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CASE REPORT

Familial syringomyelia: Incidental or hereditary?

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ABSTRACT

Syringomyelia is a rare disease of the spinal cord, and its familial occurrence is even rarer. Both genetic and environmental factors appear to be involved in familial syringomyelia. Herein, we presented a 51-year-old father and his 18-year-old son with clinically and radiologically proven syringomyelia without Chiari malformation type 1. Both had a trauma history, which could render them prone to the development of syringomyelia; however, the presence of another affected individual in the family history suggests that genetic predisposition plays a more important role in the pathogenesis of this condition. Only one previous report of familial syringomyelia originated from Türkiye, with ours being the second.

Keywords: Dissociated sensory loss, paraparesis, syringomyelia.

Syringomyelia (SM) is a rare, slowly progressive disorder of the spinal cord characterized by cerebrospinal fluid-filled neuroglial cavities or cysts lying within the cord parenchyma or the central canal, caused by disrupted cerebrospinal fluid flow dynamics. Although patients may present with variable symptoms, including muscle weakness, spasticity, pain, and progressive scoliosis, loss of pain and temperature sensation with preserved touch sensation is the characteristic hallmark at its core. The etiology of SM is diverse; it is most commonly associated with Chiari malformation type 1 (CM1). Congenital scoliosis, spinal cord tumors, trauma, and posttraumatic or infectious adhesive arachnoiditis are among other known etiologies.[1] In case of detection of no attributable cause on neuroimaging, it is labeled as idiopathic. The prevalence of SM is up to 8.2 in 100,000; however, ascertaining the true incidence of idiopathic SM is difficult.[2,3] Syringomyelia is considered a rare disease, familial cases with or without CM1 have been reported even less frequently. Herein, we reported a father and son suffering from SM.

CASE REPORT

Case 1- A 51-year-old male patient with a 12-year history of progressively worsening gait disturbance was admitted. The patient first noticed muscle weakness in the left leg, which gradually became aggravated, extending to involve the right leg. When the patient was admitted to the hospital with the complaint of gait difficulty and numbness in the hands and trunk, he was diagnosed with SM. The patient had declined the recommendation of surgical treatment five years ago. Personal history was notable only for involvement in a traffic accident as a passenger during a bus trip, 10 years before the beginning of the symptoms. The patient declared falling on his left side, resulting in swelling and bruising on the left side of the body, but had no recollection of suffering from pain, numbness, or weakness at that time. The patient's father also had gait issues, but he had not been investigated in detail. The patient's brother, a police officer younger than him by 15 years, had been evaluated for the loss of sensitivity to pain and temperature in the

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hands, leading to a diagnosis of SM, which later resolved spontaneously without any treatment. The patient's examination revealed preserved cranial nerve functions. In the upper extremity, the muscle power was normal, with brisk deep tendon reflexes. In the lower extremities, muscle strength was 3/5 with prominent spasticity, hyperactive deep tendon reflexes, bilateral extensor plantar responses, and Achilles clonus. The vibration sensation was decreased on both legs distally. The patient also had loss of pain and temperature sensation on C5-T1 dermatomes on the right and bilaterally from T2 through T12. Magnetic resonance imaging showed syrinx formation from C4 to T11, with no evidence of CM1. Only conservative treatment was recommended on neurosurgical evaluation. For the severe spasticity, the patient was commenced on baclofen, resulting in a slight improvement in gait. A written informed consent was obtained from the patient.

Case 2- The 18-year-old son of Case 1, employed as a machine operator in a factory, was admitted due to back pain. The patient also reported changes in gait with mild weakness in the left leg for six months, which had become more prominent over the last two months. The weakness did not interfere with the patient's daily living activities or cause significant concern. The patient wanted to be evaluated since his father and uncle had a diagnosis of SM. Personal history was notable for a fall during horse riding two months ago, with an emergency room evaluation at that time revealing no abnormalities. Medical records revealed a diagnosis of scoliosis, based on X-ray findings. On examination, the patient had a positive Mingazzini test in the left lower extremity and loss of pinprick and temperature sensation on the right at the T5-T10 dermatomes. Neurological examination was normal otherwise. Neuroimaging of the cord yielded a syrinx cavity extending from T4 to T9 vertebrae, with

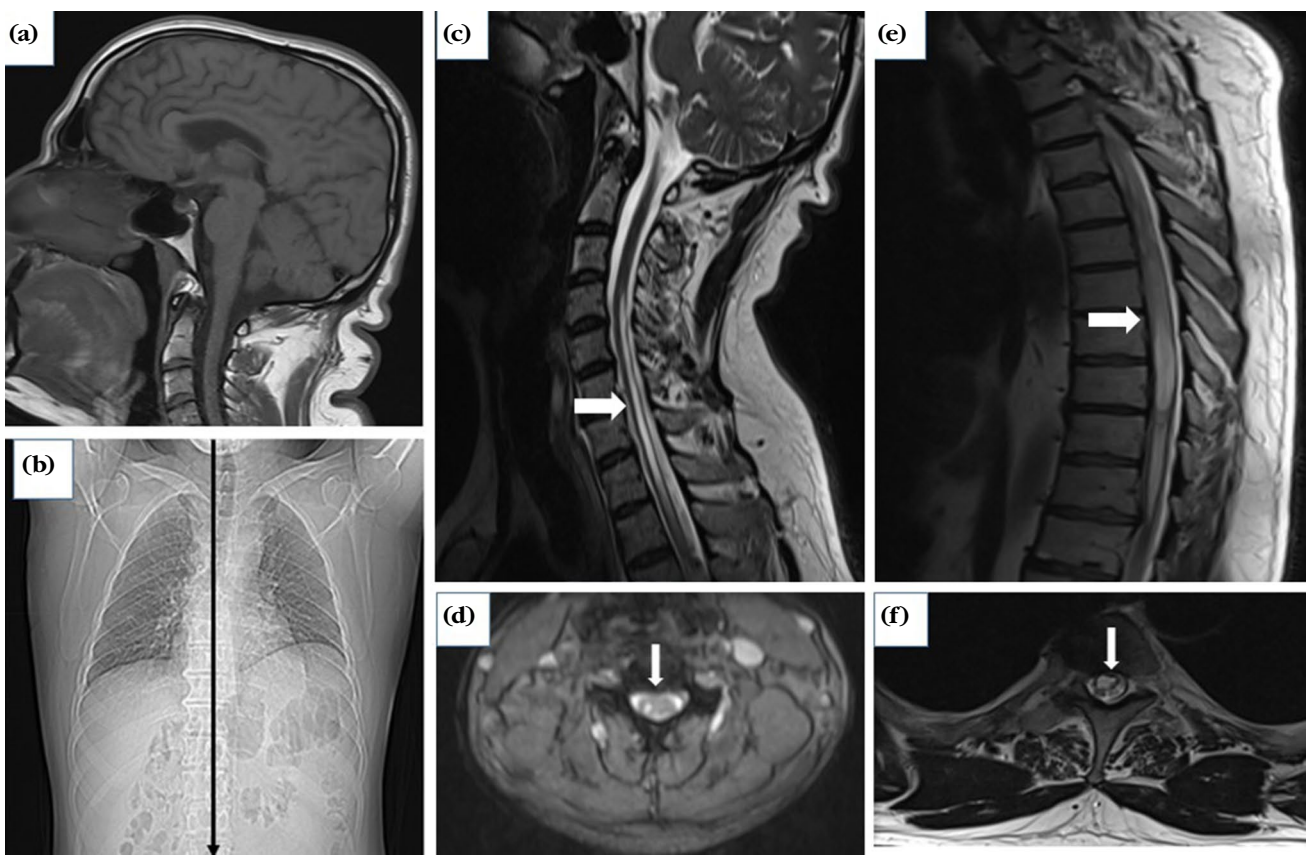

Figure 1. Images of Case 1. **(a)** Midsagittal T1-weighted magnetic resonance imaging of the craniocervical junction. **(b)** Posteroanterior radiograph of the thorax showing scoliosis. **(c, d)** Midsagittal and axial T2-weighted magnetic resonance imaging of the cervical spinal cord showing a syrinx cavity extending from C4 to T1 with a diameter of 3 mm at its widest point; **(e, f)** Sagittal and axial T2-weighted magnetic resonance imaging of the thoracal spinal cord with a syrinx cavity extending from T2 to T11 with a diameter of 8 mm at the widest point.

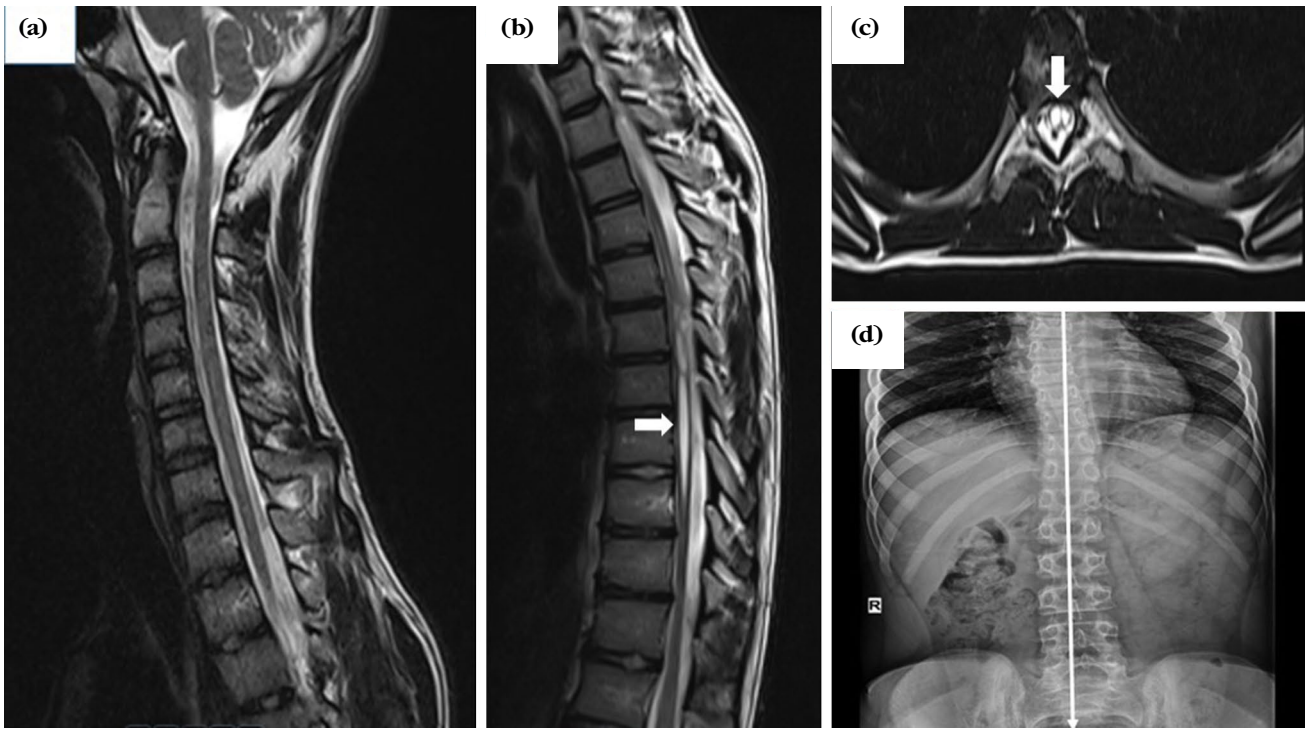

Figure 2. Images of Case 2. **(a)** Midsagittal T2-weighted magnetic resonance imaging of the craniocervical junction and cervical spinal cord with normal findings. **(b, c)** Midsagittal and axial T2-weighted magnetic resonance imaging of the thoracal spinal cord with a syrinx cavity extending from T4 to T9 with a diameter of 9.2 mm at the widest point. **(d)** Posteroanterior radiograph of the abdomen showing mild scoliosis.

prominent scoliosis. Like his father, neuroimaging yielded no hindbrain or craniocervical junction anomaly. The recommendation of neurosurgery was a conservative approach with clinical and radiological follow-up. A written informed consent was obtained from the patient.

DISCUSSION

Herein, we reported familial SM cases, involving father and son without CM1. In both cases, SM was determined by magnetic resonance imaging. There was a third case diagnosed with SM in the family history, which resolved spontaneously; however, we could not document the medical records of this patient.

Although descriptions of familial SM cases date back more than a century, cases described in the literature are rare. Since the first description of familial SM by Nalbandoff in 1899,[4] Yabe et al.[5] identified 33 cases reported in the literature, denoting the rarity of the condition. In our meticulous search of the literature, we identified 92 familial cases of SM (Table 1). Although reported from all over the world, in classification by country, most of the cases were from Russia. Before the introduction of neuroimaging techniques, the diagnosis was based on clinical data in most cases and was pathologically confirmed in only one case.

The frequency of familial SM accounted for 2 to 4% of all observed cases of SM.[5,6] Familial aggregation of SM suggests a genetic basis. Among scattered reports, familial cases were identified in two generations, siblings, twins, and, in some cases, in more distant relatives; however, siblings appeared to be more frequently affected than parents and their children. Some previous reports implicated autosomal dominant, recessive, or X-linked inheritance (Table 1). Abnormalities at the foramen magnum level, such as CM1 and basilar impression, were detected in the majority of SM cases. Structural bone malformations, including occipitalization of the atlas, Klippel-Feil syndrome, and spina bifida, were reported in association with SM.[7] The high coincidence of SM with CM1 and other skeletal abnormalities, particularly at the skull base, as well as the familial aggregation of the two, implies that there could be a genetic culprit. Avşar et al.[8] mention about the significant linkage between chromosome 8, 9, 11, 12 and 15

TABLE 1
Familial syringomyelia cases reported in the literature

Authors*	Dx	Relationship	Age (year)	Localization	CM1	Other conditions	Inheritance	Nation
Nalbandoff SS, 1899	C	Father/son			ND	ND		Russia
Preobrajenski PA, 1900	C	Father/two daughters			ND	ND		Russia
Karplus JP, 1915	C	Father/son			ND	ND		Germany
Redlich A, 1916	C	Two brothers			ND	ND		Austria
Barre JA and Reys L, 1924	C	Brother and sister			ND	ND	AR	France
van Bogaert L, 1929	P	Two sisters			ND	ND	AR	France
Klara W and Franz G, 1958	C	Two siblings			ND	Myotonic dystrophy		Austria
Shamburov DA, 1961	C	Father and son	ND/9					Russia
Tyazhkorob AM, 1962	C	Two sisters						Russia
Wild H and Behnert J, 1964	C	Identical twins			ND	Nothing		Germany
Logachev KD, 1964	C	Two families		Cervicothoracic				
Avenarius HJ et al, 1968	C	Father/son			ND	Myotonic dystrophy		Austria
Shishkina AV, 1969	C	Brother and sister Mother and daughter, nephew, cousin						Russia
Skvirskaya KB, 1970	C	Mother/son/daughter Father and two daughters Two sisters and nephew Brother and sister Mother and daughter Mother and son			ND	Nothing	AR	Russia
İkramova NT, 1970	C	Father/two sons	50/19/25	Cervicothoracic				Russia
Sirotkina VM, 1973	C	6 family, 16 person		Cervicothoracic				Russia
Nedoshivin LB and Alelekov DA, 1974	C	4 family						Russia
Lobova AA, 1975	C	Mother and son two brothers						Russia
Bentley SJ et al, 1975	C, R	Two sisters/brother/sister	54/46 51/43	C2-T6/C2-T1 C7-T1/C2-T6	+/– ND	Rheumatoid arthritis/– Nothing	AR	UK
Ishchenko MM et al, 1976	C	Two brothers/two sisters		Cervicothoracic	ND	ND	AR/AD	Russia
Caraceni T and Giovannini P, 1977		Two brothers/two sisters	47/45/42/34	C3-L2/C2-T7/ holocord/C3-L3	–/–/–/–	–/–/Scoliosis/–	AR	Italy
Gimenez-Roldan S et al, 1978	R	Father/son/daughter	50/17/7	C5-T1/C2-T6/ cervical	+/+/+	Scoliosis in all, spina bifida	AD	Spain
Erkhov IS and Martyanova SG, 1979	C	Two sisters Mother & son Twin brothers						Russia
Galai VF, 1980	R	Three sisters				Spinal Dysraphism		
Jefferson TO and Cohen C, 1982	C	Brother, sister	67/74	ND/ND	ND	Kyphoscoliosis, Mental impairment	AR	UK

TABLE 1
Continued

Authors*	Dx	Relationship	Age (year)	Localization	CM1	Other conditions	Inheritance	Nation
Busis NA and Hocheberg FH, 1985	C	Two sisters	33/50	C2-T6/C3-T8	–	Nothing	AD	USA
Duncan JS et al, 1986	R	Father/son	32/18	C2-L2/C2-T6	+/+	Nothing	AD	UK
Mallessa R and Jorg J, 1986		Identical twins/brother			–	Nothing	AD/AR	Germany
Fukada C, 1988	R	Two persons			CM2	Hypoplastic cerebellum		Japan
Mariani C et al, 1991	R	Two cases with affected relatives						Italy
Kuberger MB et al, 1991		Two brothers/one sister			ND	Nothing		Russia
Colombo A & Cislaghi MG, 1993	R	Two sisters	41/44	C3-T1/Syringobulbia	+/–	Spondylarthrosis/ Klippel-Feil syndrome		Italy
Zakeri A et al, 1995	R	Brother/sister	30/36	C2-T6/ holocord	+/+	Dextroscoliosis/levoscoliosis		USA
Wakano K, 1997	R	5 persons			–	Cervical canal stenosis		
Atkinson J et al, 1998	R	Identical twin sisters	33/ND	C6-T6/C2-T7	+/+	Nothing		USA
Milhorat TH et al, 1999	R	19 family 7 family			+/–	ND	AD/AR	USA
Seki T, 1999	R	Identical twins 2 persons			+/–	ND		Japan
Mendelevic EG et al, 2000	C	2 persons						Russia
Nagai M, 2000	R	2 persons				Spinal arachnoiditis		Japan
Yabe I et al, 2002	R	Mother/son	74/47	C4-6/C3-T8	+	Nothing		Japan
Tubbs RS et al, 2004	R	Identical twins	11/ND	T2-8/T3-9	+/–	Klippel-Feil anomaly, levoscoliosis/–		USA
Mainkurve GG et al, 2005	R	Two sisters	15/13	Holocord/C5-7	+/+	Scoliosis/nothing		USA
Robenek et al, 2006	R	Sister and two half brothers	57/44/42	Cervicothoracic/ cervical/C3-T4	–/+/+	Scoliosis/–/–	AD	Germany
Koç et al, 2007	R	Two sisters	25/24	T6-8/T7-9	–/–	Nothing		Türkiye
Weisfeld-Adams JD et al, 2007	R	Two sisters			+/+	Platybasia	AD/X-linked	UK
Pasoglou V et al, 2014	R	6 persons				Adhesive arachnoiditis		Belgium
Kuroki H et al, 2015	R	Brother and sister	17/15	C2-T1/C1-T3	+/+	Levo/dextroscoliosis		Japan
Demirci and Ünlü, 2024	R	Father and son	51/18		–/–	Scoliosis		Türkiye

Dx: Diagnosis; C: Clinically confirmed; P: Pathologically confirmed; R: Radiologically confirmed; AR: Autosomal recessive; AD: Autosomal dominant; CM1: Chiari malformation type 1; CM2: Chiari malformation type 2; ND: No documentation; * The bold ones are articles with available full text. Others are derived mainly from references 4, 5 and 8 (see supplementary document).

and CM1 with or without SM detected in some contemporary studies. As well, OLFML2A, SLC4A9, and COL4A1 are suggested as candidate genes in CM1 pathogenesis.[8] These genes have a role in extracellular matrix organization, anion exchange, and angiogenesis. Regarding the high coincidence of SM with CM1 malformation, both might have a shared genetic etiology, and these genes may also have a role in syrinx formation.

Environmental factors have also been implicated in the development of SM. Heavy work or excessive strain was noted as a precipitating factor for the formation of a syrinx.[9] A higher detection rate of SM in some geographical regions was also attributed to environmental factors. Rural inhabitants, males, and manual laborers in the Tatar Republic were reported to be more predisposed to the development of SM.[9] However, the highest number of SM cases were in isolated rural villages, where the rate of consanguineous marriages was high, further supporting a genetic basis.[6]

Different hypotheses have been put forward for syrinx formation. Although not yet universally accepted, intramedullary pulse pressure theory is considered the best in explaining the pathology, regardless of etiology.[10] According to this theory, relative increase in pulse pressure in the spinal cord compared to that in the nearby subarachnoid space due to partial or complete obstruction causes distension of the spinal cord, and hydrodynamic changes leads to accumulation of extracellular fluid in the distended cord, resulting in syrinx formation.[10]

Trauma with or without clinical spinal cord injury may lead to the development of SM, even with minor injuries.[10-12] Time to onset of the first symptoms after injury was reported to range from 2 months to 30 years.[12] Both our patients had a history of trauma, which may be an etiologically important factor for the development of SM. However, even considering trauma as a causative factor in this father and son, the possibility of a predisposition to syrinx formation cannot be excluded. Both our patients had scoliosis. Scoliosis accompanies 14 to 50% of SM cases without a CM1.[13] The pathogenesis of this coexistence has not been yet established; however, asymmetric compression of the anterior horn cells by a syrinx was postulated to cause an imbalance in the trunk muscles, leading to scoliosis.[13] The presence of holocord syrinx and syrinx length were reported as independent predictors of scoliosis.[14] Therefore, it was not surprising to detect scoliosis in a patient with a long-term diagnosis of SM. Our second case had a recent diagnosis with only minor neurological findings. The patient also had mild scoliosis, which was detected on radiographs while being examined for trauma. Taking care of the presence of scoliosis before the onset of symptoms of SM, it can be assumed that SM was already present, and neurological symptoms became evident after the trauma. Furthermore, this father and son had neuroradiologically confirmed SM. The presence of a third affected person in the family still suggests that genetic causes may be the predominant etiologic factor.

Despite the ease in confirmation of the diagnosis with the imaging of the spinal cord, the best treatment methods are still controversial. Conservative treatment is recommended to asymptomatic or pauci-symptomatic patients with clinical and radiological follow-up. Surgery is warranted for those with deteriorating neurological signs and symptoms. The employed neurosurgical methods aim to create a conduit for free movement of cerebrospinal fluid. These include craniovertebral decompression for CM1-related syringomyelia and posterior thoracic laminectomy, arachnoidolysis, or a catheter drainage of the syrinx cavity in idiopathic cases.[1,15]

In conclusion, familial SM is a rare occurrence. In reviewing the literature, we found only one familial case report from Türkiye,[16] ours being the second. Although seemingly rare, familial cases may be more common than the reported cases. Neuroimaging of asymptomatic relatives of index cases may reveal undiagnosed cases. Finally, molecular genetic studies may shed light on the heredity nature of the condition.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, analysis and/or interpretation, writing the article, other, design, materials, data collection and/or processing, references and fundings, literature review: S.D., M.D.Ü.; Control/supervision, critical review: S.D.

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