Skeletal dysplasia involving the subaxial cervical spine

Report of two cases and review of the literature

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Because skeletal dysplasias are primary disorders of bone, they have not been commonly understood as neurosurgical diseases. Nevertheless, neurosurgical complications are commonly encountered in many cases of dysplasia syndromes. The authors present two cases of skeletal dysplasia that caused overt instability of the cervical spine. One patient with a diagnosis of Gorham disease of the cervical spine was treated with prolonged fixation in a halo brace after an initial attempt at instrumentation with a posterior occiput–C4 fusion. The other patient, who at birth was identified to have camptomelic dysplasia, has been treated conservatively from the outset. Although these two patients presented with different disorders—in one patient adequate mature bone never formed and in the other patient progressive bone loss became apparent after a seemingly normal initial development—these cases demonstrate unequivocally that surgical options for fusion are ultimately limited by the quality of the underlying bone. In patients in whom the bone itself is inadequate for use as a substrate for fusion, there are currently limited treatment options. Future improvements in our understanding of chondrogenesis and ossification may lead to the design of superior methods of encouraging fusion in these patients; however, at the present time, long-term maintenance in a halo brace may, in fact, be the only treatment.

KEY WORDS • cervical instability • skeletal dysplasia • camptomelic dysplasia • Gorham disease • disappearing bone disease

Skelet al dysplasias are a heterogeneous group of disorders that have in common abnormal bone formation or remodeling (such as ossification or osteolysis). Although many types of dysplasia are quite rare, in aggregate they represent a significant disease burden, especially in the pediatric population. Skeletal dysplasias may be generalized conditions involving the entire skeleton, such as osteochondral dysplasias, or they may be limited to involvement of single bones or malformations of single groups of bones, such as fibrous dysplasia or cleidocranial dysplasia (collectively considered dysostoses). The traditional classification of skeletal dysplasias is dependent on x-ray studies of the skeleton and a description of the abnormality as it relates to the location of the bone. The need for a comprehensive classification of skeletal dysplasias prompted the creation of the “International Nomenclature of Constitutional Diseases of Bones.”

According to this classification, skeletal dysplasias, of which more than 200 have been described, are categorized into five primary groups: osteochondral dysplasias, dysostoses, idiopathic osteolytic syndromes, primary chromosomal abnormalities, and primary metabolic abnormalities.

In all skeletal dysplasias, the primary pathophysiological process is an abnormality of the underlying bone; neurological morbidity, when it occurs, is secondary to the underlying pathological bone process. Thus skeletal dysplasias have not been commonly understood as neurosurgical diseases. Nevertheless, neurosurgical complications caused by cranio cervical junction instability, associated spinal dysraphism, secondary cranial and peripheral neuropathies, and hydrocephalus occur in conjunction with many skeletal dysplasias. Although atlantooccipital instability and thoracic kyphoscoliosis are relatively common findings among the various skeletal dysplasias (specifically the osteochondral dysplasias and metabolic diseases of bone), subaxial instability is less well recognized as a feature of these disease processes. In addition, because by definition the involved bone is an abnormal substrate for fusion, treatment of these patients can be extremely challenging.

We present two cases that represent opposite ends of the spectrum of skeletal dysplasias: an infant presenting with cervical kyphosis due to a congenital defect in the develop-
opment of bone (camptomelic syndrome, an osteochondral dysplasia), and a patient with Gorham disease of the cervical spine (an idiopathic osteolytic disease). Together, these patients illustrate clinical challenges in the neurosurgical management of the subaxial spine in children with constitutional diseases of the bone.

Case Reports

Case 1

History. This infant boy was delivered by cesarian section at 38 weeks’ gestation after a routine antenatal ultrasonography study disclosed skeletal abnormalities consistent with skeletal dysplasia. The child was born with the clinical features of camptomelic dysplasia, including bowing of the distal lower extremities with anterior dimpling. The child was neurologically intact at birth.

Examination and Treatment. Computerized tomography and MR imaging of the head and spine disclosed absence of ossification of the bilateral cervical pedicles and a 90° kyphosis of the cervical spine; the apex of the deformity was located at C-3 (Fig. 1). The kyphosis was reduced when the patient was placed in a collar, and the infant was subsequently discharged home in a customized orthosis. Unfortunately, he later presented to another hospital in respiratory distress. Neurologically, the patient appeared diffusely hypotonic or “floppy,” and repeated MR imaging demonstrated signal changes in the cord that were consistent with a contusion centered at the apex of the cervical kyphotic deformity.

Clinical Course. Follow-up MR images demonstrated cord atrophy and myelomalacia, and the patient remains tetraplegic. Repeated CT scanning performed when the child was 18 months of age (Fig. 2) demonstrated partial ossification of the cervical vertebral pedicles.19

Case 2

History. This 10-year-old boy, who was previously healthy and active in baseball, in which he was a pitcher, noted a painful and stiff neck, which prompted his mother to seek medical attention for him. Conservative management failed in this patient and additional testing was performed. Findings on MR images suggested a pathological process involving the clivus. Biopsy sampling of the clivus and the occipitocervical spine revealed an evolving destructive skull base process, with expansion noted on MR images. The patient underwent a biopsy at another institution; the sample obtained demonstrated histological findings consistent with the diagnosis of Gorham disease, including increased regional vascularity with resultant acceleration of bone remodeling activity, in which osteoclasia predominated. Reactive woven bone was seen emerging within a fibrovascular marrow. Initially, the diagnosis of histiocytosis was made, and the patient was treated with a collar and observation.

Presentation, Examination, and Operation. Ten months after his initial presentation, the patient’s symptoms progressed and he presented to our institution with a loss of neck stability and torticollis. During the neurological examination, he was found to be myelopathic with hyper-reflexia in all four extremities, bilateral lateral nystagmus, and dysphagia. Repeated MR imaging demonstrated cranial settling with extension of the abnormality to include the clivus and the medial petrous pyramids, as well as the prevertebral soft tissues, the anterior arches of C-1 and C-2, and the odontoid process. The patient was placed in a halo brace and subsequently underwent transoral decompression and odontoidectomy followed by posterior occipit–C4 fusion and placement of wires.

Postoperative Course and Diagnosis. Immediately postoperatively, the patient experienced no neck pain and was neurologically intact. Several months after surgery, he began to experience trismus and disappearance of his right mandibular ramus was noted. On follow-up examination, it was discovered that there was no evidence of occipitocervical fusion and the patient was maintained in a halo brace. The definitive diagnosis of Gorham disease of the cervical spine was made, and the patient underwent low-dose radiation therapy consisting of 10 Gy in five fractions, which slowed the progression of his bone loss. Although the progression of bone erosion ceased following radiation treatment, his cervical spine remains unstable (Fig. 3).

Later Follow Up. As of his 16-year follow-up examination, the patient continued to require the halo orthosis. Since the time of his occipitocervical fixation and the initial placement of wires, avascular necrosis of the head of the femur and a symptomatic cervical syrinx, which was treated with cervical decompression, has developed. We believe that the necrosis was related to steroid therapy. The boy is bound to a wheelchair. Before he underwent hip surgery, this patient usually relied on a walker and only used a wheelchair infrequently. He is now unable to work, needs help with daily activities, exhibits hyperreflexia, and reports poor sensation and muscle strength in general. His demeanor remains pleasant, and our impres-
sion is that this is an unfortunate 26-year-old man who has maintained a remarkably calm and agreeable attitude throughout his battle with Gorham disease, while spending more than half of his life in a halo brace.

Discussion

Because of the heterogeneity of skeletal dysplasias, considerable confusion abounds in the literature with regard to the correct nomenclature of the disorders. Adding to the confusion is the rarity of some of these syndromes. The prevalence of eponymous designations (Larsen syndrome, Kniest syndrome, among others) and the practice of naming syndromes based on Greek terms used to describe dysplasia (diastrophic dysplasia, camptomelic dysplasia, and so forth) have tended to increase the confusion.

In addition, new molecular technologies have fostered a more nuanced understanding of these syndromes, which has often prompted their repeated designation and definition.

Osteochondral Dysplasia

Osteochondral dysplasias typically present in childhood with dwarfism. They are divided into three groups: defects of growth of tibia bones and/or spine, disorganized development of cartilage and/or fibrous components, and disorders of cortical diaphyseal density. Regardless of the subtype of osteochondrodysplasia, the abnormal bone development that characterizes these disorders includes craniovertebral and/or spinal involvement as the rule rather than the exception.

The most common locus of spinal instability associated with the osteochondral dysplasias (as well as with skeletal dysplasias in general) is at the atlantooccipital junction. Odontoid hypoplasia is seen in both pseudoachondrodysplasia and spondyloepiphysial dysplasia congenita. Differential diagnoses include the mucopolysaccharidoses (including Morquio, Hurler-Sheie, and Hunter syndromes); however, regardless of the cause of the atlantoaxial instability, posterior C1–2 fusion is indicated.

Osteochondral dysplasias also commonly cause kyphoscoliosis—typically those of the thoracic spine and thoracolumbar junction. Kyphoscoliosis is the hallmark of Kniest syndrome, a rhizomelic (short-limbed) form of dwarfism that results from an autosomal-dominant defect in the collagen II gene. Achondroplasia, the most common dysplasia (incidence 1 in 26,000 live births), is an autosomal-dominant short-limbed dwarfism in which stenosis of the foramen magnum, lumbar stenosis, and thoracolumbar kyphoscoliosis are commonly encountered. Congenital hypotonia and myelopathy are commonly identified; however, these may spontaneously resolve when the patient is 2 or 3 years of age. Patients who remain symptomatic may require suboccipital decompression. In contrast, lumbar stenosis occurs as a result of short lumbar pedicles and typically does not present until later in life (most commonly in the second to third decades). Treatment is generally wide laminectomy with undercutting of the facets.

In contrast, cervical subaxial instability and kyphoscoliosis are rarely prominent features of this family of disorders. Cervical instability or kyphosis has been most often described in association with diastrophic dysplasia, a rhizomelic dwarfism. Unlike spondyloepiphysial dysplasia, pseudoachondrodysplasia, and the mucopolysaccharidoses, odontoid development is normal and patients do not have C1–2 instability. Instead, the kyphotic deformity is due to cerebral body hypoplasia or dysraphism, with hypoplasia or wedging of C-3, C-4, and C-5, which causes progressive kyphosis in as many as one third of patients. Cervical kyphosis usually develops within the first 2 years of life, and, although spontaneous resolution of kyphosis has been described in patients as old as 5 years of age, halo vest stabilization is recommended once the skull is capable of holding pin fixation. Subaxial cervical instability and kyphosis have also been described in association with Larsen syndrome.

Camptomelic dysplasia is an autosomal-dominant syndrome associated with mutation of the SOX9 gene, a relative of the homeobox family of genes required for normal chondrogenesis. Camptomelic dysplasia is characterized by bowing and angulation of tubular bones and other skeletal and soft-tissue defects. Commonly associated findings include cutaneous dimpling, which can be seen with any prenatal bowing, hypoplasia of the inferior part of the scapula (bladless scapula), cleft palate, micrognathia, flat face, hypertelorism, tracheobronchial hypoplasia, phenotypic sex reversal, hypoplastic thoracic pedicles, and progressive thoracic kyphoscoliosis. In all patients with camptomelic dysplasia, the delayed ossification of the vertebral pedicles is
thought to be the result of a primary defect in the initial clustering of cartilaginous embryonic cells, which leads to faulty connections among the anterior, middle, and posterior columns of the spine and progressive thoracic kyphoscoliosis. Most patients die of respiratory distress early in infancy; however, there have been reports of variable penetrance and long-term survivors with this disorder. Treatment of kyphoscoliosis in these patients is extremely challenging, because of the vertebral immaturity. It has been suggested that a combined anterior-posterior approach is required to fix the thoracic kyphoscoliosis commonly seen in this disease. Anterior cervical arthrodesis in an infant with immature bone development, however, is not feasible, and the patients’ posterior elements appear to be essentially free floating because of the absence of development of the cervical pedicles. Therefore, we elected to observe the patient in Case 1 until ossification occurred, which has been reported to occur in a delayed fashion in patients with diastrophic dysplasia.

Osteolytic Disease (Gorham Disease)

Gorham disease, also known as vanishing bone disease, is a very rare bone disorder characterized by bone loss due to osteolysis. In contradistinction to the osteochondral dysplasias described earlier, in patients who have this disease bone development is initially normal, but subsequently the
Subaxial skeletal dysplasia

bone undergoes gradual and complete circumscribed spontaneous resorption. Fewer than 200 cases have been reported in the medical literature and its cause is not known. The condition affects both sexes equally and has been noted to be posttraumatic in many cases. Clinical onset has been reported to occur anytime from childhood to adulthood; it usually manifests unilaterally and includes focal angiomatous proliferation involving one bone or contiguous bones (such as vertebrae). Adjacent soft tissue can also be involved, producing diffuse muscle atrophy and sometimes hemangiomatous of the overlying skin. Any part of the skeleton can be affected, but Gorham disease is recognized most easily when the calvaria or mandible is involved; involvement of the thoracic cage is progressive and fatal. Because it is a rare disease, its recognition and treatment is commonly delayed; it often goes undetected and there is a lack of agreement on its treatment because there is a dearth of Class I evidence. We reviewed the appropriate literature and, to our knowledge, to date there have only been 29 reported cases of Gorham disease involving the spine. Spinal dislocation and chest involvement (chylotorax) are the most frequent causes of death associated with this disease; and kyphosis, kyphoscoliosis, and subluxation of the spine are common abnormalities noted in patients with Gorham disease.

The cause of the disease remains enigmatic. Heffez and colleagues presented a useful list of factors to help distinguish Gorham disease from other destructive bone disorders; they include a biopsy sample indicating the presence of angiomatous tissue; absence of cellular atypia; little or no osteoblastic response or dystrophic calcification; local progressive osseous resorption; a nonexpansile, nonulcerative lesion; no involvement of visera; an osteolytic radiographic pattern; and no hereditary, metabolic, neoplastic, immunological, or infectious cause. This bone disorder is largely attributed to focal lymphatic endothelial proliferation, whereby the bone is progressively destroyed and resorbed. Patients with Gorham disease present with pathological bone fractures, and death is imminent when the spinal cord or lungs are involved. Progression of the disease has been observed to cease without treatment in some cases, but regeneration of the destroyed bone is not expected.

Current treatments for Gorham disease remain debatable, but options include early surgical intervention and radiation therapy. For example, ligation of the thoracic duct can preclude fatal complications, and fusion is often indicated when the spinal cord is involved. Early administration of 30 to 40 Gy may prevent progression of the disease and provides a small chance for reconstitution of the destroyed bone. This treatment modality, however, may be best reserved for patients who would not be candidates for surgery. Medical treatments have been attempted to treat Gorham disease in the spine and tubular bones; these include administration of parathyroid hormone, calcium, vitamins D and B12, adrenal extracts, pamidronate, calcitonin, and calcium carbonate after surgery (spinal fusion); bisphosphonates; and even clodronate and interferon-α-2b. Of course, the usefulness of all these treatments is also shaped by the severity of the disease (for example, surgery would be impractical in patients with widespread vertebral involvement) and the urgency of the patient’s condition.

Gorham disease of the spine can produce severe subaxial instability, and surgical treatment for spinal involvement was chosen for eight patients with this disease according to reports in the literature. In all these patients the spine failed to fuse after the initial operation. Drewry, et al., have described the case of a 13-year-old boy with spinal instability and chylotorax associated with Gorham disease. The spine was internally stabilized after reconstruction and subsequently irradiated; the fusion remained stable for 22 months, but this is not always the case. Castleman and McNeely and Anavi and associates have reported failures of spinal fusion. Hawk and colleagues have advocated the combination of early radiation therapy with external spinal stabilization as the optimal treatment for Gorham disease with cervical spinal involvement. Of course, long-term follow-up review is the only definitive way to measure the success of fusion and the progression of the disease to adjacent skeletal and soft-tissue regions. In our opinion, the role of internal fixation in the treatment of this disease remains undefined. Although internal fixation has been associated with uniform failure, at least in the cervical spine, several factors complicate the assessment of the utility of internal fixation in this setting. The diagnosis of Gorham disease is often delayed because of the rarity of the disease and the relatively low index of suspicion it raises among clinicians. In those patients in whom the diagnosis of Gorham disease is known preoperatively, fusion performed after radiotherapy or medical stabilization of the disease may still be a reasonable alternative. This may be particularly apropos given the current availability of bone fusion enhancement products such as recombinant human bone morphogenetic protein, the use of which has not been described in this setting. Finally, regardless of the treatment strategy, because of the underlying spinal instability and the poor quality of bone, patients with this disease should be followed closely with routine plain radiography and/or CT studies. Our practice has been to obtain imaging studies every 3 months for the first 1 or 2 years after initial fixation or brace immobilization. As the patient’s clinical situation stabilizes, imaging studies can be obtained on an annual basis.

Finally, the mechanism of bone absorption remains poorly understood. Heyden and associates have proposed that perivascular cells might actually be precursor osteoclasts; the link with bone absorption can be inferred by these cells’ strong acid phosphatase and leucine aminopeptidase activities. Perhaps there are other cells involved or mechanisms by which bone is absorbed. Joseph and Bartal have postulated that mechanical force resulting from increased pressure associated with hypervascular tissues is responsible for the bone absorption. As in all skeletal dysplasias, multiple mechanisms of bone destruction directly related to the intrinsic pathophysiology of the disorder as well as the dynamic biomechanics of the spine are likely to contribute to cervical instability.

Conclusions

We have presented two cases in which skeletal dysplasia caused overt instability of the cervical spine. In one case, we treated the patient with prolonged halo fixation after initially attempting instrumentation with a posterior occiput–C4 fusion. In the other case, we treated the patient conservatively from the outset. Although these two patients presented with different symptoms—one patient did not have adequate mature bone and the other experienced
progressive bone loss after initial normal bone development—these cases demonstrate unequivocally that surgical options for fusion are ultimately limited by the quality of the underlying bone. In patients in whom the bone itself is inadequate as a substrate for fusion, there are currently few treatment options. In our opinion, based on our experience with these disorders, long-term maintenance in a halo brace may, in fact, be the only treatment. Future improvements in our understanding of chondrogenesis and ossification may lead to superior methods to encourage fusion in these patients.

References