SCHWARTZ-JAMPEL SYNDROME ASSOCIATED WITH SENSORIMOTOR POLYNEUROPATHY: REPORT OF THREE SIBLINGS

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Abstract- ***Schwartz-Jampel syndrome (SJS) is a rare disorder characterized by myotonia, joint contracture, facial dysmorphism and growth retardation. We present three siblings (two sisters and one brother) 19, 24 and 27 years old from consanguineous healthy parents with SJS. Their clinical features were similar to those previously described. Motor and sensory nerve conduction study (NCS) were compatible with a sensorimotor polyneuropathy. Myotonic discharges, complex repetitive discharges, myokymic discharges, positive sharp waves and fibrillation potentials were seen on EMG needle examination and MUPs were prominently neurogenic. One of the sisters had mental retardation and hypothyroidism from infancy. Thus, this is the first known report of sensorimotor polyneuropathy and hypothyroidism in SJS and the first reported family with SJS from Iran.***

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Key Words: ***Schwartz-Jampel syndrome, polyneuropathy, hypothyroidism***

INTRODUCTION

Schwartz-Jampel syndrome (SJS) also known as chondrodystrophic myotonia and osteochondromuscular dystrophy is a rare disorder with clinical characteristics mostly of autosomal recessive inheritance, myotonia, joint contracture, facial dysmorphism and growth retardation (1). Patients with normal intelligence and others with mental retardation have been described (2). This syndrome usually begins in childhood, although patients with earlier onset at birth or during the neonatal period have been described. The biochemical defect is in perlecan (HSPG2) and genetic linkage studies have mapped the gene to human chromosome 1p34-p36.1 (3,4) in families of different ethnic origins but not in the neonatal form (SJS type 2) (5-7).

An autosomal recessive inheritance has been agreed upon but some families with dominant inheritance have also been reported (8,9).

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We describe the first known family with SJS from Iran that additionally had sensorimotor polyneuropathy. Hypothyroidism as the cause of mental retardation was also noted in one of them.

Case 1

The older sister, S.M., 27 years old, was born at full term with normal vaginal delivery to consanguineous healthy parents. Early motor and language development appeared to be normal and she began to walk at 10 months of age. At 3 years her gait gradually became abnormal and changed to tiptoe walking. Her parents noticed the facial and hand myokymia for the first time at this age. At the age of 12, flexion deformity in lower extremities developed which made walking more difficult. Several orthopedic operations on the lower extremities were without any benefit and she began to use cane at the age of 20 years. She developed weakness in hand muscles and difficulty in writing from 12 years of age. She complained of painful muscle cramps in lower extremities after exercise.

Her parents are first cousins. She has a 24 years old sister (HM) and a brother aged 19 (DM) and both of them are involved with the same disease process. No other member in her family has a similar problem.

Examination at the age of 27 showed that she was 145 cm tall and weighed 52.5 kg. Mental function was completely normal. Her face was pinched and displayed narrow palpebral fissure, small mouth, and receding chin. Other dysmorphic signs were high arched palate, puckered lips, pigeon chest, flexion contractures of the knee joints and equinovarus deformity. The abdomen, respiratory and cardiovascular systems were unremarkable.

Neurological examination showed nystagmus in lateral gaze and typical myokymia in chin and periocular muscles. There was also some delay in opening the eyes. Motor examination showed atrophy of distal muscles and relative hypertrophy in thigh and gluteal muscles. Myokymia was also seen in dorsal hand interossei. There was no percussion myotonia. The lower extremity and axial muscles were stiff on manual examination. Muscle strength was considerably decreased in distal muscles

especially in foot dorsiflexion and finger abduction/ adduction. All the deep tendon reflexes were absent. Pinprick and touch senses were normal. Position sense was disturbed in distal lower extremities. Cerebellar exam was normal. She walked on her knees without help but couldn't stand or walk on her feet without cane. Her gait was stiff and on her toes.

Routine blood and urine labs were normal. Screening tests for metabolic defects revealed no abnormality (urine amino acid electrophoresis, thyroid function tests, TORCH study). Radiographic bone studies from thoracolumbar spine and hips were normal and slight degenerative changes were seen in both knee joints.

A Medelec Synergy electromyography was used for electrophysiologic studies. Sural, median and ulnar sensory nerve action potentials were absent bilaterally. Motor nerve conduction studies revealed very low amplitude CMAPs with increased distal latencies and decreased nerve conduction velocities. The conduction slowing in some nerves was very prominent and in the demyelinating range (Table 1).

Concentric needle electromyography (EMG) showed persistent spontaneous activity in all investigated limbs and facial muscles. These discharges were increased by needle displacement. Some sounded like myotonic discharges with crescendo-decrescendo character and sometimes it appeared like complex repetitive discharges. Myokymic discharges with bursts consisting of 3-5 single motor unit potentials with 50-60 Hz intraburst frequency was also noted more prominently in facial and distal limb muscles. On voluntary contraction, motor unit potentials were high amplitude and polyphasic with increased duration.

Carbamazepine was started and slowly increased to 200 mg three times a day. She feels better with less stiffness in her mucles. She can walk with difficulty without aid on her feet after 6 months on carbamazepine. The drug did not influence the myokymias.

Case 2

The little sister, H.M., 24 years old was delivered without incident after a normal pregnancy. Then, there was a prolonged neonatal jaundice and a delay in psychomotor development. She had a weak cry and poor sucking and an enlarged tongue. After six months, hypothyroidism was diagnosed and after that she has been on levothyroxine. She began to sit at nine months and walk at the age of two. Her gait was abnormal since the age of 3. She uttered her first words at four years. When she was 8-9 years old, her gait deteriorated due to knee joint contracture and her hands became clumsy. Gradually flexion contracture increased in the knee joints and to a lesser extent in the hip and ankle joints She had prominent mental deficit and read just two classes.

Examination at the age of 24 showed that she was 146 cm tall. Her facial features were similar to her greater sister (S.M.) except for a more prominent blepharospasm (Fig. 1). She also had thoracic kyphosis and flexion contracture of the kness (Fig. 2). The abdomen, respiratory and cardiovascular systems were normal.

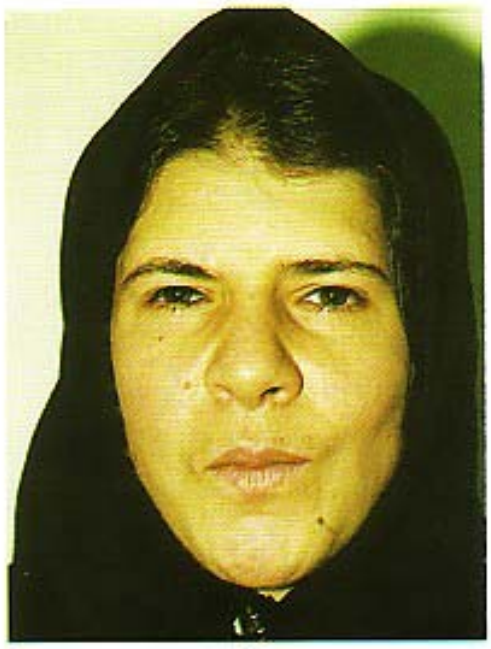

Fig. 1. Facial features in case 2

Fig. 2. Thoracic kyphosis and flexion contracture of the knees in case 2

Table 1. Nerve conduction studies

Case 1							
		Latency (msec)		Amplitude (motor= mV) (sensory= µV)		Conduction velocity (m/s)	
Nerve Stimulated	**Stimulation site**	**Rt**	**Lt**	**Rt**	**Lt**	**Rt**	**Lt**
Median (m)	wrist	8.65	5.75	0.2	0.4		
	Elbow	NR	12.25	NR	0.4	---	22
Ulnar (m)	Wrist		4.95		0.8		
	Below Elbow		10.80		0.5		30.8
	Above Elbow		12.55		0.5		40
Peroneal (m)	Ankle	NR		NR			
	Fibula	NR		NR			
Tibial	Ankle	6.35		0.3			
	Knee	16.3		0.1		28.1	
Median (s)	Wrist	NR	NR	NR	NR		
Ulnar (s)	Wrist	NR		NR			
Sural (s)	Calf	NR		NR			

Table 2. Nerve conduction studies

Case 2							
		Latency (msec)		Amplitude (motor= mV) (sensory= µV)		Conduction (msec)	
Nerve Stimulated	**Stimulation site**	**Rt**	**Lt**	**Rt**	**Lt**	**Rt**	**Lt**
Median (m)	wrist		4.4		1.7		
	Elbow		9.3		1.7		40.8
Ulnar (m)	Wrist		4.65		1.5		
	Below Elbow		8.6		1.0		40.5
	Above Elbow		10.2		0.7		56.2
Peroneal (m)	Ankle	NR		NR			
	Fibula	NR		NR			
Tibial	Ankle		4.3		0.3		
	Knee		14.8		0.2		30.3
Median (s)	Wrist		NR		NR		
Ulnar (s)	Wrist		NR		NR		
Sural (s)	Calf		NR		NR		

Table 3. Nerve conduction studies

Case 3							
		Latency (msec)		Amplitude (motor= mV) (sensory= µV)		Conduction (msec)	
Nerve Stimulated	**Stimulation site**	**Rt**	**Lt**	**Rt**	**Lt**	**Rt**	**Lt**
Median (m)	wrist		7.5		1.0		
	Elbow		13.2		1.0		40.4
Ulnar (m)	Wrist		4.65		3.4		
	Below Elbow		9.5		3.0		35.1
	Above Elbow		11.7		2.9		45.5
Peroneal (m)	Ankle	NR					
	Fibula	NR					
Tibial	Ankle		NR	NR	NR		
	Knee		NR	NR	NR		
Median (s)	Wrist		NR		NR		
Ulnar (s)	Wrist		NR		NR		
Sural (s)	Calf	NR		NR			

M=motor study, s=sensory study, Rt=right, Lt=left, NR=no response, ADM=abductor digiti minimi, APB=abductor pollicis brevis

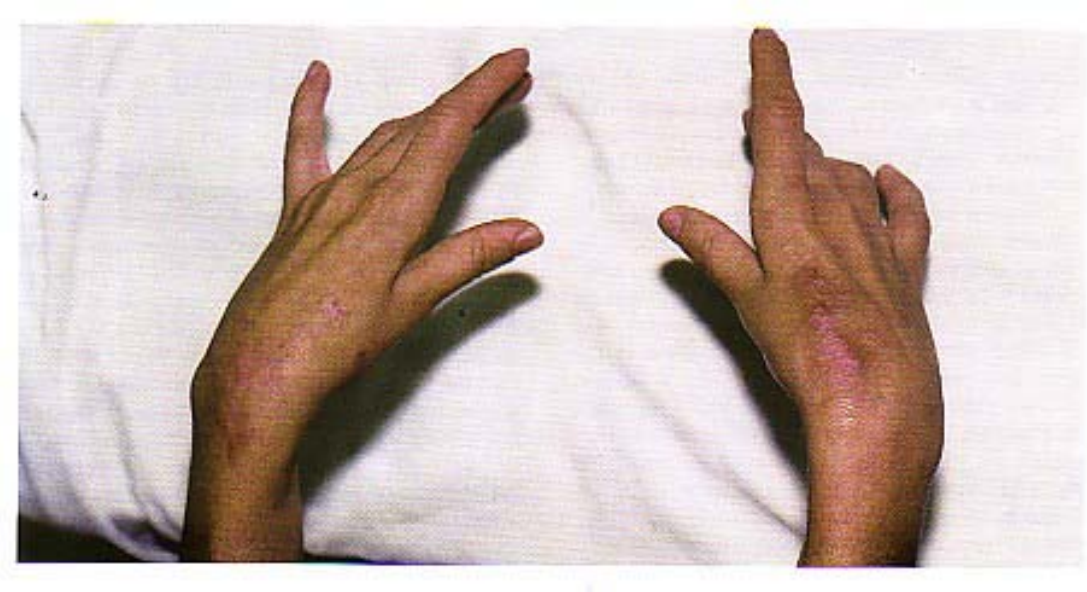

Fig. 3. Musculer atrophy in case 2

On neurological examination, nystagmus and myokymia in face and distal limb muscles and delay in opening the eyes were seen. Distribution of weakness, muscular atrophy (Fig. 3) and hypertrophy were similar to her sister. All deep tendon reflexes were absent and position sense was disturbed in distal lower extremities. Her gait was stiff, wide based, and on her toes.

Routine blood and urine labs and radiologic study of spine, hip and knee were similar to that of her sister.

Median, ulnar and sural SNAPs were absent. Median, ulnar and tibial CMAPs were low amplitude with slightly increased distal latencies and mild conduction slowing (Table 2). Three Hz repetitive nerve stimulation was done and recorded from abductor digiti minimi muscle without any significant decrement. No obvious facilitation or postexcercise exhaustion was noted. EMG neeldle examination findings were the same as S.M.

She also had symptomatic improvement with Carbamazepine.

Case 3

The 19 year old brother, D.M., was the result of uncomplicated normal vaginal delivery. Early motor and language development appeared to be normal. Her elder sister says that he had rippling in facial muscles before his first birthday. He began to walk at 15 months. He was more or less normal until 10 years when his gait became abnormal and flexion contracture in lower extremities developed. Mental function was normal.

Examination at the age of 19 showed that he was 170 cm tall. His facial dysmorphism was as previously mentioned in his sisters In addition, he had a prominent short neck. Flexion contracture in the hip joints was seen. He also had facial and limb myokymia, distal weakness and atrophy, generalized areflexia, and impaired position and vibration senses in lower extremities. His neurological examination was otherwise the same as his sisters.

Routine serum and urine labs were normal except for a mildly increased serum creatine kinase level (603, normal range: 25-125). Chest and skeletal radiographies were normal. Electrocardiography and echocardiography were also normal. Nerve conduction studies were the same as H.M. and indicative of an axonal-type sensorimotor polyneuropathy (Table 3). EMG findings were also the same as his sisters.

Carbamazepine was prescribed and symptomatic improvement was noted.

DISCUSSION

The three siblings presented here showed all the main clinical features of SJS. These include facial dysmorphism, skeletal abnormalities, muscle stiffness and myokymia (3). The usual pattern of inheritance in most previously reported families and in our family was autosomal recessive but autosomal dominant inheritance has also been reported (8,9). About 100 cases have been reported since the first description in 1962 (10). There is considerable variability in clinical expression of the disorder (11) even in the same family (3) and some cases without osteoarticular involvement have been reported (11). Three different phenotypes of SJS have been described (12): Type 1A, usually recognized in childhood with moderate bone dysplasia or skeletal

changes without dysplasia. Our patients can be classified in this group. Type 1B, similar to type 1A but recognizable at birth with more prominent bone dysplasia. Type 2, manifests at birth, usually lethal with bone dysplasia. Linkage of SJS type 1 to human chromosome 1p34-p36 has been shown in families of different ethnic origins (3,4) but type 2 is genetically distinct and not mapped to the aforementioned locus (5-7). Recently, the underlying molecular genetic defect in three consanguineous SJS families was identified. Nicole et al. described mutations in the gene that encodes perlecan (HSPG2), a heparin sulphate proteoglycan (13). This is highly expressed in basement membrane and cartilage, which may explain the skeletal deformities in SJS. There is no sequence homology between perlecan and ion channels, so it is unclear how mutations in HSPG2 lead to muscle membrane hyperexcitability (14).

Muscle wasting in distal limb and shoulder girdle muscles (8), areflexia (15) and weakness are common findings in SJS. Sensory examination is normal (8). Nerve conduction velocities are normal (11, 15-17), sometimes with decreased CMAP amplitude. The electromyography shows persistent or intermittent spontaneous activity described as complex repetitive discharges (15,16), myotonic discharges (8,11,15-17) and Myokymic discharges (8). MUPs are normal (17), myopathic (11,15) or slightly neurogenic (8). In contrast to usual clinical and electromyographic features of SJS, our patients had markedly abnormal position and vibration sense and electrophysiologic evidence of sensorimotor polyneuropathy. Although the changes were more in favor of axonal-type polyneuropathy, some of the findings in the older sister (S.M.) were suggestive of a demyelinating process (conduction block, increased distal latency and prominent conduction slowing). No other cause for the polyneuropathy in this family was found. The only previously described electrophysiologic sensory finding in SJS was due to carpal tunnel syndrome (CTS) (18,19). The reported case didn't have any symptom or sign in favor of CTS and entrapment was only detected electrophysiologically.

Mental retardation has been previously reported in 25% of cases (2,15), not associated with any obvious metabolic or endocrine defect. Two twin sisters with mental retardation and microcephaly have been reported (20). One of our cases (H.M.) was hypothyroid since infancy and her mental retardation was probably due to this cause. Coarse facial features, stiffness, muscle hypertrophy, myedema are frequently seen in association with cretinism. Although, rare association of myotonic dystrophy and hypothyroidism is reported (21), but as far as we know, no hypothyroid patient with definite clinical and electrophysiologic features of SJS has been reported. Additional evidence of central nervous system involvement in SJS documented by abnormal somatosensory evoked potential has been seen in four patients (22).

No definite treatment for SJS is available. Numerous pharmacologic treatments have been used in an attempt to diminish the continuous muscle activity associated with SJS. Carbamazepine has produced the most promising results in previously reported cases (23,24). Our patients also had symptomatic improvement with carbamazepine.

In conclusion, this is the first family with SJS reported from Iran. Additionally, we report the first known association between sensorimotor polyneuropathy and SJS. One of our patients was mentally retarded due to hypothyroidism. Symptomatic improvement with carbamazepine was also obvious in this family.

REFERENCES

1. Fowler WM, Layzer RB, Taylor RG et al. The Schwartz-Jampel syndrome: its clinical, physiological and histologic expressions. J Neurol Sci 1974; 22: 127-46.

2. Paradis CM, Gironda F, Bennett M. Cognitive impairment in Schwartz-Jampel syndrome: a case study. Brain Lang 1997; 56(2): 301-5.

3. Gontaine B, Nicole S, Topaloglu H et al. Recessive Schwartz-Jampel syndrome (SJS): confirmation of linkage to chromosome 1p, evidence of genetic homogenesity and reduction of the SJS locus to a 3-cM interval. Hum Genet 1996; 98(3): 380-5.

4. Nicole S, Ben Hamida C, Beighton P et al. Localization of the Schwartz-Jampel Syndrome (SJS) locus to chromosome 1p34-p36. 1 by homozygosity mapping. Hum Mol Genet 1995 Sep; 4(9): 1633-6.

5. Brown KA, al-Gazali LI, Moynihan LM, Lench NJ, Markham AF, Mueller RF. Genetic heterogeneity in Schwartz-Jampel syndrome: two families with neonatal Schwartz-Jampel syndrome do not map to human chromosome 1p34-p36. 1 Med Genet 1997; 34(8): 685-7.

6. Cormier-Daire V, Superti-Furga A, Munnich A et al. Clinical homogeneity of the Stuve-Wiedemann syndrome and overlap with the Schwartz-Jampel syndrome type 2. Am J Med Genet 1998; 78(2): 146-9.

7. Superti-Furga A, Tenconi R, Clementi M et al. Schwartz-Jampel syndrome type 2 and Stuve-Wiedemann syndrome: a case for "lumping". Am J Med Genet 1998; 78(2): 150-4.

8. Pascuzzi RM, Gratianne R, Azzarelli B, Kincaid JC. Schwartz-Jampel syndrome with dominant inheritance. Muscle Nerve 1990; 13(12): 1152-63.

9. Ferrarini E, Perniola T, Krajewska G, Serlenga L, Trizio M. Schwartz-Jampel syndrome with autosomal dominant inheritance. Eur Neurol 1982: 21(3): 137-46.

10. Schwartz O, Jampel RS. Congenital blepharo-phimosis associated with a unique generalized myopathy. Arch Opthalmol 1962; 68: 52-7.

11. Figuera LE, Jimenez-Gil J, Garcia-Cruz MO, Cantu JM, Schwartz-Jampel syndrome: an atypical form. Am J Med Genet 1993; 47: 526-28.

12. Giedion A, Boltshauser E, Briner J et al. Heterogeneity in Schwartz-Jampel chondro-dystrophic myotonia. Eur J Pediatr 1997; 156(3): 214-23.

13. Nicole S, Davoine C-S, Topaloglu H et al. Perlecan, the major proteoglycan of basement membranes, is altered in patients with Schwartz-Jampel syndrome (chondro-dystrophic myotonia). Nat Genet 2000; 26: 480-83.

14. Davies NP, Hanna MG. The skeletal muscle channel-opathies: basic science, clinical genetics and treatment. Curr Opin Neurol 2001; 14(5): 539-51.

15. Ishpekova B, Rasheva M, Moskov M. Schwartz-Jampel syndrome: clinical, electromyographic and genetic studies. Electromyogr Clin Neurophysiol 1996; 36(3): 151-5.

16. Christova LG, Alexandrov AS, Ishpekova BA. Single motor unit activity pattern in patients with Schwartz-Jampel syndrome. J Neurol Neurosurg Psychiatry 1999; 66(2): 252-3.

17. Spaans F, Theunissen P, Reekers AD, Smit L, Veldman H. Schwartz-Jampel syndrome: I. Clinical, electromyographic, and histologic studies. Muscle Nerve 1990; 13(6): 516-27.

18. Cruz Martinez A, Arpa J, Perez Conde MC, Ferrer MT. Bilateral carpal tunnel in childhood associated with Schwartz-Jampel syndrome. Muscle Nerve 1984; 7(1): 66-72.

19. Cruz Martinez A, Arpa J. Carpal tunnel syndrome in childhood: study of 6 cases. Electroencephalogr Clin Neurophysiol 1998; 109(4): 304-8.

20. Pinto-Escalante D, Ceballos-Quintal JM, Canto-Herrera J. Identical twins with the classical form of Schwartz-Jampel syndrome. Clin Dymorphol 1997; 6(1): 45-9.

21. Brumlick J, Maier RJ. Myxedema and myotonic dystrophy. Arch Intern Med 1972; 129: 120.

22. Singh B, Biary N, Jamil A, Al-Shawartz-Jampel syndrome: Evidene of central nervous system dysfunction. J Child Neurol 1997; 12: 214-17.

23. Squires L, Prangley J. Neonatal diagnosis of Schwartz-Jampel syndrome with dramatic response to Carbamazepine. Pediatr Neurol 1996; 15: 172-4.

24. Topaloglu H, Serdaroglu A, Okan M, Gucuyener K, Topcu M. Improvement of myotonia with carbamazepine in three cases with the Schwartz-Jampel syndrome. Neuropediatrics 1993; 24(4): 232-4.