten lifespan. No definite data exist on whether this is also true for type IB shortens lifespan. Type II definitely shortens lifespan, with most patients not surviving to adulthood.

Much of the morbidity of SJS types IA and IB is related to the discomfort associated with the muscle stiffness and to problems with blepharospasm. As many as 20% of affected patients are mentally retarded. However, many patients are of normal or even superior intelligence. Skeletal abnormalities and other physical deformities may cause psychological morbidity in some individuals. Like a number of other myopathies, SJS is associated with an increased risk of malignant hyperthermia.

Physical Examination: The dysmorphic features of SJS are usually evident on physical examination. Most patients are short with narrow palpebral fissures (Blepharophimosis), flattened facies, and micrognathia. Some patients show blepharospasm in addition to the blepharophimosis. The muscles are stiff and they can be either hypertrophic or reduced in mass.

Bony Abnormalities include the following:

- Joint deformities and limitations of joint motion.
- Coxa valga.
- Irregularity of the capital femoral epiphyses.
- Kyphosis.
- Short neck.
- Pectus carinatum.

Differential Diagnoses:

- Charcot-Marie-Tooth and Other Hereditary Motor and Sensory Neuropathies.
- Congenital Muscular Dystrophy.
- Congenital Myopathies.
- Myasthenia Gravis.
- Myokymia.
- Periodic Paralyses.
- Stiff Person Syndrome.

INVESTIGATIONS:

Blood Tests: Blood tests may show minor elevations of serum creatine kinase or aldolase. However, in many cases, these enzyme levels are normal. Now that the genes are known, sequencing or polymerase chain reaction (PCR) assay studies could be performed, but the specific genes are still not

available as tests that can be ordered from a commercial laboratory. Physicians might consider referring suspected cases to genetic clinics that have affiliations with groups actively researching SJS so that genetic studies can be performed.

Imaging Studies: Imaging studies are of little use. Spinal films reveal kyphosis. Radiographs can reveal other skeletal deformities but generally are not necessary for diagnosis.

Muscle Biopsy: Muscle biopsy findings of patients with SJS are consistent with a myopathy.

Histologic Findings: Minor, ultrastructural abnormalities have been described in SJS, but no specific electron microscope signature is known for the disorder. Light microscope findings are usually suggestive of a myopathy. Variations in muscle fiber size are common. As the individual ages and the disease becomes more advanced, fat and connective tissue may replace muscle fibers.

EMG and Nerve Conduction Studies: The symptoms of muscle stiffness and of difficulty relaxing the muscles may prompt EMG and nerve conduction studies in a patient. Typically, the nerve conduction findings are normal.

The EMG needle study may show continuous discharges. These discharges frequently have the individual appearance of positive sharp waves or fibrillations, but they occur in runs of many discharges.

In some cases, the discharges have been described as myotonic, which suggests a waxing and waning character. In other cases, the discharges have not shown waxing or waning. In such cases, they would be considered complex, repetitive discharges.

Treatment Considerations: The treatment of Schwartz-Jampel syndrome (SJS) aims to reduce the abnormal muscle activity that causes stiffness and cramping. Treatment may include nonpharmacologic modalities, medication (including botulinum toxin) or surgery.

Nonpharmacologic modalities and strategies such as massage, warming, gradual warm-up prior to exercise, and gradual stretching may obviate the need for medications.

Surgical Treatment: A variety of surgical techniques have been used effectively, including orbicularis oculi myectomy, levator aponeurosis resection, and lateral canthopexy.¹⁰

Medication Summary:

Medications used in the Treatment of Schwartz-Jampel Syndrome (SJS) include the following:

- Anticonvulsants Phenytoin, carbamazepine.¹¹
- Antiarrhythmic agents Mexiletine, procainamide, quinidine.
- Antimalarials Quinine.
- Neuromuscular blocking agents Botulinum toxin.

Some anticonvulsants appear to reduce excess muscle cell depolarization, while the antiarrhythmics may reduce or regulate the firing rate of skeletal muscle cells, much as they do in cardiac cells. Botulinum toxin blocks neuromuscular transmission through a multistep process.

The antimalarial drug quinine appears to increase the refractory period for muscle discharge, exerts a curare like action on the motor endplate, and alters the intracellular calcium distribution in a way that makes the muscle less excitable.

CASE REPORT: A 9 years male attending the tertiary eye Centre in central India presented with complaints of diminution of vision in both the eyes, inability to open eyes since 3 years duration, mild muscle stiffness and unusual facial features gradually worsening since 6 years duration. A complete ocular examination revealed an impaired visual acuity (Unaided), which improved to 6/12 in both the eyes with pin hole, on refraction the patient, was found to have myopic astigmatism, though vision improved to 6/12. External ocular examination revealed blepharophimosis syndrome, hypertrichosis. Conjunctiva, cornea looked normal. Anterior chamber depth was normal. The crystalline lens was normal in both the eye. Vitreous cavity and, retina appears to be normal in both the eyes. Optic disc was normal. A typical facial appearance, poor dental hygiene, unusual flattened facies with a puckered facial appearance. Various differential diagnoses were kept in mind and a thorough past history and past treatment as well as hospital records were seen. A medical past history revealed there was no consanguity in the family.

There is no significant history revealed. The patient had a normal hospital delivery with antenatal, intranatal and post natal periods all uneventful. Baby after birth was fully vaccinated and achieved all the milestones in time. At the age of 3 years the patient's mother noticed his difficulty in walking, with a slight change in facial appearance. Then the baby was taken to various hospitals in central India. Ophthalmologists regularly reviewed the growing baby as he was having difficulty in opening both the eyes. At the same time the baby started having mild grade muscle stiffness and myotonia, while weight and the height of the baby for his age was below normal. The baby experienced progressively increasing muscle stiffness for which he was given some muscle relaxants by the neurologist. The patient is still taking the treatment, as per the informant though the dose was adjusted according to his growing height and weight. The patient had history of a slight delay in mental status. Other investigations in the past revealed a pigeon like chest as evident by X–Ray chest, ECG echocardiography was showing some abnormality. ECHO was suggestive of sub aortic VSD (L to R shunt). EMG pointing towards myopathy while other investigations did not point towards any conclusive diagnosis. Based on EMG findings and characteristic joint and facial features our patient's diagnosis was Schwartz Jampel syndrome.



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Fig. 3: Defective electromyograph

Visual acuity	In both eye Unaided 6/24, BCVA 6/12
	Unaided 6/24, BCVA 6/
Face	Puckered facial appearance, less mass
Eyelids	Blepharospasm, Blepharophimosis,
	Hypertrichosis.
Conjunctiva, cornea,	Normal
anterior chamber	
Iris, pupil, lens	Normal
Fundus	WNL
Schirmers test	Full wetting
Schirmers test IOP	Full wetting WNL
Schirmers test IOP Refraction	Full wetting WNL Simple Myopic astigmatism
Schirmers test IOP Refraction Corneal sensations	Full wetting WNL Simple Myopic astigmatism Normal in all sectors

X – Ray chest	Revealed pigeon like Chest
ECG	Showing abnormality
Echocardiography	Revealed Subaortic VSD (L to R shunt)
Electromyography	Revealed diffuse mayopathic disorder.
Table 2: Investigations	

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DISCUSSION:

- Electromyography reveals myotonia, Responsible for blepharophimosis, unsteady gait, short stature, myopia etc.
- On the basis of EMG findings and facial Features, we diagnosed the case.
- Management indicated in narrow Palpebral fissure is levator muscle Resection and spectacles for high myopic Astigmatism. Carbamazepine leads to Improvement of symptoms. Treatment with carbamazepine, initiated in infancy, can produce marked resolution and continuous improvement of myotonia, blepharospasm and joint stiffness, resulting in lessening of the chest deformity and contractures.⁸ The contractures are progressive until mid-adolescence but thereafter, usually become static. The myotonia may improve spontaneously in later childhood.
- Individuals with SJS should be cautioned regarding life-threatening complications that may arise during anesthesia. Micrognathia and jaw muscle rigidity may pose mechanical difficulties during intubation. Higher doses of muscle relaxants such as rocuronium may be required to facilitate tracheal intubation; probably because of the lowered degradation rate of acetylcholine.⁹ malignant hyperthermia during anesthesia is a potentially lethal complication. In view of the autosomal recessive mode of inheritance of this disorder, genetic counseling may be appropriate as the risk of recurrence is 25% or 1 in 4.

CONCLUSION: Schwartz-Jampel syndrome (SJS) is characterised by myotonia and osteoarticular abnormalities. Around 100 cases have been described in the literature so far. The clinical manifestations appear soon after birth. The myotonia results in a characteristic facies with blepharophimosis and a puckered facial appearance. Low-set ears, external ear anomalies and micrognathia have also been reported. Limited joint mobility leads to an unsteady gait. Joint stiffness is progressive, reaching its peak during adolescence. Flattening of the vertebral bodies, hip dysplasia, bowing of the diaphyses and irregular epiphyses are often observed. The clinical picture also includes short stature, hirsutism, myopia and small testes.

Transmission is autosomal recessive. The causative gene for SJS, HSPG2 (1p36), encodes perlecan, a major component of the cellular matrix. Electromyography reveals myotonia and the osteoarticular anomalies are visible on radiographs. The perlecan deficiency can be detected by immunocytochemical analysis of skin and muscle biopsies or by analysis of fibroblast cultures. The differential diagnosis should include Stuve-Wiedemann syndrome, which differs from SJS by the type of skeletal anomalies reported and its more severe early prognosis. Severe forms of congenital myotonia and myotonia associated with sodium channel mutations should also be considered in the differential diagnosis. Treatment of the myotonia is problematic but some studies have suggested that carbamazepine leads to improvement of symptoms. The disease appears to stabilize after adolescence.

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