

CHAPTER 1

Anatomic Aspects of Bone Ossification and their Magnetic Resonance Counterparts

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1.1 Endochondral ossification

Endochondral ossification is the process by which a bone develops from a pre-existing model composed of hyaline cartilage. It begins around the sixth week of fetal development and continues into the individual's twenties. Most bones of the body, including the vertebrae, ribs, sternum, scapula, pelvis, and bones of the limbs, develop in this way [1,2].

Ossification proceeds in the following fashion: the center of the cartilage model is invaded by mesenchymal stem cells which form the primary center of ossification. Later, at each end of the cartilage model, secondary centers of ossification appear (Figure 1.1). These centers of ossification gradually encroach on the remaining cartilage, ultimately replacing it completely (except at the articular surfaces) by the time skeletal maturity is reached [1,3,4]. The cartilage model is important as the source of longitudinal bone growth. The ossification of the cartilage model is a well-organized process which could be subdivided into several phases [1,3,4].

1.1.1 Primary center of ossification (fetal life)

Chondrocytes at the center of the cartilaginous model (the diaphysis) begin to increase in number and size. The chondrocytes' hypertrophy is followed by their apoptosis, matrix calcification, and vascular invasion. The blood vessels bring with them mesenchymal stem cells that will give rise both to osteoblasts and osteoclasts. The invading cells stimulate the removal of the calcified cartilage and its replacement by trabecular bone and bone marrow.

1.1.2 Growth plate

As the bone marrow cavity expands toward the epiphyses, the chondrocytes at the epiphyseal margin proliferate

rapidly, forming longitudinal columns of flattened cells. Thus, the primary growth plate is interposed between the cartilaginous epiphysis and the newly generated bone (bone marrow cavity). The growth plate is composed of zones of resting, proliferative, maturing, and hypertrophic chondrocytes, and of calcification.

Zone of resting cartilage. This region, farthest from the marrow cavity, consists of typical hyaline cartilage that as yet shows no sign of transforming into bone.

Zone of cell proliferation. A little closer to the marrow cavity, chondrocytes multiply and arrange themselves into longitudinal columns of flattened lacunae.

Zone of cell hypertrophy. Next, the chondrocytes cease to divide and begin to hypertrophy.

Zone of calcification and bone deposition. Minerals are deposited in the matrix between the columns of lacunae and calcify the cartilage. Apoptosis of hypertrophic chondrocytes occurs. Each column is converted into a longitudinal channel, which is immediately invaded by blood vessels and marrow from the marrow cavity. Osteoblasts line up along the walls of these channels and begin depositing concentric lamellae of matrix, while osteoclasts dissolve the temporarily calcified cartilage.

Within the growth plate, chondrocyte proliferation (zone of cell proliferation) is balanced by chondrocyte apoptosis and the replacement of the calcified cartilage with bone (zone of bone deposition). In this way, the width of the growth plate during development is maintained while the bone increases in length [1,3,4].

1.1.3 Secondary centers of ossification (later in development)

Roughly spherical secondary centers of ossification form within the cartilaginous epiphyses. The secondary ossification center becomes hollowed out by the same process

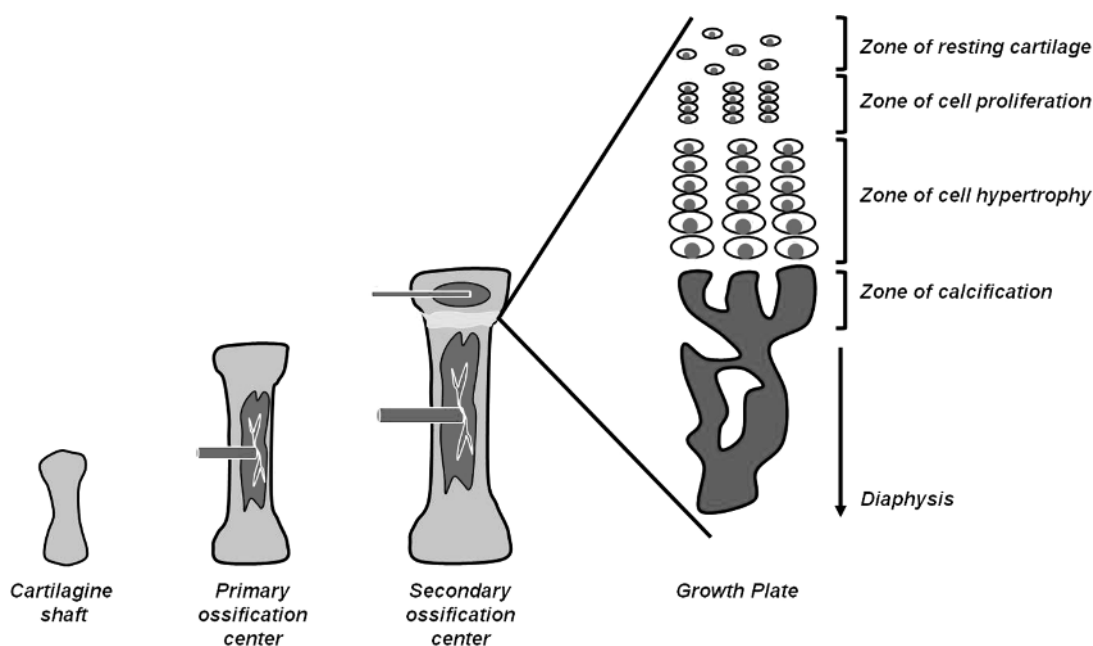


Figure 1.1 Endochondral ossification is the process. To see a color version of this figure, please see Plate 1.1.

as occurs in the diaphysis, generating a secondary marrow cavity in the epiphysis. This cavity expands outward from the center, in all directions. In bones with two secondary ossification centers, one center lags behind the other in development, so at birth there is a secondary marrow cavity at one end while chondrocyte growth has just begun at the other [1].

The appearance and development of secondary centers of ossification is a well-organized process. It has been shown that this process is driven by vascular endothelial growth factors (VEGFs). Immediately prior to the vascular invasion of the epiphysis, a positive reaction to VEGF is localized in chondrocytes of the epiphyseal cartilage close to the capsule insertion. During the development and expansion of the secondary ossification center, VEGF expression is higher in chondrocytes but decreases when the epiphysis is diffusely ossified. VEGF is also expressed by mesenchymal cells present in and around the fibrous tissue where the secondary ossification center will develop [2,5].

Vascular corrosion casts confirm that vessels that penetrate into the epiphysis arise primarily from the periosteal and capsular networks, and vascular connections with the diaphyseal circulation are not evident. Hence the epiphyseal microcirculation is distinct from that of the diaphysis, and arises from the vessels present in the capsule and the periosteal networks. In young animals the only capillaries are bone marrow sinusoids and a few subchondral capillaries. In adult animals small vessels run between the clusters of sinusoids forming the trabecular circulation. Capillary sprouts from sinusoids are observed both in young and adult animals. Thus, in adults, different proper microcirculatory districts can be distinguished in the epiphysis: (i) the sinusoidal network, which supplies the hematopoiesis of the bone marrow

and the adjacent osteogenic tissue, and (ii) the bone tissue microcirculation, limited to small vessels that supply the metabolism and the remodeling of bone tissue [2,5,6].

These observations demonstrate that VEGF production by chondrocytes begins a few days after birth, supports the rapid vascular growth from the surrounding soft tissues, and is chronologically related to the development of the secondary ossification centers [2,5,6].

The microvascular organization and its adaptation to epiphyseal growth represents the morphologic basis for understanding the interaction between the different tissues in developing and adult epiphyses, with most of the basic research performed on the rat model [2,5,6].

1.2 Longitudinal bone growth

Longitudinal bone growth continues until puberty when chondrocyte proliferation ceases and the primary and secondary centers of ossification fuse. A thin layer of cartilage covering the joint surface remains throughout adulthood, protecting the underlying bone and providing a smooth surface for articulation [1,3,4].

The region of transition from cartilage to bone at each end of the primary marrow cavity is called the metaphysis. By the late teens to early twenties, all remaining cartilage in the epiphyseal plate is generally consumed and the gap between the epiphysis and diaphysis closes. The primary and secondary marrow cavities then unite into a single cavity, and the bone can no longer grow in length [1,3,4].

The junctional region where they meet is filled with spongy bone, and the site of the original epiphyseal plate is marked with a line of slightly denser spongy bone called the epiphyseal line.

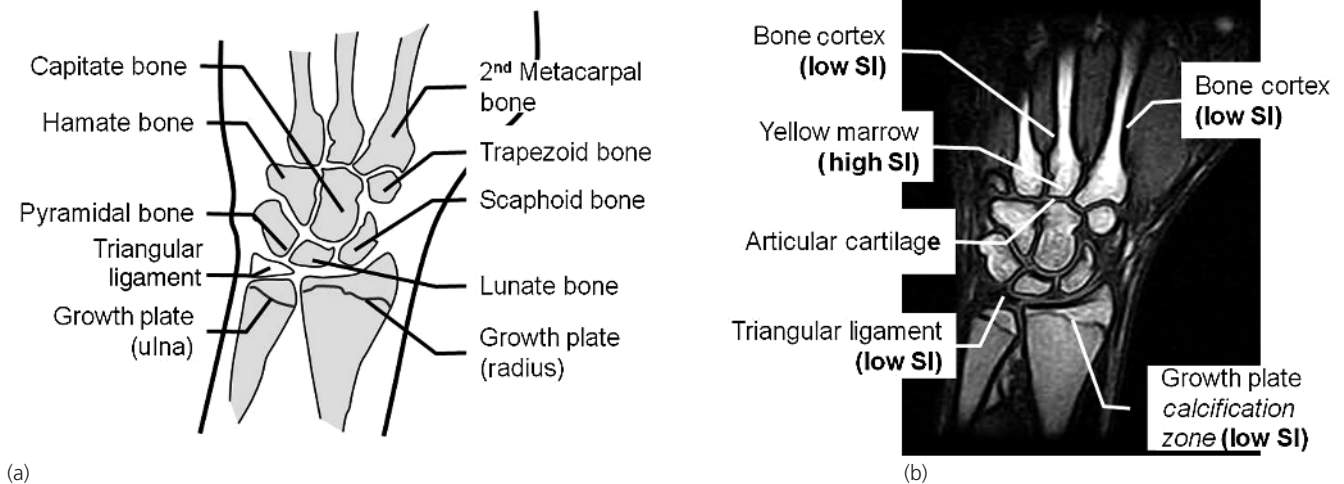


Figure 1.2 Anatomy of the wrist and its magnetic resonance (MR) counterpart: (a) anatomic drawing of wrist and hand bones; (b) magnetic resonance image (MRI) of the wrist in a 17-year-old male. The MR aspect of bone cortex, ossification center, articular cartilage, and growth plate are visible. Bone cortex is characterized by a low signal intensity (SI); the ossification center has a high SI due to its content in adipose (yellow) bone marrow and possesses an outer bony shell (low intensity). The articular cartilage is characterized by a homogeneous intermediate SI. The growth plate of the distal radius is well shown. The zone of calcification is recognizable by its low SI. This zone contains matrix that is highly mineralized. In the growing healthy child, the zone of calcification should be continuous and uniform. In infants and young children, the growth plate is a flat disk. Normal growth proceeds unevenly; thus, the growth plate becomes undulating as evident in this image. The triangular ligament is indicated.

When the epiphyseal plate is depleted, the epiphysis has “closed” because no gap between the epiphysis and diaphysis is visible on X-ray. The epiphyseal plates close at different ages in different bones and in different regions of the same bone. The state of closure in various bones is often used in forensic science to estimate the age at death of a subadult skeleton [1,3,4].

1.3 Magnetic resonance aspects of endochondral ossification

Magnetic resonance (MR) imaging can study in detail the dynamic process of skeletal growth and maturation [7]. The bone cortex is of very low signal intensity (SI) on images obtained with all sequences (Figures 1.2 and 1.3). The periosteum can be observed as a thin, low-SI, linear structure that parallels the bone cortex; this appearance is due to its composition of collagen fibers, fibroblasts, and osteoprogenitor cells. The articular cartilage is a highly organized form of hyaline cartilage and can be observed on water-sensitive images as a thin hyperintense rim surrounding the less well-organized hyaline cartilage of the developing epiphysis (Figures 1.2 and 1.3). Moreover, it can show details on: (i) bone marrow conversion, (ii) epiphyseal cartilage, and (iii) growth plate [7].

1.3.1 Bone marrow

Conversion from hematopoietic to fatty marrow is a well-recognized process that occurs throughout childhood in a predictable and reproducible pattern. In later pregnancy and during the first weeks of life, a larger marrow space becomes evident and the SI of the shafts of the bone

reflects the marrow composition [7,8]. In the neonate, the marrow is entirely hematopoietic. Hematopoietic (red) bone marrow is mostly composed of red blood cells; however, it contains a substantial amount of fat (almost 40%) [9]. In contrast, fatty (yellow) marrow is composed of 80% fat. Owing to the exquisite sensitivity to fat of MR imaging, marrow SI reflects the fat content both in the yellow marrow and in the red marrow [7,9]. Accordingly, on T1-weighted images, the SI of normal hematopoietic marrow is low (similar to or higher than that of muscle) while high SI is present when it is converted to fatty marrow. The higher water content of hematopoietic marrow results in a higher SI on images obtained with a water-sensitive MR sequence. The conversion from red to yellow bone marrow (Figure 1.2) begins during the first year of life and is almost complete by the time of skeletal maturity in the appendicular skeleton; in contrast, this process proceeds in the axial skeleton throughout life. Marrow conversion occurs in a predictable pattern [7,9]. Within the body, the transformation occurs from the periphery (phalanges of the fingers and toes) to the center (humeri and femora). In each bone, epiphyseal conversion to fatty marrow occurs first [10] and the transformation continues in the diaphysis and proceeds as a front toward the metaphyses [9]. More detailed description of changes in the bone marrow are described in Chapter 7.

1.3.2 Epiphyseal cartilage

In the infant, epiphyseal cartilage is of homogeneous intermediate SI on T1-weighted images and is of relatively low SI on water-sensitive images (Figures 1.2 and 1.3).

Ossification usually begins in the center of the cartilaginous epiphysis, either as a single center or as multiple

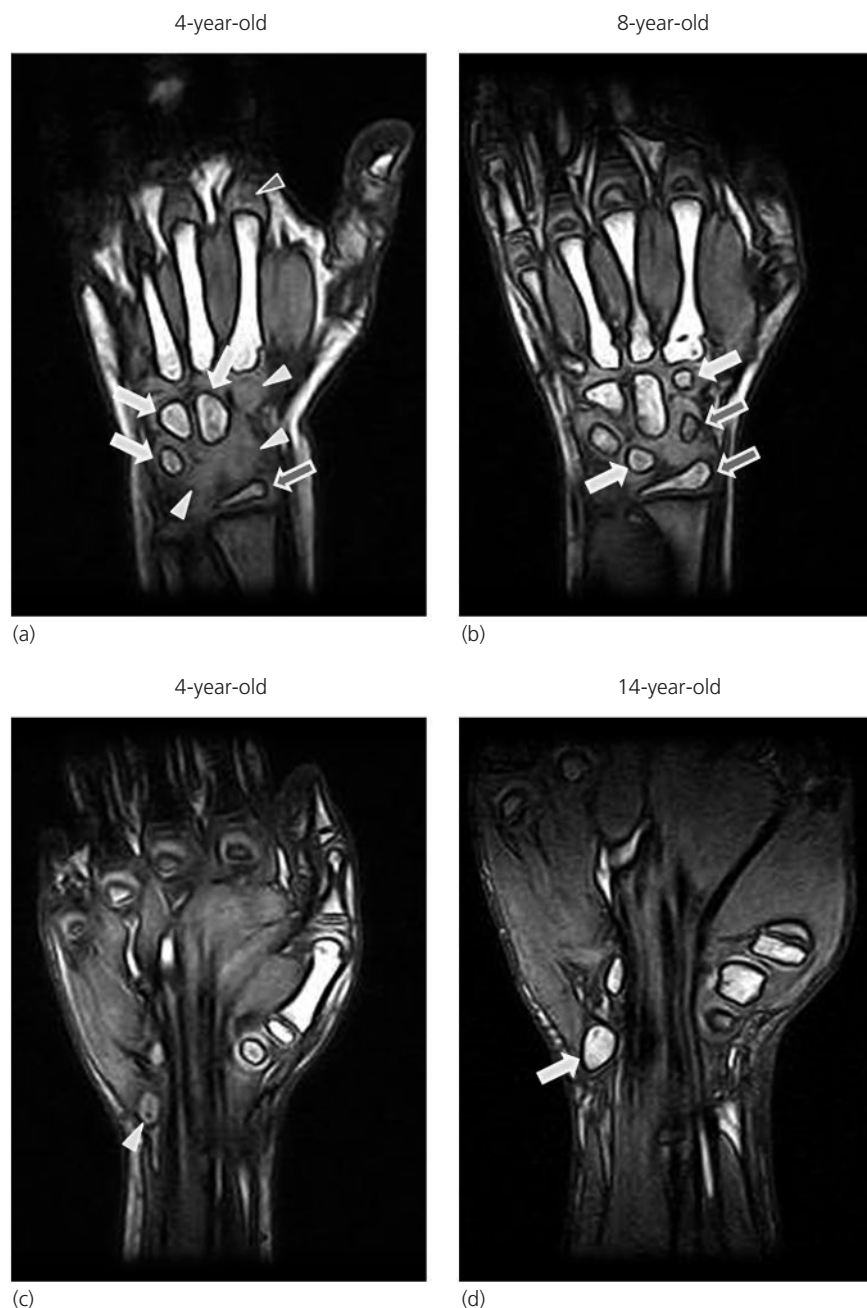


Figure 1.3 Carpal bones develop in a pattern similar to that of the epiphyses of long bones. For this reason, these epiphyseal equivalents show early marrow conversion, develop from spherical or hemispherical physes, and can show irregular ossification. The ossification of carpal bones occurs in a predictable pattern and has been used to estimate the age and potential to grow. (a) In a 4-year-old male, the ossification centers of hamate, capitate, and pyramidal bone are present (arrows). The cartilaginous shaft of lunate, trapezoid, and scaphoid bone are recognizable (arrowheads). The epiphyseal cartilage of metacarpal bones (arrowhead) demonstrates homogeneous intermediate signal intensity (SI). The secondary center of ossification is present in the distal epiphysis of the radius (arrow) and it is characterized by an outer bony rim. (b) In an 8-year-old male, the ossification centers of lunate, trapezoid, and scaphoid bone are present (arrows). Notably, the SI of scaphoid bone is low (arrow) if compared with other bones; the lower SI could be due to early and only partial conversion of hematopoietic bone marrow to adipose bone marrow because the ossification center of the scaphoid bone appears later (approximately at age 6) in comparison with the other carpal bones. (c, d) The appearance of the vacuolization and ossification center of the pisiform bone is the last to occur and appears around the age of 10–11 years in males (arrowhead, cartilaginous shaft; arrow, ossification center). To see a color version of this figure, please see Plate 1.2.

small areas that subsequently coalesce [11]. Initially, the newly formed ossification center contains hematopoietic marrow [4] and therefore the SI is low. The ossified epiphysis then undergoes rapid marrow transformation and within months shows uniform fatty SI [7].

The enlargement of secondary centers of ossification is similar in architecture to the primary physis and, accordingly, an outer bony rim may be observed and is analogous to the metaphysis of the shaft (Figures 1.2 and 1.3).

1.3.3 Growth plate

The growth plate, or physis, has at least two distinct regions on routine clinical MR images (Figure 1.2). There is a cartilaginous zone that is of intermediate to high SI on water-sensitive images. This region is relatively unap-

parent on T1-weighted images because it fuses with the adjacent similar SI of the unossified epiphysis. This region corresponds to and likely includes the zones of resting cartilage, cell proliferation, and cell hypertrophy [12]. A second region characterized by low SI on all sequences includes the zone of calcification. This zone contains matrix that is highly mineralized. In the growing healthy child, the zone of calcification should be continuous and uniform [7,12].

In infants and young children, the growth plate is a flat disk. Normal growth proceeds unevenly; thus, the growth plate becomes undulating. The thickness of the growth plate remains uniform during normal growth. The thickness of the growth plate reflects the rate of growth. As maturation approaches, the growth plate thins and ulti-

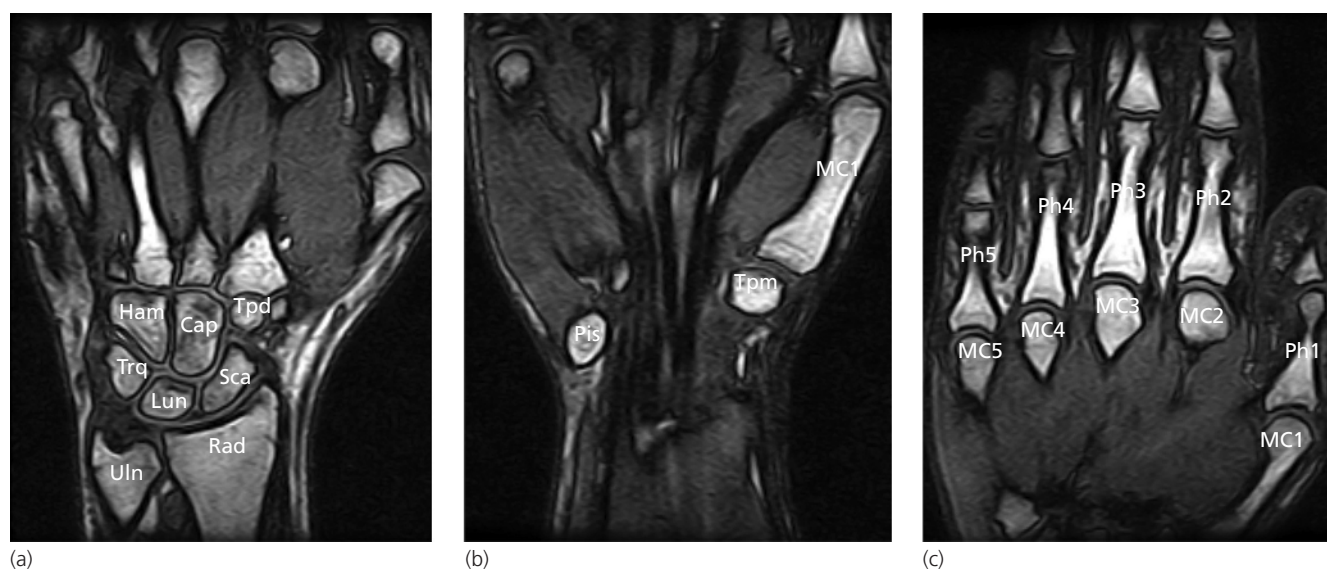


Figure 1.4 (a, b) An MRI of a normal mature wrist showing all the bones. This should be used as a reference figure for subsequent figures showing the developing wrist in children. (c) MRI of the hand showing phalanges (Ph) and metacarpal (MC) bones. Cap, capitate; Ham, hamate; Lun, lunate; MC1, first metacarpal bone; Pis, pisiform; Sca, scaphoid; Tpd, trapezoid; Tpm, trapezium; Trq, triquetrum.

mately disappears with physiologic closure, leaving a physeal scar. This scar, possibly representing the zone of calcification, eventually regresses.

1.4 Wrist and carpal bones

Carpal bones and apophyses develop in a pattern similar to that of the epiphyses of long bones [13]. For this reason, these epiphyseal equivalents show early marrow conversion, develop from spherical or hemispheric physes, and can show irregular ossification.

Due to the excellent tissue contrast resolution of MRI, it is possible to visualize the following:

- Cartilage shaft;
- Ossification center with red marrow;
- Yellow marrow conversion; and
- Ossification process with the outer bony rim.

The ossification of carpal bones occurs in a predictable pattern (Table 1.1). Capitate and uncinate bones are the first to show ossification centers (second to fourth month) while the pisiform is the last (ninth to twelfth year).

Standard radiograph analyses of the left wrist have been used for decades to estimate the age and potential to grow following the published standards established by Greulich and Pyle, Tanner, and the FELS method [14,15]. MR offers an alternative as a noninvasive nonionizing radiation method of examination, eliminating the risks associated with standard radiography. More detailed description and illustration of the maturation process of the bones of the wrist and hand are described in Chapters 4 and 5. Complete fusion occurs at the age of 17–18 years [14,15].

In summary, the various histologic features of maturation of the skeleton occur in a predictable fashion and

Table 1.1 Mean age of ossification center appearance in carpal bones

Bone	Female	Male
Hamate	2 months	4 months
Capitate	2 months	4 months
Pyramidal	2 years	3 years
Lunate	3 years	4 years
Trapezium	3 years	4 years
Trapezoid	4 years	6 years
Scaphoid	4 years	6 years
Pisiform	9 years	12 years

timeline in the normal individual. Because of the high tissue contrast available with MR imaging, these features can be shown in detail using this modality. These processes are illustrated in Chapters 4 and 5. The deviation from normal, due to a variety of underlying conditions, are the subject of many of the other chapters in this book (Figure 1.4).

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