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Post syringomyelia progressive muscular atrophy: A late sequel to syringomyelia?

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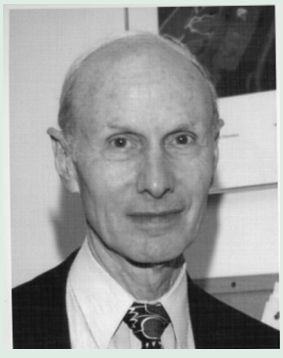
Abstract: We review eight cases of syringomyelia with late sequelae of progressive muscular weakness that suggested the diagnosis of amyotrophic lateral sclerosis (ALS). We propose that this is not ALS, but rather a novel syndrome with distinguishing clinical features; sensory deficits from the initial syrinx, relative sparing of the cranial region, and a slower rate of progression. Imaging studies did not reveal re-expansion of the syrinx, nor any other structural pathology to explain the progressive motor degeneration. Spinal cord regions (cervical, thoracic, lumbosacral) involved on initial presentation predicted the regions of late progression of motor neuron loss, suggesting that pathogenesis may involve an initial loss of motor neurons due to the syrinx, and then age related loss as seen in post-poliomyelitis progressive muscular atrophy. We conclude that these cases are examples of a novel syndrome of post-syringomyelia progressive muscular atrophy.

Subjects: Medicine; Neurology; Neurosurgery

Keywords: syringomyelia; chiari malformation; amyotrophic lateral sclerosis; post polio progressive motor atrophy

1. Introduction

Patients treated for syringomyelia (SM) of various types, including Chiari related, and SM with post-traumatic and post-inflammatory etiologies, currently may survive for many years, although with some degree of functional impairment. This is the result of early and more accurate diagnosis, more effective treatment, and improved care of intercurrent problems that may have led to patient deaths in earlier years (Barnett & Jousse, 1973). We have encountered a smaller number of patients who



Ulrich Batzdorf

ABOUT THE AUTHORS

Ulrich Batzdorf's primary clinical and research focus is on the treatment of Chiari Malformation, syringomyelia and spinal cord tumors. He has served on the UCLA neurosurgical faculty since 1966, and is Professor Emeritus of Spinal Neurological Surgery. Michael C. Graves, Professor Emeritus of Neurology, has been at UCLA since 1978 with interests in clinical EMG, neuromuscular diseases, and in research and clinical care of patients with amyotrophic lateral sclerosis.

PUBLIC INTEREST STATEMENT

Syringomyelia is the name for a fluid-filled cavity in the spinal cord due to either birth defects or sometimes to injuries or infections. Surgical treatment usually is effective in relieving symptoms. In this paper we describe a new complication in eight patients who were initially treated surgically with a good outcome, but who years later developed progressively increasing weakness. This was not due to re-expansion of the initial cavity so repeat surgery was not an option. We conclude that these patients have a condition that resembles a serious neurological disease, amyotrophic lateral sclerosis (ALS), except that they have little or no involvement of swallowing and speaking, and that they have a much longer survival. This is unlikely to be coincidental ALS. This is the first report of post-syringomyelia progressive muscular atrophy.

underwent appropriate and successful surgical treatment of SM and subsequently developed late motor deterioration without imaging evidence of syrinx cavity re-expansion. The present study describes these patients and examines possible explanations for their delayed clinical deterioration.

2. Methods

With IRB approval, a retrospective search of SM cases in the authors' practices yielded eight cases with late progressive deterioration. All except three (cases 1, 3 and 8) had surgery done by one of the authors, (UB). The goal was to test the hypothesis that the motor neuron loss was distinguishable from that of ALS, and may involve age related motor neuron loss in regions initially involved by the SM. We reviewed early presentation, types of early surgical treatment, and details of late, progressive deterioration Regions of neuraxis involvement (cranial (Cr), cervical (C), thoracic (T), and lumbosacral (LS)), and upper and lower motor neuron signs, used in the diagnosis of ALS (Ludolph et al., 2015), as well as SM related sensory findings, and complaints of pain were specifically abstracted. All records showed that initial history, neurological exam, and imaging were supportive of the initial diagnosis of SM, and late onset of motor neuron loss. Family histories were all negative for ALS (Table 1).

The rate of motor neuron loss in normal aging was obtained from published studies that used either electrophysiological (Gawel & Kostera-Pruszczyk, 2014; Murga Oporto, Menendez-de Leon, Bauzano Poley, & Nunez-Castain, 2003; Yerdelen, Koc, & Sarica, 2006) or postmortem pathological (Suzuki, Goto, Yanai, Shibata, & Hisamitsu, 2005; Terao et al., 1996) methods. The number of motor units in a given muscle at ages 20 and 80 were read from graphs of age *vs*. motor unit number, and these two points determined the age-related rate of motor neuron loss.

3. Results

3.1. Case 1

This 60 yo male reported headache and shoulder weakness since age 18. At age 30 Chiari malformation and SM were diagnosed and treated with posterior fossa decompression and shunting of the syrinx to the subarachnoid space. He was first seen at UCLA at age 50, after a fractured left humerus. Initial exam (UB) showed weakness of shoulder abduction and intrinsic hand muscles, left more than right. MRI showed no re-expansion of the syrinx. EMG studies showed chronic denervation-reinnervation in C5 to C7 muscles bilaterally and C8 muscles on the left. Over the ensuing 10 years he experienced progressive atrophy and weakness of muscles of the arms. On re-evaluation at age 60 he had severe deltoid and biceps weakness, and C5 and C6 cervical foraminal narrowing on MRI. EMG demonstrated chronic denervation as well as fibrillations in C5 and C6 supplied muscles. A C5 and C6 radiculopathy was suspected and he was treated with an anterior discectomy and fusion with foraminal microdissection to decompress the C5 and C6 nerve roots, but no improvement was seen 11 months later. His legs remained asymptomatic.

3.2. Case 2

This woman recalled many years of headaches exacerbated by sneezing and several years of arm numbness when she first noted leg weakness at age 55. MRI at that time demonstrated a Chiari malformation and SM. Exam showed sensory loss to pain and temperature in the whole body sparing the face, and mild weakness of the arms and legs. She was treated with posterior fossa decompression (UB), resulting in symptomatic improvement. However, six months later she had more progression of her leg weakness, and a re-exploration with reduction of the cerebellar tonsils was carried out . On examinations at ages 66 and 67 findings were unchanged from those at age 55, although she reported ambulation difficulties. By age 73, she required a walker and had significantly more leg weakness, decreased sensation to pain in the face, and normal reflexes. MRI again demonstrated ample CSF around the cord indicating that the syrinx had not re-expanded.

3.3. Case 3

This 80 yo man had progressive pain, sensory loss and weakness since age 64 had initially presented with paraparesis and T2 sensory level at age 42. Laminectomy revealed subarachnoid blockage at

Table 1. Summary of clinical features of the 8 cases. For regions of neuraxis involvement, C—cervical, T—thoracic, LS—lumbosacral

			Early clinical		Late clinical progression		
Case no.	**Age onset**	**Etiology of SM**	**Age at first surgical treatment**	**Clinical signs regions of spinal involvement at onset or time of early surgery**	**Symptoms progression late spinal regions involvement**	**Age at late evaluation**	**Interval initial onset to onset of progression**
1	18	Chiari	31	Headache, shoulder weakness (C)	Motor, left arm only(C)	56	25 years
2		Chiari	52	Headache, Right hand sensory loss, leg weakness (C, T, LS)	Progressive motor atrophy and weakness. (C, T, LS)	72	20
3	52	Post-inflammatory	43	Leg weakness (C, T, LS)	Progressive pain, and sensory loss in left arm and both legs. (C,T,LS)	73	30
4	30	Chiari	36	Left arm and leg weakness (C, T, LS)	Weakness, Pain (C, T, LS)		20
5	39	Post trauma	39	Sensory UE, Motor (C, T)	Motor (C, T, LS)	64	25
6	38	Chiari	39	Headaches, sensory loss in right arm and both legs (C)	Progressive muscular atrophy of the hands, sensory loss legs. (C)	48	10
7	32	Chiari	32	Muscular atrophy and weakness both hands, R > L, sensory loss legs. (C, T, LS)	Pain, arms legs, Muscular atrophy of left arm. (C, T, LS)	52	20
8	12	Chiari	32	Sensory, pain (C, LS)	Motor UE, LE (C, LS)	39	20 years

T2 with xanthochromic CSF below that level, and the surgeon's impression was a treated bacterial infection. Postoperatively, he recovered leg strength and walking over three weeks time and ambulated independently. At age 50 bilateral arm pain, and leg weakness led to diagnosis of SM. He presented at UCLA at age 58 with increased pain in the arms, spastic gait, with MRI demonstration of a syrinx extending from C3 to T2. Follow up visits over the ensuing 6 years documented a stable motor examination, until age 64 when he experienced more severe bilateral arm and leg weakness with pain and sensory deficit. EMG of the upper extremities revealed chronic denervation in C5 through T1. Imaging showed no evidence for syrinx re-expansion. A percutaneous needle drainage of the syrinx cavity did not result in improvement.

3.4. Case 4

This 87 year old woman first noted left arm weakness and walking difficulties at age 34. By age 36 she had right arm numbness, severe left arm and bilateral leg weakness, and was using a wheelchair. A neurosurgeon diagnosed SM and performed a laminectomy and drainage, resulting in improved walking and left arm strength, and improved right arm sensation. At age 40 she was walking with a cane. She first presented at UCLA at age 58 with worsening gait. At that time her cranial nerves were normal, motor exam revealed just anti gravity strength on the left and grade 4 on the right arm. Her tone was increased on the left side, and reflexes were hyperactive, more so on the left. Sensation was decreased to pain more on the right side including arm chest and leg. MRI showed a Chiari I malformation with a syrinx from C1 to T10. She was treated with a suboccipital craniotomy, resection of the arch of C1, and duroplasty (UB). She described modest improvement in her strength and walking initially, but by age 61 was once again unable to walk and was using a wheelchair. MRI showed that the syrinx was still collapsed. At age 68 she was examined and noted to have less than anti-gravity strength in the left arm, grade 4 weakness of the right arm with marked weakness and atrophy of the intrinsic hand muscles. Her course we complicated by cerebrovascular disease and dementia, but by age 80 she was quadriplegic with hyperactive reflexes.

3.5. Case 5

This 68 yo male presented at age 39 with right hand paresthesias and weakness. EMG was reported as normal. MRI revealed a syringomyelic cavity from C4 to T6. He was treated with laminectomy and duroplasty (UB), resulting in improved sensory symptoms and no motor or functional deficits. Subsequent imaging of the spine showed collapse of the syrinx. However, by age 49 he had leg weakness. Examination showed profound weakness, atrophy and fasciculations of muscles in the arms and legs. Reflexes were diminished to absent. Sensory exam was normal except for a small area of decreased pin sensation over the right triceps. MRI showed cervical spinal cord atrophy and a collapsed syrinx cavity. Over the ensuing 9 years he lost all functional use of the upper and lower extremities. He had mild dysarthria. He was using non-invasive positive pressure ventilation (NIV). Examination showed normal cranial nerves, profound atrophy and fasciculations in the arms and legs. Cranial release reflexes were normal. He had increased biceps, knee, and adductor reflexes. Sensory exam was unchanged. EMG showed widespread denervation in upper and lower extremities.

3.6. Case 6

This 48 yo woman noted numbness and burning pain of the right hand, and intermittent arm fatigue since age 36, and a cough related headache. At age 38, on initial consultation, her arm strength was normal and she had decreased pain and cold sensation in both arms and chest. MRI showed a Chiari type I malformation and SM. She was treated with suboccipital craniectomy and placement of a pericranial dural graft (UB). Post operatively, MRI showed collapse of the syrinx cavity. At age 48, 10 years after surgery, she had bilateral arm atrophy and weakness and extension of her sensory deficit into the lower extremities. MRI continued to show collapse of the syrinx cavity. Lower extremity motor function remained intact.

3.7. Case 7

This 52 yo man had a 10 year history of hand weakness, with a Chiari malformation identified on MRI at age 38. On his first visit at UCLA (UB), he had intrinsic hand muscle atrophy and weakness, slight iliopsoas and quadriceps weakness, and a sensory deficit to temperature over his left neck and shoulder extending to the elbow, and another area of sensory loss over the fifth finger. MRI demonstrated the Chiari malformation including a posterior fossa arachnoid cyst, and a C1 to T9 syrinx widest at C7 to T2. He was treated with suboccipital craniectomy and dural graft (UB). The arachnoid cyst was identified and drained. His pain improved and his hand weakness remained stable until age 49. By age 52 he had severe atrophy and weakness of his intrinsic hand muscles, and some grade 4 weakness in the legs. Sensory exam was intact to temperature, but decreased to pin in the arms. Reflexes were absent in the arms, diminished in the legs. MRI showed no re-expansion of the syrinx and was unchanged in the 12 years since surgery.

3.8. Case 8

This 48 yo man had presented to the ALS clinic at age 39 with progressive weakness and atrophy of the arms and legs progressing over approximately 8 years. At age 12 he had experienced pain and sensory loss in the arms and chest, and at age 32 Chiari malformation and syringomyelia were diagnosed and surgically treated (elsewhere). He also complained of dyspnea at rest and was using NIV continuously. Exam showed tongue fasciculations, palmomental reflex, and complete paralysis of muscles in the arms and legs except for trace movement at elbows and knees. Reflexes were absent except for trace hip adductor jerks. Sensory exam showed decreased pinprick in the left arm and chest. EMG showed widespread denervation in the arms and legs. Over the ensuing 7 years while followed in the ALS clinic he has lost all movement of the arms and legs, developed hypophonic speech, and glabellar, snout, palmomental, and jaw reflexes. He has mild dysphagia, and uses NIV assistance. His sensory deficit has remained stable.

In summary, records of 8 SM patients (five males and three females) with late onset progressive neurological deterioration were reviewed. The mean age at first presentation and treatment was 33 years, (range 12–52). The interval from initial treatment until the recognition of the progressive neurological worsening ranged from 10–30 years, (mean 21.25 years).

Four (cases 1, 5, 6 and 7) of the 8 patients had initial motor involvement of only the arms. The late progression in three of these four was also restricted to the arms, the single exception being a patient (case 5) with initial arm involvement, who later developed progressive leg symptoms and findings. This patient had early imaging evidence of cervical and thoracic involvement extending only to T5. The other four patients (cases 2, 3, 4 and 8) had initial motor weakness that involved arms and legs, and all of these showed late progression that also involved both arms and legs.

Three patients (numbers 4, 5, and 8) had slowly progressive weakness and atrophy of the arms and the legs, which was profound so as to suggest a diagnosis of ALS. Unlike ALS, however, these patients had sensory deficits related to the initial syrinx, and usually did not have hyperactivity of reflexes. Cranial nerve findings and respiratory weakness were relatively late in disease process. EMG studies in 2 of these patients showed a widespread loss of motor neurons similar to that found in ALS.

4. Discussion

This is the first description of late motor progression in SM not explainable by structural recurrence of the syrinx. Previous reports of CM1 related SM indicate that syrinx size and symptom duration are predictors of progressive myelopathy and that syrinxes may spontaneously resolve, associated with stabilization of clinical deterioration (Bogdanov, Heiss, & Mendelevich, 2006; Bogdanov & Mendelevich, 2002). Other reports of long term follow up of patients with syringomyelia have not mentioned the late progression that we report here (Bogdanov et al., 2006; Joseph et al., 2013; Roy, Slimack, & Ganju, 2011). At UCLA during the time period in which these eight cases were seen, one of the authors (UB) treated 183 SM patients suggesting a prevalence of 4%, much higher than the

lifetime risk of ALS (about 1 in 1,000). Although this estimate is subject to bias, it does suggest that the long term risk of late progression in treated SM patients may be significant and underreported.

Like the 8 SM cases, poliomyelitis survivors may experience progressive motor weakness decades later. The limbs that were most affected by acute polio are also at greatest risk for late progressive weakness decades later (Trojan & Cashman, 2005). In seven of the eight SM cases, the region of spinal cord initially involved predicted the region where late progression was to be seen. Three of the four patients with early involvement restricted to the arms showed late progression also restricted to the arms. Those four patients with clinical and imaging evidence of involvement extending below the cervical region showed late progression in both the arms and the legs. A single case (case 5) did to follow this rule.

A proposed mechanism for late polio progression involves age related loss of surviving motor neurons (Trojan & Cashman, 2005). In normal subjects, an age related motor neuron loss of 5–8% has been estimated by both electrophysiological studies (motor unit number estimation) (Gawel & Kostera-Pruszczyk, 2014; Murga Oporto et al., 2003) and postmortem studies (Suzuki et al., 2005; Terao et al., 1996). This late loss of motor neurons may also explain the late deterioration in our SM cases.

Three patients had profound arm and leg weakness reminiscent of ALS, but with mostly lower motor neuron disease, sparing the bulbar region. Previous papers have noted what may be an association of ALS with trauma and with structural disease such as cervical compressive myelopathy (Yamada, Furukawa, & Hirohata, 2003), and also with SM (Hamada et al., 1990), and that SM can mimic motor neuron disease (Visser et al., 2002). Also SM has been reported in familial ALS with Klippel Feil syndrome, due to a genetic defect in the TGF-β signaling pathway (Jamrozik, Gawel, Szacka, & Bakon, 2015). From a clinical point of view, it is difficult to distinguish late progression of motor deficit in SM from ALS. Indeed, several of our patients had a clinical diagnosis of ALS. It is not known if associations of SM and ALS are causal or merely coincidental. The observation that early involved regions predict late progression suggests that age-related motor neuron loss plays a role.

In summary, these eight cases had early onset of SM with initial stabilization or improvement with treatment, followed later by progressive motor weakness suggesting ALS. Clinical features include sensory deficits from the initial syrinx, but no evidence of syrinx re-expansion nor any other structural pathology. Compared to ALS, these cases had relative sparing of the cranial region, and a slower rate of progression. Furthermore, spinal cord regions (cervical, thoracic, lumbosacral) involved on initial presentation predicted the regions of late progression of motor neuron loss, suggesting an initial loss of motor neurons due to the syrinx, and then age related motor neuron loss as seen in post-poliomyelitis progressive muscular atrophy. We conclude that these cases define a novel syndrome: post-syringomyelia progressive muscular atrophy.

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Competing Interests
The authors declare no competing interest.

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