Differential Diagnosis of Secondary Center of Ossification Abnormalities

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Abstract

Background: An abnormal secondary center of ossification (SCO) is a topic infrequently considered in orthopaedic literature but may result in significant morbidity and mortality in the pediatric patient. There exists a paucity of literature which may assist clinicians when assessing these uncommon pathologies.

Methods: Available literature was surveyed and the differential diagnosis of abnormal SCO was organized according to radiographic findings.

Results: This review article provides clinicians with an evidence-based quick-reference guide in approaching SCO pathologies. First, it discusses the basic anatomy and physiology of the pediatric skeleton. Secondly, it describes the basic types of irregular SCO one may encounter based on radiographic findings.

Conclusions: This discussion of SCO pathologies assists clinicians in approaching the differential diagnosis of an infrequently encountered, yet clinically significant, set of orthopaedic presentations.

Keywords: Pediatric; Orthopaedic; Secondary center of ossification; Epiphysis; Stippled epiphysis; Hypoplastic epiphysis; Dysplastic epiphysis; Hyperplastic epiphysis; Epiphysis necrosis; Precocious Epiphysis; Multiple epiphyses; Rickets; Osteomalacia; Chondroblastoma

Introduction

The anatomy of a child’s bone may be divided into its basic components: the epiphysis, physis, metaphysis, and diaphysis. An appreciation of the growth and function of each structure is critical whenever a clinician encounters pathologies in the pediatric skeleton. The following review discusses the differential diagnoses of abnormal secondary centers of ossification (SCO), a topic which is infrequently considered in orthopaedic literature, but may result in significant morbidity and mortality in the pediatric patient. It provides the fundamental tools in approaching children with this condition in two ways: First, by surveying the basic anatomy and physiology of the pediatric skeleton. Second, by describing the basic types of irregular SCO one may encounter. The following discussion will assist clinicians in developing a practical approach towards the differential diagnoses of abnormal secondary centers of ossification.

Anatomy and growth of the pediatric skeleton

Primary centers of ossification: During week eight of embryological development, bone arises from osteoblasts in the primary centers of ossification (PCO). In all long bones, the diaphysis is the single primary center of ossification and forms the shaft of the bone. In contrast, vertebrae and flat bones consist of multiple PCO. As a child develops, the diaphysis undergoes appositional growth with layers of peristeal membranous osseous tissue deposited over the original enchondral model. The shaft enlarges circumferentially but does not lengthen longitudinally [1-3].

The Epiphysis and the secondary center of ossification: The epiphysis flanks each end of the long bone and rests upon the physis. A joint is formed when an epiphysis articulates with
an adjacent epiphysis of the bone. The epiphyseal physis lies perpendicular to the axis of the long bone and is responsible for longitudinal growth. In newborns, almost all epiphyses are exclusively cartilaginous and accordingly, are not seen on radiographs [4,5]. Secondary centers of ossification often develop within the cartilaginous epiphysis, permitting the epiphysis to expand globally (i.e. all directions) by enchondral ossification.

However, the number and location vary with each bone. In most long bones, the epiphysis at each end contains a SCO but in some, such as the phalanges and clavicles, the SCO only forms at one end [6,7]. Sometimes, multiple epiphyseal ossification centers form, such as in the humerus, which contains two proximal and four distal SCO. In particular bones, one single cartilaginous epiphysis divides into two SCO, such as with the proximal tibial epiphysis and tubercle apophysis [8].

The Apophysis: The apophysis is essential to bone motion and stability as it is the attachment site for musculotendinous structures. Unlike the epiphysis, it does not usually articulate with adjacent bones and its physis lies parallel or oblique to the axis of the long bone, so it does not contribute to longitudinal growth. However, in flat bones, the apophyses participate in circumferential growth and in vertebrae, elongate the processes. The ends of particular bones function like an articular cartilage as it is the attachment site for musculotendinous structures. Unlike the epiphysis, it does not participate in circumferential growth and in vertebrae, elongate the processes. The ends of particular bones function like an articular cartilage that is responsible for feeding osteoprogenitor cells and thus, the metaphyseal branches are crucial to osteogenic and chondrocytic cell differentiation. Periosteal blood also flows through branches in the zone of Ranvier to support chondroblast differentiation. This specialized zone contributes to circumferential growth of the primary physis [1].

Growth: In long bones, growth occurs via enchondral ossification at the physis [5,13]. The primary physis is responsible for the majority of growth, contributing to 95% of the bone's length, while the secondary physis contributes the remaining 5% [14]. Most activity is concentrated in the proliferative, columnar, and hypertrophic zones, where physeal chondrocytes steadily increase in volume [15]. Long bone length is positively related to final chondrocyte volume and therefore, the rate of bone growth is affected by changes in chondrocytic activity [13]. A similar process of chondrocyte enlargement occurs in the epiphysis, where a much smaller physis surrounds the SCO [16]. However, unlike cartilage in the primary physis, the epiphysis develops a superficial layer of cartilage that is incapable of ossification. This layer forms articular cartilage, a structure essential to normal joint movement.

The Metaphysis: The metaphysis is the flared end of the shaft that connects the diaphysis to the physis. Its spongy, trabecular center is encased in a thin layer of cortical bone.

The Physis: Often referred to as simply the physis, the primary physis rests between the epiphysis and metaphysis. There also exist epiphyseal and apophyseal phases. These phases share similar structures and function with its primary counterpart [2].

Blood supply: The primary physis is an avascular structure and is supported by branches from three blood supplies: epiphyseal arteries, metaphyseal arteries, and periosteal arteries from the zone of Ranvier [11]. Branches from epiphyseal vessels are essential for the longitudinal growth of long bones as these vessels primarily nourish the germinial, proliferating and columnar cell zones. Originating from the epiphyseal arteries in the SCO, epiphyseal vessels traverse through cartilaginous canals in the resting zone to terminate in the proliferative zone [12]. In the unossified epiphysis, these canals are oriented in a parallel, longitudinal pattern but after the SCO develops, the canals assume a radial pattern.

Branches from metaphyseal arteries have a less direct influence on bone growth. These branches derive from periosteal vessels that penetrate the metaphysis peripherally and combine with intermedullary blood. These vascular channels then traverse through the gaps left by dying cartilage cells in the zone of provisional calcification. The branches are responsible for feeding osteoprogenitor cells and thus, the metaphyseal branches are crucial to osteogenic and chondrocytic cell differentiation. Periosteal blood also flows through branches in the zone of Ranvier to support chondroblast differentiation. This specialized zone contributes to circumferential growth of the primary physis [1].
and distribution of epiphyseal stippling is crucial in evaluating the differential diagnoses and prognosis (Table 1).

**Table 1:** The differential diagnosis of stippled secondary centers of ossification includes the following conditions, each possessing their own unique radiographic findings [39].

| Condition                                           | Radiographic findings                                                                 |
|-----------------------------------------------------|---------------------------------------------------------------------------------------|
| Chondrodysplasia punctata, rhizomelic type          | Punctate calcifications in the proximal humerus and femur                           |
|                                                     | Symmetrical distribution                                                             |
|                                                     | Absent stippling in the axial skeleton                                               |
|                                                     | Severe epiphyseal changes after stippling resolution                                 |
| Chondrodysplasia punctata, Conradi-Hünermann        | Punctate calcifications at the ends of the long bones, processes of vertebrae, carpal and tarsal bones, and ischiopubic bones |
|                                                     | Asymmetrical distribution                                                            |
|                                                     | Less severe epiphyseal changes after stippling resolution                            |
| Warfarin embryopathy                                | Stippled calcifications in the appendicular and axial skeleton                       |
| Zellweger syndrome                                  | Stippled calcifications of the hips and patellas                                      |

Radiographic findings of stippled secondary centers of ossification.

**Table 2:** The differential diagnosis of hypoplastic, dysplastic, and dysgenetic secondary centers of ossification include the following conditions, each possessing their own unique radiographic findings [40].

| Condition                                           | Radiographic findings                                                                 |
|-----------------------------------------------------|---------------------------------------------------------------------------------------|
| Nail-patella syndrome                               | Hypoplasia of capitellum and radial head                                             |
|                                                     | Hypoplasia of the lateral aspect of distal humerus                                    |
|                                                     | Increased carrying angle of elbow                                                     |
|                                                     | Hypoplastic absent patellas                                                           |
|                                                     | Hypoplasia of the lateral portions of the distal femoral epiphyses                    |
| Spondyloepiphyseal dysplasia congenital             | In infancy, delayed bone age with absent ossification of the knee epiphyses and pubic bones |
|                                                     | In childhood, severely delayed ossification of femoral heads                           |
|                                                     | Varying degrees of epiphyseal and metaphyseal abnormalities                           |
| Multiple epiphyseal dysplasia                       | Irregular epiphyses (flat in Ribbing type, small in Fairbank type)                    |
|                                                     | Mild shortening of tubular bones                                                     |
|                                                     | Normal metaphyses                                                                     |
|                                                     | Early, progressive osteoarthritis                                                     |
| Kniest dysplasia                                    | Irregular, late-appearing proximal femoral epiphyses                                  |
|                                                     | In childhood, large and deformed epiphyses                                            |
|                                                     | Short and broad femoral necks                                                        |
|                                                     | Broad metaphyses                                                                     |
|                                                     | Short tubular bones                                                                  |
| Stickler syndrome                                   | Deficient ossification of the lateral portions of proximal tibial epiphysis and metaphysis |
|                                                     | Downward slanting of the lateral end of proximal tibias                               |
|                                                     | Knock-knee deformity                                                                 |
| Chondroectodermal dysplasia                         | Coarse trabecular pattern ('flocky' ossification) of the bone structure of metaphyses and epiphyses |
|                                                     | Severe epiphyseal deformation                                                        |
| Parastreptomatic dwarfism                           | Late-appearing, small, irregular femoral heads                                       |
|                                                     | Mild irregularities of proximal femoral metaphyses                                    |
|                                                     | Spontaneous resolution of the abnormalities, with formation of normal femoral heads   |
| Meyer dysplasia                                      | Deficient ossification of the lateral portions of proximal tibial epiphysis and metaphysis |
|                                                     | Downward slanting of the lateral end of proximal tibias                               |
|                                                     | Knock-knee deformity                                                                 |

Radiographic findings of hypoplastic, dysplastic and dysgenetic secondary centers of ossification.

**Hypoplastic, Dysplastic, Dysgenetic Centers of Ossification:** An abnormal appearing epiphysis may be described as hypoplastic, dysplastic, and/or dysgenetic. Hypoplastic epiphyses are undersized or form later than normal. Dysplastic epiphyses appear irregular, and dysgenetic epiphyses result from defective development. The occurrence of such epiphyseal abnormalities may be explained by a number of causes (Table 2). Since epiphyseal ossification corresponds with skeletal
growth, epiphyseal hypoplasia may be a normal physiologic indicator of delayed bone maturation. Asymmetrically sized epiphyses may also be normal in the growing child. However, in the context of an isolated hypoplastic epiphysis, the differential diagnosis includes trauma and infection [22]. Several systemic disorders may result in generalized epiphyseal hypoplasia, dysplasia and dysgenesis. Often, the primary defect is abnormal development of physeal cartilage and SCO. In some children, the number or arrangement of chondrocytes may be affected. In others, there may be excessive matrix formation or areas of matrix degeneration. These abnormalities result in delayed epiphyseal ossification and epiphyses that may appear flattened and fragmented [23].

**Hyperplastic center of ossification:** Children may present with large epiphyses, either localized to specific sites or generalized throughout the skeleton. In dysplasia epiphysealis hemimelica, or Trevor disease, affected epiphyses are enlarged due to cartilaginous overgrowth. It typically affects males, between the ages of 2-14 years old [24]. On radiographs, multiple foci of ossification may be visualized medial or lateral to the affected epiphysis. As its name suggests, there is hemimelic distribution of the abnormal growth with respect to the epiphysis, typically on the medial side. With time, an irregular epiphyseal bone mass forms, which leads to limb malalignment and precocious osteoarthritis. In infantile multisystem inflammatory disease, there is generalized distribution of enlarged epiphyses [25]. Affected children develop periostitis and osteoporosis. Given the significant long-term sequelae, it is essential to diagnose presentations of enlarged epiphyses (Table 3).

Table 3: The differential diagnosis of hyperplastic secondary centers of ossification includes the following conditions, each possessing their own unique radiographic findings [41].

| Condition                                             | Radiographic findings                                                                 |
|-------------------------------------------------------|---------------------------------------------------------------------------------------|
| Dysplasia epiphysealis hemimelica                      | Multiple small foci of ossification adjacent to the medial or lateral aspect of the affected epiphysis. Coalescence with the epiphysis to form an irregular, lobulated bone mass. Limb misalignment. Precocious osteoarthritis. |
| Infantile multisystem inflammatory disease             | Epiphyseal enlargement, irregularities, and fragmentation. Metaphyseal widening. Periostitis. Osteoporosis. |
| spondylo-megaepiphyseal - metaphyseal dysplasia        | Large epiphyses. Metaphyseal irregularities. Defective vertebral body ossification.    |

**Aseptic Necrosis of the Secondary Center of Ossification:**

The epiphysis and its ossification center is sustained by a limited blood supply. This area is thus particularly vulnerable to ischemic necrosis when its vasculature is compromised. Most children present with isolated, unilateral involvement, although they may also be affected bilaterally or at multiple sites. The differential diagnoses may be divided into primary and secondary etiologies. An example of primary osteonecrosis is Legg-Calvé-Perthes disease, which affects the proximal femoral epiphysis in children. Secondary processes, such as Kienböck disease of the lunate, are precipitated by traumatic events [26]. Family history is relevant when assessing a child with osteonecrosis as some disorders suggest autosomal dominant inheritance, despite trauma often being a causative factor [27,28].

Radiographically, the process of epiphyseal ischemic necrosis is similar among the different disorders, regardless of their pathogenesis and anatomic site. During the initial phase of cellular death, no radiographic changes are seen. Then, a radiolucent area surrounds the focus of necrosis and represents osteoporotic bone undergoing osteoclastic resorption. The necrotic area becomes radiodense as it develops a reactive interface with surrounding tissue. As the reactive interface remodels, the radiodense focus is bounded by a radiolucent edge, representing osteoclastic resorption of the interface. Meanwhile, the area surrounding the necrotic focus and reactive interface undergoes osteoblastic bone formation and appears relatively dense. Finally, the epiphysis becomes fragmented and the articular surface appears flattened as it collapses [29].

**Precocious ossification and multiple ossification centers:**

Advanced bone maturation is a characteristic finding in several osteochondral dysplasias. Patients with Larsen syndrome, a primarily autosomal dominant disorder, experience ligamentous hyperlaxity and multiple joint dislocations. On ultrasonography, a capital femoral ossific nucleus may be found in children with
Larsen syndrome as early as six days old, whereas unaffected children usually develop this site after three months old. On radiographs, advanced bone age and unique accessory SCO, such as in the calcaneus, are visible [30]. Children with Desbegous dysplasia, an autosomal recessive disorder, also demonstrate precocious ossification, possibly years in advance of their peers. Unique SCO are often seen in radiographs of the metacarpals and phalanges. In summary, the presence of precocious ossification and accessory SCO may be suggestive of osteochondral dysplasias [31-33].

**Rickets and Osteomalacia**

There are more than 50 diagnoses in which either rickets or osteomalacia are prominent features [34]. However, there are significantly less diseases in which both are simultaneously present (Table 4). Rickets describes deficient mineralization of the physis, specifically at the zone of provisional calcification. Osteomalacia refers to inadequate calcium hydroxyapatite deposition on bone matrix [35]. Before complete ossification of the physis, both rickets and osteomalacia may coexist. Characteristic radiographic findings are seen in children with rickets, particularly in the physes of the tibia, distal femur, proximal humerus, distal radius, and distal ulna. There may be metaphyseal cupping and fraying, as well as bone rarefaction. The physis appears widened, irregular, and hypodense. In the context of osteomalacia, the appearance of rachitic growth plates may aid in narrowing the differential diagnoses.

**Table 4:** The differential diagnosis of rickets and osteomalacia include the following conditions, each possessing their own unique radiographic findings [42].

| Condition                | Radiographic findings                                      |
|--------------------------|------------------------------------------------------------|
| Rickets                  | Widened, cupped, frayed metaphyses                         |
|                          | Undermineralized metaphyses                                |
|                          | Small, underossified epiphyses                             |
| Hypophosphatasia tarda   | Rickets-like metaphyseal changes                           |
|                          | Large unossified metaphyseal defects                       |
|                          | Fragile, bowed long bones                                  |
| Vitamin A intoxication   | Cupped, splayed distal femoral metaphyses                  |
|                          | Cortial hyperostosis                                       |
| Achondroplasia           | Infancy: flaring and medial slanting of distal femoral metaphysis |
|                          | Childhood: inverted-V metaphyseal appearance, medial metaphyseal abnormalities |
| Pseudoachondroplasia     | Irregular, widened, cupped metaphyses                      |
|                          | Small, dysplastic epiphyses                                |
| Metaphyseal acroscyphodyplasia | Cupped metaphyses at the knee                       |
|                          | Cone-shaped epiphyses                                      |
|                          | Deformed femoral condyles                                  |

**Neoplastic and tumor-like lesions**

**Chondroblastomas:** Chondroblastomas are rare, benign tumors that predominantly affect the epiphysis or apophysis of long bones. These tumors comprise of less than 1% of primary bone tumors and 9% of benign bone tumors. Such growths are thought to develop from chondroblasts in the epiphyseal SCO, most commonly affecting the femur, humerus, and tibia. On radiographs, chondroblastomas appear as well-defined lucent lesions with central calcifications. Margins are smooth or lobulated, and the lesion is surrounded by a thin sclerotic rim (Figures 1-6). A third of patients demonstrate joint effusion [36]. Atypical features include extension of the tumor into the metaphysis or soft tissues [37-46]. When radiographs lack typical findings and appear nonspecific, chondroblastomas may be confused with other epiphyseal lesions (Table 5).
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Table 5: The differential diagnosis of tumor-like epiphyseal lesions include the following conditions, each possessing their own unique radiographic findings.

| Condition                              | Radiographic findings                                      |
|----------------------------------------|----------------------------------------------------------|
| Clear cell chondrosarcoma [37]         | Sclerotic rim surrounding slow-growing epiphyseal lesion  |
| Dysplasia epiphysealis hemimelica [43] | Involves one side of epiphysis, particularly at the distal tibia and distal femur |
|                                        | MRI most helpful due to cartilaginous nature              |
| Pseudocyst [44]                        | Radiolucent lesion, often in proximal humerus and calcaneus |
|                                        | Represents increased cancellous bone formation            |
| Bone abscess [45]                      | Thick sclerotic rim, no central calcifications            |
|                                        | Serpentine, radiolucent tract extending to physis         |
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