Case Report

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Radiology Section

Schwartz-Jampel Syndrome: A Case Report with Clinical and Phenotypic Insights

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ABSTRACT

Schwartz-Jampel Syndrome (SJS) is a rare autosomal recessive disorder characterised by myotonia, craniofacial dysmorphism and skeletal dysplasia, resulting from pathogenic variants in Heparan Sulfate Proteoglycan 2 (HSPG2). Pathogenic variants disrupt perlecan function, resulting in abnormal cartilage development and impaired neuromuscular transmission. A three-year and five-month-old male presented with blepharophimosis, generalised muscle stiffness, delayed motor milestones and gait abnormality. Electromyography demonstrated continuous spontaneous myotonic discharges. Radiographs revealed metaphyseal dysplasia with epiphyseal abnormalities. Molecular testing identified three heterozygous HSPG2 variants with parental carrier status, consistent with compound heterozygosity. Carbamazepine and structured rehabilitation were administered. Follow-up demonstrated reduction in myotonia, improved gait parameters and decreased fall frequency. In early-onset myotonic disorders, SJS should be considered with characteristic craniofacial and skeletal features. Symptomatic treatment with sodium-channel–blocking agents and multidisciplinary rehabilitation may confer functional benefit.

Keywords: Compound heterozygosity, Electromyography, HSPG2, Myotonia, Skeletal dysplasia

CASE REPORT

A three-year and five-month-old male child, born to non consanguineous parents, presented with bilateral ptosis, progressive stiffness of the elbows and knees and difficulty rising from the sitting position, noted from two years of age. The gait was abnormal with outward deviation of the ankles, accompanied by frequent falls. Intermittent dysphagia had been present for the preceding 1.5 years. Developmental history revealed delayed acquisition of motor milestones, whereas cognitive, language and social development were normal.

Symptoms progressed gradually, and the child developed a persistent flexed posture of both elbows and increasing gait stiffness. There was no history of seizures, regression, perinatal insults, or similar complaints in family members.

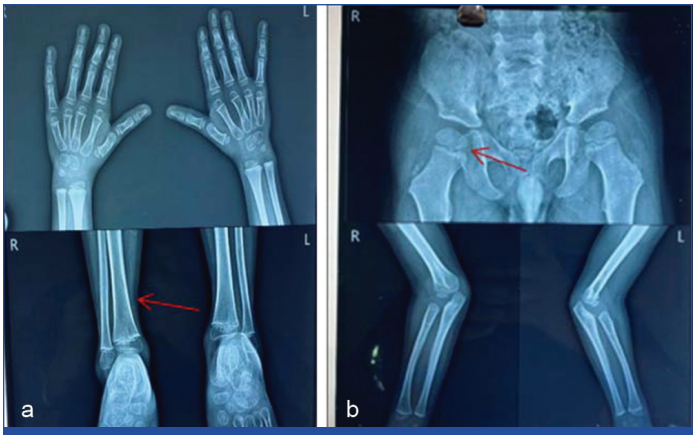
Physical examination revealed a dull, mask-like facial expression, blepharospasm and low-set ears with generalised muscle rigidity. Gait was short-stepped and stiff. No facial asymmetry, focal neurological deficits, or signs of peripheral neuropathy were noted. Systemic examination of cardiovascular, respiratory and abdominal systems was normal. Clinical photographs demonstrated blepharophimosis, bilateral ptosis, facial hypotonia and flexed elbow posture with ankle deformity, consistent with the described phenotype [Table/Fig-1a-e].

Electromyography was performed in both proximal and distal muscles. Serum creatine phosphokinase levels were elevated. Needle electromyography was carried out at multiple sites, including the right deltoid, right biceps, right first dorsal interosseous, right vastus lateralis and right tibialis anterior muscles. The study demonstrated continuous spontaneous myotonic discharges at rest. Nerve conduction studies were within normal limits, with normal motor and sensory conduction velocities and amplitudes, indicating no evidence of peripheral neuropathy. Radiographs of long bones showed metaphyseal dysplasia with irregularity of the epiphyses [Table/Fig-2a,b].

Parental segregation analysis was performed to clarify the inheritance pattern of the identified variants. The analysis demonstrated that the c.646G>C variant in exon 5 was inherited from the mother, while the p.Gln1180 variant in exon 28 was inherited from the father. In addition, the p.Lys896Lys synonymous variant located in intron 21 was detected in the heterozygous state in one of the parents, indicating carrier status. These findings confirm that the proband harbours variants on separate alleles, consistent with an autosomal recessive compound heterozygous inheritance pattern, which is in keeping with the genetic basis of SJS.

Based on American College of Medical Genetics and Genomics (ACMG) criteria [1], the c.646G>C (exon 5) variant represents a missense alteration affecting a conserved residue. In silico prediction tools suggested a damaging effect and segregation analysis supported its disease association; therefore, this variant was classified as likely pathogenic. Similarly, the p.Gln1180 (exon

[Table/Fig-1]: Clinical features of SJS: a) Blepharophimosis with bilateral ptosis; b) Low-set ears and flat facial expression; c) Persistent elbow flexion posture; d) Ankle valgus deformity with gait stiffness; e) Generalised muscular rigidity.



[Table/Fig-2]: Radiographic findings; a) Metaphyseal irregularity of long bones; b) Epiphyseal dysplasia and undertubulation.

28) missense variant, located within a functionally important region of the protein, was predicted to be deleterious by multiple computational models and demonstrated segregation with disease within the family, leading to its classification as likely pathogenic. In contrast, the p.Lys896Lys variant, a synonymous/splice regulatory change in intron 21, lacked definitive functional or population-level evidence of pathogenicity and was thus categorised as a Variant of Uncertain Significance (VUS). Genetic testing was performed using Whole Exome Sequencing (WES), and the detected variants were subsequently validated by Sanger sequencing along with parental segregation analysis.

Carbamazepine was initiated at 10 mg/kg/day in two divided doses, with gradual titration to 15-20 mg/kg/day based on clinical response and tolerability. Concurrent neurological rehabilitation, including stretching exercises, gait training and orthotic support, was continued as part of the multidisciplinary management.

Over a two-month follow-up period, significant clinical improvement was observed. Gait speed increased, stride length improved, and double support time decreased, indicating enhanced stability and mobility. The frequency of falls markedly declined. No adverse drug reactions or deterioration of motor function were noted.

The family received genetic counselling, addressing prognosis, recurrence risk and the role of early rehabilitation and orthopaedic surveillance.

The SJS is primarily caused by biallelic loss-of-function mutations in the HSPG2 gene, encoding perlecan, a proteoglycan essential for cartilage maturation and neuromuscular junction stability [4,5]. Defective perlecan results in persistent muscle stiffness, distinctive facial features, short stature and progressive musculoskeletal deformities, typically presenting in early childhood, while cognition is usually preserved [6]. Facial manifestations described in literature include blepharophimosis, narrow palpebral fissures, pursed lips and micrognathia [7,8].

Genetically, SJS exhibits marked allelic heterogeneity, with disease-causing variants distributed across multiple functional domains of the HSPG2 gene. Previous work has demonstrated that truncating or splice-site variants tend to produce more severe skeletal phenotypes, whereas missense mutations are associated with milder forms [5,9,10]. In contrast to many previously reported cases, the present patient demonstrated three heterozygous variants, with both parents identified as carriers, supporting compound heterozygosity despite lack of consanguinity. This pattern resembles the molecular architecture reported in non consanguineous families by Lin PY et al., and Padmanabha H et al., and underscores the importance of genetic testing even when family history is negative [11,12].

Therapeutically, management of SJS remains symptomatic, targeting muscle hyperexcitability and functional mobility. Improvements in stiffness and gait have been reported with carbamazepine and other sodium-channel blockers, particularly in type 1A disease [13,14]. The notable reduction in myotonia and functional improvement observed in this child after carbamazepine therapy is consistent with these reports and supports its use as a first-line pharmacologic option. Additionally, the use of multidisciplinary rehabilitation, as applied in this case, parallels recommendations from previous literature emphasising orthopaedic, ophthalmologic and neurologic surveillance [11].

Systemic complications in SJS, including ocular involvement, respiratory difficulties and feeding issues, have been variably documented, particularly in severe skeletal phenotypes [5]. Although the present child experienced intermittent dysphagia, there were no respiratory complications, consistent with the generally milder systemic involvement seen in early-onset type 1 disease. Few cases have been described from the literature in [Table/Fig-3] [2,11,12,15].

Study (year)	Country/ population	Genetic findings	Key clinical features	Radiologic/EMG findings	Management	Outcomes
Padmanabha H et al., 2018 [12]	India, 7-year-old boy	Compound heterozygous HSPG2 mutation; one novel	Stiffness, facial dysmorphism, equinovalgus, hypertrophic muscles	EMG: dive-bomber myotonia; Skeletal dysplasia	Sodium channel blockers	Symptomatic benefit; mutation confirmed by Next-Generation Sequencing
Dave M et al., 2020 [2]	India, 15-year-old female	Genetic testing unavailable	Blepharophimosis, muscle stiffness, growth retardation	EMG: spontaneous repetitive discharges	Muscle relaxants, Botox	Symptomatic improvement; multidisciplinary care
Lin PY et al., 2021 [11]	Taiwan, single case	Novel pathogenic HSPG2 mutation	Myotonia, facial dysmorphism, gait issues	EMG: myotonia	Supportive therapy	Expanded genotype-phenotype database
Vahed IE et al., 2024 [15]	Iran, 2 sisters, consanguineous parents	Biallelic HSPG2 loss-of-function; novel variants	Myotonia, mask-like facies, GI bleeding (rare)	Not specified	Supportive; genetic counseling	Severe phenotype; GI complications highlighted
Present study,	India, 3.5-year-old male	Three heterozygous HSPG2 variants; both parents carriers	Blepharospasm, stiffness, delayed milestones, abnormal gait	EMG: spontaneous myotonia-like discharges; X-ray: metaphyseal dysplasia	Carbamazepine+ physiotherapy	Improvement in myotonia at 2-month follow-up

[Table/Fig-3]: Mini-review of Schwartz–Jampel Syndrome (SJS) [2,11,12,15].

DISCUSSION

The SJS is an extremely rare congenital disorder characterised by myotonia and skeletal dysplasia, with a global prevalence estimated at less than one in 100,000 individuals [2]. The syndrome was first described by Schwartz and Jampel in 1962, who reported children with blepharophimosis and generalised myopathy [3].

CONCLUSION(S)

The SJS is a rare autosomal recessive myotonic disorder caused by pathogenic variants in HSPG2, resulting in characteristic craniofacial dysmorphism, skeletal abnormalities and persistent

muscle stiffness. Early identification, multidisciplinary surveillance and genetic counselling are essential to optimise outcomes and clarify genotype-phenotype correlations.

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