Chiari Type I malformation and syringomyelia in unrelated patients with blepharophimosis

Report of two cases

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Syringomyelia is a rare, mainly sporadic disease of the spinal cord, which is associated with 80% of cases in which a Chiari Type I malformation is also present. A mendelian transmission of syringomyelia (autosomal dominant or recessive) has been proposed in approximately 2% of reported cases. The association of syringomyelia with hereditary diseases ( Noonan’s syndrome, phacomatoses) has been mentioned frequently in the literature.

The authors report the presence of a Chiari Type I malformation accompanied by syringomyelia in two unrelated patients affected by a familial Type II blepharophimosis–ptosis–epicanthus inversus syndrome (BPES). The first patient was a 35-year-old woman who presented with a right C-8 root paresia. The second case involved a 20-year-old man who complained of cervical radicular pain. Both belong to families in which BPES was segregated in an autosomal dominant modality, but other family members had no known neurological symptoms. To the authors’ knowledge, such a combination has never been described. Perhaps the possible involvement of a genetic component in some cases of Chiari Type I–associated syringomyelia will someday be debated.

KEY WORDS • syringomyelia • Chiari malformation • blepharophimosis

Syringomyelia is considered to be a noninherited developmental disorder of the spinal cord, most frequently found in association with a Chiari Type I malformation.2 However, rare familial cases have been reported in which autosomal dominant or recessive inheritance was present.4,5,23 Chatel, et al.,6 suggested that the incidence of inherited syringomyelia is approximately 2%. An association between syringomyelia and inherited diseases such as Noonan’s syndrome or phacomatoses has also been mentioned.3,11,18 Blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) is an autosomal dominant condition involving abnormal eyelid development.16 It is characterized by short palpebral fissures, droopy eyelids, and an inverted inner canthal fold arising from the lower lid. Two clinical subtypes have been identified: in Type I, females are infertile, whereas in Type II female fertility is normal and transmission occurs through both sexes.50 Affected individuals have normal intelligence. Some progress has been made in understanding the molecular genetic basis of BPES. There are reports of linkage analysis that implicate the 3q2 chromosomal region1 and more recently the 7p13-p21 region.13 These findings imply genetic heterogeneity of the syndrome. We present two unrelated patients, each with a Chiari Type I malformation, syringomyelia, and a Type II BPES. To our knowledge, this is the first report of such an association.

Case Reports

Case 1

Examination. This 35-year-old woman complained of muscle cramps and weakness of the fourth and fifth fingers of her right hand. A horizontal nystagmus was noted on neurological examination. She was also found to have significant atrophy of the thenar and hypothenar muscles, with an ulnar claw of the right hand. Tendon reflexes were absent in the upper and increased in the lower limbs, and plantar responses were flexor. No sensory loss was noted. She had a blepharophimosis with short palpebral fissures, ptosis, and an epicanthus inversus (Fig. 1 left).

Neuroradiological Studies. The radiological examination revealed lumbar scoliosis, with the convexity toward the left. Magnetic resonance (MR) imaging of the spine dem-
onstrated a syrinx extending from C-1 to T-4 and a Chiari Type I malformation (Fig. 1 right). Chromosomal analysis showed a normal female karyotype (46, XX).

Family History. There was no consanguinity (Fig. 2). The family history was consistent with an autosomal dominant transmission of a Type II BPES, but other family members had a normal neurological history. Nevertheless they refused to undergo a systematic MR imaging investigation to exclude the possibility of asymptomatic Chiari disease.

Surgical Techniques and Operative Results. A standard suboccipital craniectomy was performed with no improvement in neurological signs and symptoms. The postoperative MR image revealed no decrease in size of the syrinx cavity. One year later the patient underwent syringoperitoneal shunt placement because of neurological deterioration. Her postoperative neurological status remained stable.

Case 2

Examination. This 20-year-old man complained of a right cervical radicular pain and right arm weakness. On examination, he exhibited significant atrophy of the right shoulder musculature. Motor examination demonstrated a moderate weakness in the muscles of the right arm and shoulder with no loss of pinprick and temperature sensation. Proprioception and coordination were intact. He presented with BPES syndrome (Fig. 3 upper) and had normal intelligence. No other abnormal findings were noted.

Neuroradiological Studies. Plain x-ray films of the spine demonstrated a C1–3 block consistent with a Klippel–Feil anomaly. Hypertrophy of the right transverse process and a left cervical rib were also noted. On MR imaging of the spine a syrinx extending from C-2 to T-6 and a Chiari Type I malformation were revealed (Fig. 3 lower). Chromosomal analysis showed a normal male karyotype (46, XY).

Family History. There was no consanguinity and other family members had no known history of neurological problems (Fig. 4). The mother (II6) and the brother (III4) of the patient had the same ocular abnormality, and the results of their neurological examinations were normal. The MR image of the spine in individual III4 showed no Chiari malformation or syringomyelia.
Surgical Technique. A wide suboccipital craniectomy combined with C1–2 laminectomy was performed. The foramen magnum was enlarged and a duraplasty was positioned over the enlarged volume of the posterior fossa.

Operative Results. A favorable outcome was obtained: the patient experienced total relief of pain immediately after the operation. The postoperative MR images revealed a decrease in size of the syrinx cavity. Five years later, results of follow-up clinical and radiological examinations remained unchanged.

Discussion

The pathogenesis of syringomyelia is unclear. Factors in the enlargement of the cavities include a filling mechanism and a movement of fluid under pulsatile influences. Many presumed causes have been advocated, including hindbrain-related syringomyelia, spinal tumors, meningeal fibrosis, or spinal bone deformities. Hindbrain herniation (by birth injury or Chiari malformation) is the most common causal factor reported. Syringomyelia is generally sporadic and fewer than 20 cases of the familial form have been reported so far in the literature. Pedigree analysis has indicated autosomal dominant or autosomal recessive transmission. Malessa and Jörg reported the case of a family with monozygotic twins in which only one of the twins suffered from syringomyelia, but they had an affected brother. For the authors, this report was evocative of an autosomal mode of inheritance with a variable penetrance in this family. These familial descriptions and the frequent association of syringomyelia with other inherited diseases such as phacomatoses led them to suggest that some syringomyelia could be secondary to mutations in genes influencing spinal cord development. Neurofibromatosis is the most common dysembryogenetic disease associated with syringomyelia but the latter has also been described in von Hippel–Lindau disease.

Noonan’s syndrome has been mentioned in connection with cervical syringomyelia. A case of radiographically diagnosed Type I autosomal dominant osteopetrosis associated with syringohydromyelia has been described by Sari and Demirci, and the association with an oculoauriculovertebral syndrome (Goldenhar’s syndrome) has also been reported. Neurofibromatosis is the most common dysembryogenetic disease associated with syringomyelia but the latter has also been described in von Hippel–Lindau disease.

There is an increased incidence of skeletal abnormalities in patients with syringomyelia. Basilar impression of the skull has been found in one-third of patients with this disease. Basilar impression has an autosomal dominant mode of inheritance in patients with and without syringomyelia. Idiopathic levscoliosis is rare but is often associated with a syrinx, as was the case for the first patient in our study. Our second patient had radiological abnormalities indicative of a Klippel–Feil anomaly with a C1–3 fusion, and the association of this anomaly with syringomyelia has frequently been reported.

Blepharophimosis syndrome is an autosomal dominant malformation that results in a smaller opening of the eyes and may severely impair visual function. It is likely that Type I BPES (with female infertility) results from a contiguous gene syndrome involving the genes required for normal eyelid development and for ovarian function. Recent studies have demonstrated a genetic heterogeneity in Type II BPES with at least two different locations. Pedigree analysis has indicated that the BPES gene involved in the chromosome 7p locus shows reduced expressivity and/or penetrance.

In the two families included in our study, the inheritance pattern was consistent with Type II BPES. Syringomyelia was diagnosed in only one patient in association with this syndrome. Other family members had no known neurological complaints but MR imaging of the spine was performed in only one case. It is conceivable that some family members remained stable with, for example, a Chiari I malformation. Moreover, a reduced penetrance cannot be excluded. Chiari malformation and syringomyelia may represent unusual manifestations of the BPES syndrome. Alternatively, familial syringomyelia may be more common.
common than a review of the literature indicates. The coincidental finding of syringomyelia with BPES syndrome has, to our knowledge, never been reported. Future studies may determine whether there is a genetic predisposition rather than an environmental cause in some instances of syringomyelia and BPES that is not evident at present.

References

Fig. 4. Chart showing pedigree of the second patient’s family. He is indicated by an arrow. Black shading in symbols indicates individuals clinically affected with blepharophimosis; gray shading indicates individuals affected with Chiari Type I malformation and syringomyelia. Roman numerals refer to generation number and Arabic numerals to position within generation.

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