X-linked hypophosphatemic rickets: cases series and literature review with a focus on neurosurgical management

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ABSTRACT

X-linked hypophosphatemic rickets (XLH) is an X-linked dominant disease caused by mutations in the Phosphate-Regulating Endopeptidase X-Linked (PHEX) gene. Due to its rarity and the wide range of clinical manifestations, management of the disease can be challenging due to several associated clinical implications that may arise during follow-up. The neurological complications associated with XLH are the most severe and often less known, which lead to important comorbidities. With the aim of summarizing the available knowledge on neurosurgical intervention in patients with XLH, we present four emblematic cases with disorders requiring neurosurgical evaluation. Relevant diagnostic delay was seen in two of these cases, with another case demonstrating that complications requiring neurosurgery may be present even in patients with few symptoms. The last case stresses the need for care of adult patients who can present with undiagnosed comorbidities. We also carried out a narrative review on neurosurgical interventions in patients with XLH. Through case reports and a review of the literature, focus is placed on the role of the neurosurgeon in the management of patients with XLH. In fact, neurosurgical intervention can often provide stable outcomes for craniosynostosis and clinical improvement for symptoms related to spinal stenosis. Thus, the neurosurgeon can aid in optimizing management of patients with XLH and should be a member of both adult and pediatric multidisciplinary teams. Lastly, additional studies are needed to determine if the early use of burosumab in infants can help to avoid complications in the long term.

Keywords: Arnold-Chiari type 1 syndrome, Craniostenosis, Neurosurgical complications, X-linked hypophosphatemic rickets

Introduction

X-linked hypophosphatemic rickets (XLH) is an X-linked dominant rare disease caused by mutations in the Phosphate-Regulating Endopeptidase X-Linked (PHEX) gene (Xp22.11). The protein encoded is a phosphate-regulating endopeptidase that regulates the expression of fibroblast growth factor 23

(FGF23) (1). Aberrations in the PHEX protein give rise to high serum concentrations of FGF23, which inhibit the activity of 1α-hydroxylase in the kidney, thus leading to hypophosphatemia and low levels of serum vitamin 1,25-dihydroxyvitamin D (2). Patients affected by XLH show marked hypophosphatemia, and decreased synthesis of 1,25-dihydroxyvitamin D, rickets, osteomalacia, odontomalacia, and short stature, in addition to complications including osteoarthritis, enthesopathies, spinal stenosis, and hearing loss (2,3). XLH is the most common form of inherited phosphate wasting with a prevalence that ranges from 1.7 per 100,000 children to 4.8 per 100,000 adults (4,5). Patients frequently develop clinical symptoms during the first or second year of life (2). Initial treatment consists of supplementation with oral phosphate and active vitamin D (2). However, in a substantial proportion of patients treatment is not entirely successful (6-8), especially in terms of lower limb deformities, short stature, and dental abscess. In addition, around 65% of children with XLH will require orthopedic

surgery (6-9). This is probably related to the aim of treatment approaches toward reduction of alkaline phosphatase (ALP) serum levels to improve rickets and promote skeletal growth without normalization of serum phosphate (2).

Starting in 2018, to overcome unsuccessful management of XLH, a new treatment approach has been made available, namely burosumab, which is a fully human monoclonal IgG1 antibody that neutralizes FGF23, and approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) based on the results of pivotal clinical trials (10-12). In children with XLH, burosumab has been shown to improve renal tubular phosphate reabsorption, serum phosphate levels, growth, and rickets (10-12). In addition, burosumab had a good safety profile and is associated with clinically relevant benefits for patients in terms of pain and physical health scores (12,13).

Due to the rarity of XLH and the wide range of clinical manifestations, diagnosis is sometimes delayed, especially in mild cases. Moreover, management of the disease can be challenging due to several associated clinical implications that may arise sooner or later during follow-up. Therefore, it is widely accepted that the management of XLH patients requires a multidisciplinary approach (2). The neurological complications associated with XLH are the most severe and often less known, which lead to important comorbidities for patients. In most cases, when neurological symptoms arise neurosurgical evaluation and intervention is often required. Craniosynostosis and Arnold-Chiari type 1 malformation leading to syringomyelia in some cases are two of the most severe complications of XLH that should be considered during management. However, only a few reports are available in the literature and there is limited evidence about the management of patients with XLH and disorders requiring neurosurgery (14-16).

With the aim of summarizing the available knowledge on neurosurgical intervention in patients with XLH, we present four emblematic cases with disorders requiring neurosurgery. We also carried out a narrative review on neurosurgical interventions in patients with XLH. These aspects are worthy of discussion in light of the increasingly evident need for multidisciplinary management of patients with XLH.

Case presentations

Case 1

This female patient was born in 2000 and diagnosed with XLH at the age of 3.5 years, presenting with tibial varus, short stature, and anomalies of dental enamel. Molecular analysis confirmed the suspicion of XLH with the presence of a heterozygous frameshift mutation (c2019_2021delACCinsCCTCA [p.Pro674LeufsX14]) in the *PHEX* gene. The child started treatment with phosphate salts and calcitriol. During follow-up, improvement of rickets was achieved with regular stature growth, below the midparent target height. Body mass index (BMI) was always in the normal range for age and sex. Growth and biochemical parameters at diagnosis are shown in Table I.

At the age of 14 years, the patient experienced pain in the right forearm and reduced sensitivity in the right hand. Since the symptoms persisted, the patient underwent a neurologic evaluation that did not find cranial nerve deficits in strength, function, or coordination, and symmetrical reflexes were evoked at all four limbs. An electroneurographic study was performed with negative results. For persistent hypoesthesia

TABLE I - Growth assessments and biochemical parameters at diagnosis and last visit

	Case 1		Case 2		Case 3		Case 4	
	Diagnosis	Last visit	Diagnosis	Last visit	Diagnosis	Last visit	Diagnosis	Last visit
Age (years)	3	22	2	13	3	12	44	45
Height (m)	0.966	1.52	0.946	1.495	0.83 (−3.36)	1.242 (−3.8)	1.335	1.335
Weight (kg)	16.1	48	15	47	10 (−3.6)	23.8 (−2.9)	35.7	36.3
BMI (kg/m²)	17.3	21	16.8	21	14.5 (−0.56)	15.4 (−0.4)	20	20.5
Pi (mg/dL)	2.9	2.5	2.7	2.8	2.1	2.5	1.9	3.4
ALP (IU/L)	1413	143	1236	1096	908	290	67	59.9
PTH (pg/mL)	54	77	92	51	25	24	29.9	50.1
25-OHD (ng/mL)	N.A.	N.A.	N.A.	15	9.8	8.5	18.7	13.2
TRP (%)	N.A.	N.A.	N.A.	N.A.	66.6	N.A.	N.A.	85.3
TmP/GFR	N.A.	2.13	1.67	2.32	1.40	2.9	N.A.	2.9

25-OHD = 25-hydroxyvitamin D; ALP = alkaline phosphatase; BMI = body mass index; GFR = glomerular filtration rate; N.A. = not available; Pi = inorganic phosphate; PTH = parathyroid hormone; TmP = tubular maximum reabsorption of phosphate; TRP = renal tubular reabsorption of phosphate.
See (26) as a reference for pediatric normal laboratory values.

in the arm and right hand, three years after the onset of the first symptoms, the patient underwent a cervical magnetic resonance imaging (MRI), which showed hypoplasia of the basiocciput and a small posterior cranial fossa, with descent of the cerebellar tonsils through the foramen magnum for a maximum distance of about 1 cm. A significant hydro-syringomyelic cavity was observed extending from the cranio-cervical region up to a plane passing through D10-D11, with a more evident finding in the mid-dorsal site (Fig. 1). The patient underwent occipito-cervical decompression surgery with coarctation of the cerebellar tonsils and autologous duroplasty with postoperative significant improvement of syringomyelia.

In the years after surgery the patient did not show any severe neurological symptoms. There is some deformity at the level of the rib cage, with some pain, for she underwent orthopedic evaluation. In June 2021, she was started on burosumab (compassionate use, patient >20 years) with the aim of improving phosphate levels and painful symptoms. Growth and biochemical parameters at last visit are shown in Table I.

Case 2

A male patient is the second child of a mother affected by non-genetically confirmed XLH and not investigated for XLH prenatally or after birth. At 18 months of life, due to tibial varum the child underwent radiological evaluations at another center near his hometown. The X-ray survey showed no cranial bone lesions, thinning of the cranial theca, and
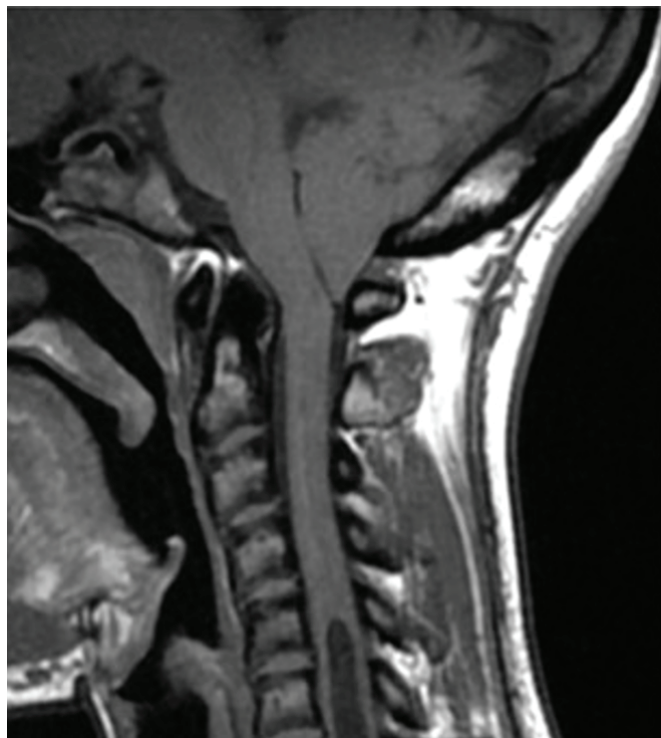

Fig. 1 - Magnetic resonance imaging showing significant hydro-syringomyelic cavity extending from the cranio-cervical region up to a plane passing through D10-D11 in case 1.

moderate curvature of the femurs and tibias with varus knee and hypoplastic acetabular cavities. An enlarged and frayed appearance of the distal femoral and tibial metaphyses was seen, associated with bone trabeculation and slightly rarefied cortical profiles. Further biochemical evaluation showed elevated serum ALP (1,236 IU/L), reduced serum phosphate (2.7 mg/dL) with serum parathormone slightly above the upper normal level (92 pg/mL) (Tab. I), which confirmed the suspicion of hypophosphatemic rickets.

Molecular analysis of *PHEX* revealed the nonsense variation C.2104 C>T (p.R702X) in both the patient and his mother. The child promptly started treatment with phosphate salts and calcitriol. At 30 months, turricephaly, microcephaly, and prominence of the sagittal and coronal sutures were observed. Some episodes of headache associated with vomiting were reported and he was referred to our center. Computerized tomography (CT) showed pansutural craniosynostosis, enlarged fingerprints (Fig. 2), and ectasia of the cerebellar tonsils. Fundus oculi examination revealed papilledema and MRI of the brain showed tortuous optic nerves. The child was referred for neurosurgical evaluation.
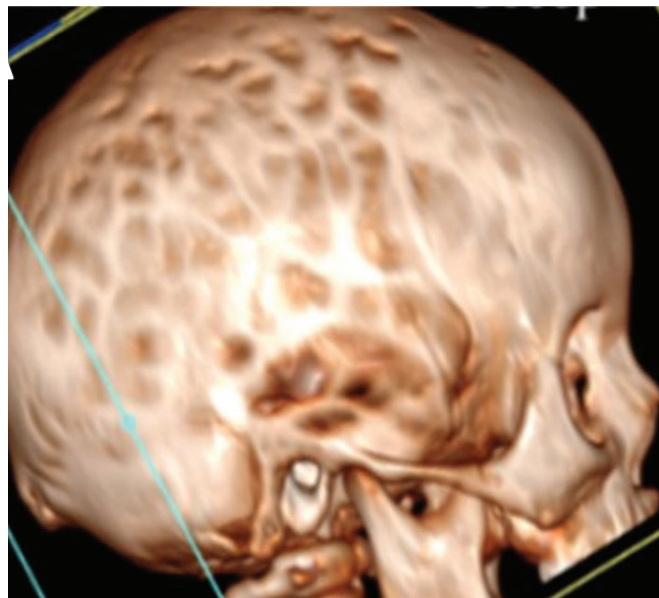

Fig. 2 - Cranial computed tomography image of case 2 showing pansutural craniosynostosis with enlarged fingerprints and ectasia of the cerebellar tonsils.

Invasive monitoring of intracranial pressure was initiated, confirming intracranial hypertension. The child underwent cranial vault expansion by distraction osteogenesis.

At postoperative follow-up, the patient showed dolichocephalic morphology and a stable brain MRI with no worsening of ectasia of the cerebellar tonsils (3 mm). Pale papilla was present on the right side, and the patient had reduced vision (right eye 4/10, left eye 8/10). Renal function and metabolic compensation were both within normal limits.

During follow-up the patient continued his regular treatment with active vitamin D and phosphate salts, regular monitoring of cranial MRI, renal ultrastructure, growth and skeletal features that eventually showed renal hyperechoic spots, lumbar scoliosis, plantar flatness, and minimal varus deformity of right tibia and femur. The growth trend was good and with straightening of the lower limbs. The patient did not show any dental abnormalities or abscess, and dental health was within normal limits. Growth and biochemical parameters at last visit are shown in Table I.

Case 3

A male patient with a family history of bone deformities and maternal short stature was diagnosed with XLH at 1.3 years of age for lower limb deformities and hypophosphatemia (*PHEX* mutation: p.Trp520Ter). Conventional therapy with alfacalcidol and phosphates was initiated at diagnosis with suboptimal results in both biochemical and growth responses.

At the age of 8 years, he started burosumab, with moderate biochemical response (improvement in ALP and Rickets Severity Score [RSS], but without recovery of hypophosphatemia; Tab. I). At the age of 11 years, the patient started to complain of headache and was referred for neurosurgical evaluation. Somatic characteristics related to rickets, with dolichocephalic caput, frontal bossing, and recess at the level of the coronal suture were observed. A high-resolution CT scan showed complete synostosis of the sagittal suture associated with marked reduction of the squamous suture.

A Chiari I malformation was diagnosed by MRI (Fig. 3A). No syringomyelia was seen at the level of the medulla. Venous sequences by MRI angiography showed the absence of signal at the level of the transverse sinuses, with the presence of collateral venous circulation (Fig. 3B, C), which could lead to intracranial hypertension due to reduction of liquor reabsorption in the venous system.

As the patient did not have papilledema, strict follow-up was started without neurosurgical intervention. Growth and biochemical parameters at last visit are shown in Table I.

Case 4

The patient is the 44-year-old mother of patient 3, and was previously misdiagnosed with achondroplasia. She was diagnosed with XLH at the age of 35 following diagnosis of her 11-month-old child. She had no family history of XLH. Stature and biochemical parameters at diagnosis are shown in Table I. At the age of 5, she underwent bilateral corrective tibial osteotomy for varus. Osteotomy for valgus deformity of the right knee was performed when she was 14 years old.

At initial evaluation, biochemical markers were calcium 9.0 mg/dL, phosphate 1.9 mg/dL, creatinine 0.59 mg/dL, ALP 67 U/L, parathyroid Hormone (PTH) 29.9 pg/mL, and 25-OH vitamin D 18.7 ng/mL. She was started on treatment with calcitriol 1 mg/day. Potassium dihydrogen phosphate plus disodium hydrogen phosphate (602 mg plus 360 mg), two tablets twice a day, was also added. In March 2022, she started treatment with burosumab (compassionate use, patient >20 years) to normalize phosphate levels and reduce pain. Biochemical parameters at last visit are shown in Table I. She referred that at the age of 43 she had undergone neurosurgical evaluation for headache.

An Arnold-Chiari type 1 malformation was diagnosed by MRI with cerebellar tonsils that engaged in the conjugation frame (for about 3 mm). Furthermore, the medullary cord at the level of the soma of C6 showed a modest extension of the ependymal canal of the syringomyelia type with clinically relevant cephalic expansion (Fig. 4). The patient chose to postpone the indicated surgical procedure.

Discussion

The present cases provide the opportunity to highlight several points regarding diagnosis and management of patients with XLH. In case 1, a severe Arnold-Chiari malformation was observed by MRI. Considering the first appearance of symptoms, imaging examination was not promptly carried out. We investigated the reasons of this diagnostic delay that could have been dramatically harmful for our patient. First, the patient mostly described her symptoms as a chronic condition with moderate pain or hypoesthesia in her hand. This condition may have been considered for treatment with anti-inflammatory drugs ex juvantibus, but not for immediate evaluation with cerebral MRI. However, we believe that the main reason for the diagnostic delay resides in the unawareness of Arnold-Chiari type 1 malformations in
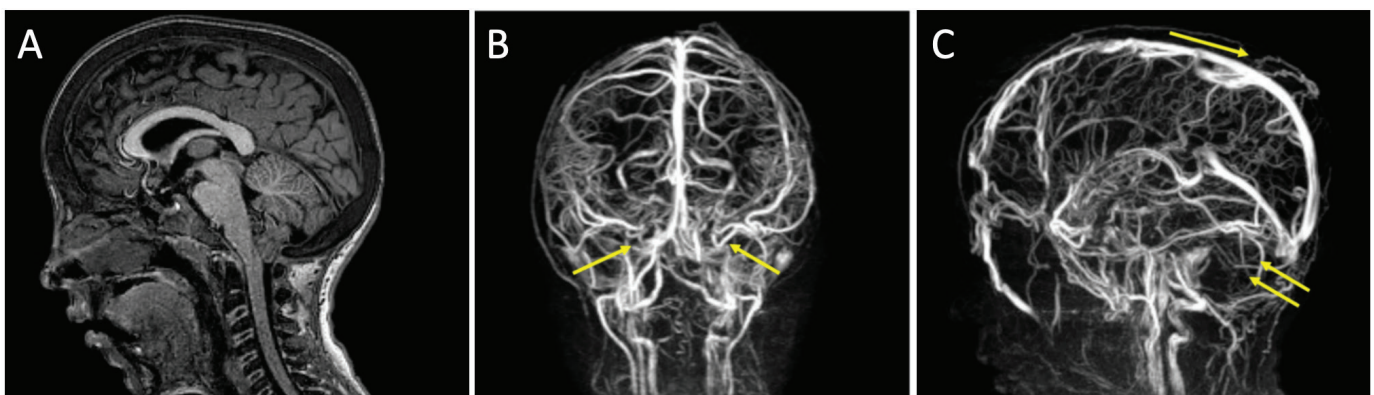

Fig. 3 - Case 3. **A)** Chiari type 1 malformation evident by MRI. **B, C)** Venous sequences by MRI angiography showing the absence of signal at the level of the transverse sinuses, with the presence of collateral venous circulation. MRI = magnetic resonance imaging.
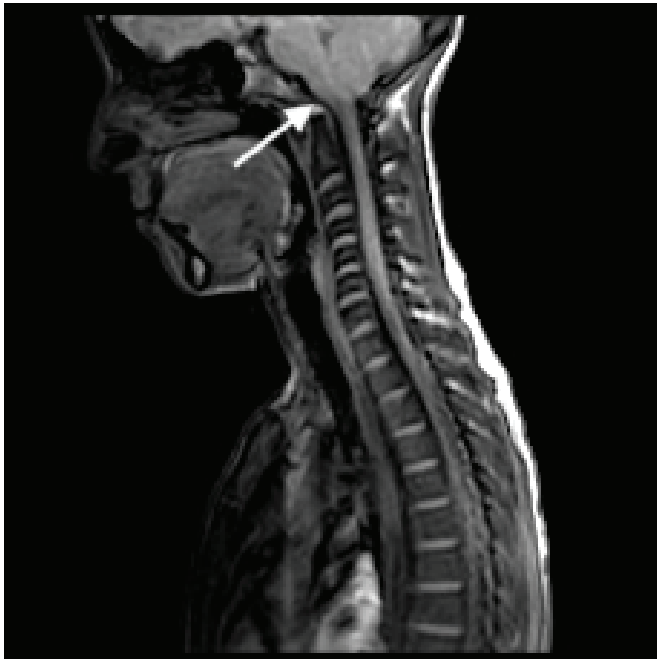
Fig. 4 - Magnetic resonance imaging of Arnold-Chiari type 1 malformation in case 4.

XLH patients, since this is the first patient we managed with this association. Notwithstanding, the patient had a good clinical outcome despite the severe radiologic picture. This may therefore raise the question of when MRI should ideally be performed to screen XLH patients for Arnold-Chiari type 1 malformation.

In case 2, a relevant diagnostic delay can also be noted, even if the patient was born to a mother known to have XLH but not genetically confirmed. It is possible to hypothesize that if the diagnosis of the mother had been genetically confirmed, her son would have been investigated in the first months of life by molecular analysis of *PHEX.* In our opinion, if the patient was correctly diagnosed with XLH due to *PHEX* variation in the first months of life, he could have undergone regular follow-up of skeletal features and neurosurgical workup, and thus surgery at an earlier age, which may potentially have avoided the patient's symptoms. Craniosynostosis can be observed in about 60% of patients with XLH (14,15). Notwithstanding, only a fraction of patients will require surgery, which is possibly related to delayed or missed diagnosis of sutural synostosis. Therefore, all patients with XLH should undergo careful monitoring of cranial morphology and head circumference, and the patency of anterior fontanelle size during the first year of life (2). Other neurosurgical complications due to complete or partial fusion of cranial sutures include protrusion of the cerebellar tonsils developing the Arnold-Chiari malformation and in some cases syringomyelia (16).

Case 3 demonstrates that complications requiring neurosurgical evaluation may be present even in patients with few symptoms, and thus there is the need for a high degree of suspicion and early referral for proper follow-up. In addition, the question arose as whether to operate or not when faced

with a rather late diagnosis of craniosynostosis in the absence of clear evidence of intracranial hypertension and no symptoms related to Chiari syndrome. Careful ophthalmologic, neurological, and neuroradiological monitoring is therefore mandatory in this case in order to evaluate the need for surgical treatment. Lastly, case 4 stresses the need for care of adult patients who can present with undiagnosed comorbidities. In this patient, XLH was diagnosed late only following a diagnosis of XLH in her child. Together, these cases demonstrate that clinicians should pay greater attention to complications of XLH, with an emphasis on early diagnosis and treatment. Clinical guidance is also needed regarding the possibility to carry out neurosurgical screening by nuclear magnetic resonance (NMR) in all patients diagnosed with XLH, or only in those with craniostenosis or its complications.

We carried out a literature search on PubMed to identify cases of XLH that were treated with neurosurgical approaches using the keywords: "X-linked hypophosphatemic rickets," "neurosurgical complications," "Arnold Chiari type 1 syndrome," and "craniostenosis." A total of 18 cases were identified (Tab. II). Broadly, two types of interventions were performed, cranial vault remodeling for craniosynostosis and laminectomy for spinal stenosis at various levels. These types of interventions are thus reflective of some of the most commonly observed associated complications of XLH. In all the cases reported, cranial vault remodeling was considered successful with a stable outcome at various follow-up times. In four of the five cases in which laminectomy was carried out, the outcome was considered favorable with clinical improvement. However, in the case reported by Kuether and Piatt in a 12-year-old patient with a large syrinx from C2 to T7 with significant foramen magnum stenosis and an Arnold-Chiari type 1 malformation, suboccipital craniectomy and C1 laminectomy with duroplasty did not lead to any significant improvement despite significant reduction in the diameter of the cervical thoracic spinal cord syrinx at 3 months after surgery (17). Two years after the intervention, the syrinx collapsed except for a small residual from T2 to T6.

In a cranial CT survey of 44 patients with XLH of variable age, even in the absence of symptoms, 26 cases of sagittal craniosynostosis were found, which was associated more frequently with the onset of dental abscesses and a higher incidence of Arnold-Chiari type 1 syndrome (15). The cranial index thus seems useful to identify patients in which it is easier to find an Arnold-Chiari type 1 syndrome. These authors highlight that sagittal craniosynostosis is frequent in patients with XLH, and that the association with Arnold-Chiari syndrome is also relatively common. Moreover, it was documented that cranial malformations appear to be associated with very severe rickets (15). In cases of craniosynostosis that occur after early childhood, hypophosphatemic rickets must be considered in the differential diagnosis (18).

In our case 1, the presence of an Arnold-Chiari type 1 malformation was not associated with craniosynostosis. Furthermore, the insurgence of neurological comorbidities in cases 1 and 2 does not seem to be related to the severity of rickets. Due to the rarity of disease, a clear correlation between genotype and phenotype in these two cases could not be evaluated.

TABLE II - Summary of publications in patients with XLH undergoing neurosurgical management

Author, year	No. of cases	Age at presentation	Reason for intervention	Intervention	Outcome
Vega et al., 2016 (18)	7	1 to 9 years	Craniosynostosis, scaphocephaly	Cranial vault remodeling	Stable
Yamamoto and Onofrio 1994 (27)	1	42 years	Severe spinal canal stenosis from T4 to T10	Thoracic laminectomies	Favorable
Soehle and Casey, 2002 (28)	1	44 years	Calcified intervertebral disc, marked cervical cord compression at C6/C7	Anterior cervical discectomy/fusion with autologous bone graft	Favorable
Riccio et al., 2016 (29)	1	49 years	Multilevel thoracic stenosis	Posterior decompression at T4-T5, T8-T9, T9-T10, and T11-T12, via a minimally invasive approach	Favorable
Kuether and Piatt, 1998 (17)	1	12 years	Large syrinx from C2 to T7, with significant foramen magnum stenosis and a Chiari type 1 malformation	Suboccipital craniectomy and C1 laminectomy with duroplasty	No significant clinical improvement, after 2 years syrinx collapsed except for a small residual from T2 to T6
Jaszczuk et al., 2016 (20)	3	>2 years	Sagittal suture craniosynostosis	Cranial vault expansion	Stable
Dunlop and Stirling, 1996 (30)	1	49 years	Compression at T7, less at T5, T6, and T9	Decompressive laminectomy from T6 to T10	Full recovery
Murphy, 2009 (31)	1	11 years	Craniosynostosis, scaphocephaly	Cranial vault expansion	Normalization
Migliarino et al., 2022 (32)	2	7 years (twins)	Craniosynostosis, scaphocephaly	Cranial vault expansion	Not described

In the literature, for many years these particular cranial conformations were not defined as craniosynostosis, but have often been associated with the underlying pathology, even if surgically treated scaphocephaly has been reported for decades. In 1984, it was hypothesized that cholecalciferol intoxication may trigger craniosynostosis (19). While today this seems like an unlikely hypothesis, there is still some concern that vitamin D may lead to premature closure of cranial sutures. In the 44-case cohort published by Rothenbuhler et al, in 60% of patients there was a synostosis of the sagittal suture and therefore scaphocephaly (15). While the shape of the skull is relatively unaltered, the suture of the skull is observed at later times, indicating the need for close observation, especially since clinical examination of the skull may provide evidence of cranial synostosis (20). In clinical practice, it is recommended to screen children with sagittal synostosis and children with Chiari malformation for hypophosphatemia and increased ALP, regardless of cranial morphology.

The presence of pain, physical abnormalities, and decreased function and mobility will further isolate patients with XLH with substantial psychological consequences (21). This is an example of the strong need, on the national level, for transition programs that include specific actions that patients view as priorities. Preparation for transfer and a multidisciplinary approach may thus enhance successful transition (22). The transition from childhood to adulthood is usually difficult in rare diseases. The number of patients that transfer to adult healthcare is still limited, with deep impact on their quality of life. It has been further suggested that specific pediatric and adult XLH teams be used to aid in the transition to adulthood care (23), and with attention to local protocols (24). This is also highly relevant considering that complete phenotypic rescue is rarely achieved in these patients, and chronic symptoms warrant multidisciplinary specialist care (25). Patient management and coordination of various medical disciplines is thus a cornerstone starting with diagnosis, and to optimize therapy and reduce the burden of disease (25).

With this in mind, herein the role of the neurosurgeon was highlighted, demonstrating that neurosurgical intervention can often provide stable outcomes for craniosynostosis and clinical improvement for symptoms related to spinal stenosis. Thus, the neurosurgeon can aid in optimizing management of patients with XLH and should be a member of both adult and pediatric multidisciplinary teams. Lastly, additional studies are needed to determine if the early use of burosumab in infants and adults can help to avoid complications in the long term.

Acknowledgment

Statement of Ethics

Written informed consent for publication (including images) has been obtained from the patients. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The article is exempt from Ethical Committee approval since it is related only to four case reports.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Disclosures

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