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**Early fetal development of the rotator interval region of the shoulder with special reference to topographical relationships among related tendons and ligaments**

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Running title: Fetal rotator interval

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**Abstract**

*Purpose* There is little information on the early fetal development of the rotator interval region of the shoulder, particularly with regard to whether topographical relationships among the ligaments and tendons change during development.

*Methods* We examined the histological sections (transverse or frontal) of right or left shoulder in 20 mid-term human fetuses (7-15 weeks of gestation).

*Results* The biceps tendon had an accompanying bursa-like cavity before the joint cavitation. The bursa for the tendon remained open to the joint cavity until 12 weeks. When reaching the glenoid, the biceps tendon involved and carried mesenchymal tissue around the coracoid process (the future coracohumeral ligament) toward the infraspinatus tendon. Until 10 weeks, the primitive glenohumeral ligament was established as simple collateral ligaments on the inner or humeral side of the rotator cuff tendons and the biceps long tendon. However, the subscapularis tendon crossed, attached to, and reformed the upper structure of the superior glenohumeral ligament.

*Conclusions* The early development of the coracohumeral ligament suggests that it is a primitive and basic structure. However, we hypothesize that mechanical demands from the subscapularis tendon and biceps long tendon are likely to

change the primitive form of the rotator interval to the adult morphology, including the superior glenohumeral ligament. The significant modification evident during early fetal development suggests that anatomical reconstruction after rotator cuff tears should not be based on the “ideal” anatomy, especially that of the superior glenohumeral ligament, but on individual requirements.

Level of Evidence: III or IV (this is my opinion, please choose only 1)

Key words: shoulder joint, rotator interval, biceps long tendon, subscapularis tendon, superior glenohumeral ligament, human fetus

## **Introduction**

The rotator interval is defined as a triangular structure, in which the coracoid process form the base, the anterior margin of the supraspinatus forms the upper border, and the superior margin of the subscapularis muscle-tendon unit forms the lower border<sup>1</sup>. The rotator interval is not a weak capsular region but a complex network of macroscopically recognizable tendinous and ligamentous structures<sup>2</sup>. Arai

et al. (2009)<sup>3</sup> recently detailed the morphology of the supportive structures for the biceps long tendon, such as the superior glenohumeral ligament. However, there is little or no information on the fetal topographical anatomy of the rotator interval region of the shoulder because the majority of previous studies have focused on histogenetic aspects, such as collagen fiber maturation, rather than anatomy<sup>4-7</sup>. Does the subscapularis tendon or the biceps tendon modify the primitive morphology of the interval during the early development?

However, at the start of our study, there has been a lack of information on simple issues such as whether or not biceps long tendon develops before the joint cavitation. In a study of a fetus with a crown-rump length (CRL) of 30 mm (at and around 8 weeks of gestation), Aboul-Mahasen and Sadek (2002)<sup>4</sup> described that the biceps long tendon was separated from the humeral head by a small cavity. Giuliani Piccari Scarpa et al. (1977)<sup>8</sup> demonstrated a bursa-like structure, but the fetuses they examined were at a stage later than that of the joint cavitation (CRL 50 mm; at and around 9 weeks).

Therefore, using specimens forming part of the collection of the Universidad Complutense, Madrid, the present study was conducted to clarify developmental changes in the topographical relationships among the tendons and

ligaments in and around the rotator interval region. Using low-magnification photographs, we tried to demonstrate the process of development of these structures.

### **Materials and Methods**

The study was performed in accordance with the provisions of the Declaration of Helsinki 1995 (as revised in Edinburgh 2000). We examined the paraffin-embedded histology of 20 mid-term fetuses (unilaterally obtained from each of 20 fetuses; 12 left and 8 right shoulders) at 7-15 weeks of gestation (five fetuses each at 7 week, 8 or 9 week, 12 week and 15 week). The fetuses of “8 or 9 week” were difficult to discriminate in the present morphology. The paraffin blocks employed contained all parts of the shoulder and thoracic wall. All specimens were part of the large collection kept at the Embryology Institute, Universidad Complutense, Madrid, and were products of miscarriages and ectopic pregnancies managed at the Department of Obstetrics at the university. Approval of the study was granted by the university ethics committee.

After routine procedures for paraffin-embedded histology, sections

were cut horizontally or frontally with a thickness of 5  $\mu\text{m}$ , at intervals of 20  $\mu\text{m}$ . There were around 100 sections for each shoulder. Most sections were stained with hematoxylin and eosin (HE), while some were subjected to immunohistochemical staining for vimentin (one of the intermediate filament components) because it is likely to be expressed at sites subjected to high mechanical stress<sup>9</sup>. The primary antibody used was rabbit polyclonal anti-human S100 protein (Dako Cytomation, Kyoto, Japan). The secondary antibody was labeled with horseradish peroxidase (HRP), and antigen-antibody reactions were detected using the HRP-catalyzed reaction with diaminobenzidine (with hematoxylin counterstaining). Although we observed the left or right shoulder in each of 20 fetuses (see above), all figures are prepared according to the same orientation, i.e., the coracoid process is located in the left-hand side of the figure.

## Results

The muscle anlage around the shoulder was identifiable at 7 weeks of gestation. At this stage, when the shoulder joint cavity had not yet formed, the

biceps long tendon was accompanied by a slit-like space in the tissue running along the medial side of the humerus (Fig. 1). This space remained as a bursa-like structure until 12 weeks, when it became continuous with the joint cavity (Figs. 2 and 3). Although semi-serial and not serial sections were used, we were unable to find any communication between the early joint cavity and the bursa-like space along the biceps long tendon at 7 and 9 weeks. In the bursa-like space, the primitive synovial membrane was not evident until 10 weeks (Figs. 2C and 3A), and another membrane separated the biceps tendon from the joint cavity (Fig. 3B). The biceps tendon insertion to the glenoid labrum was established by 9 weeks (Fig. 2EF), and later (10 weeks) faced the joint cavity (Fig. 3C). Notably, when the biceps long tendon extended to the glenoid, it involved and carried mesenchymal tissue around the coracoid process (Figs. 1B, 2BC and 3B) towards the infraspinatus tendon (Figs. 2D and 4CD; the future coracohumeral ligament). The rotator interval became evident at 12 weeks (Fig. 4) and the biceps long tendon occupied a large part of it. At 15 weeks, the space around the biceps tendon became wide and the supraspinatus tendon approached the superior aspect of the interval (Fig. 5).

The rotator cuff covering the humeral head appeared initially as an

insertion of the infraspinatus at 9 weeks (Fig. 2). Similarly to the biceps long tendon, the tendons of the supraspinatus, infraspinatus and subscapularis were located together outside the joint cavity and separated from it by a thick membranous structure, possibly the joint capsule, covered by a primitive glenohumeral ligament (Fig. 3E). This primitive glenohumeral ligament appeared to be established as a transient but complete collateral ligament. After 12 weeks, however, it became modified so that the rotator cuff tendons became attached to the humeral head (Fig. 4D). The glenoid labrum, at the medial edge, was tightly connected to the coracoid process (Fig. 4CD): this connection was crossed by and attached to the developing subscapularis tendon, but the primary connection was maintained via the coracohumeral ligament (Figs. 5BC). Notably, at this crossing, the primitive glenohumeral ligament switched its position from the inner side of the subscapularis tendon to the outer aspect (Fig. 5AB).

The major part of the rotator cuff was formed by the infraspinatus tendon (Figs. 2C and 3B). Initially, this tendon was connected with the primitive coracohumeral ligament and, together, these structures covered the humeral head (Fig. 2CD). Additionally, from the superior and superficial side, the supraspinatus tendon joined the infraspinatus tendon: this morphology became evident later than

12 weeks (Figs. 4C and 5DE). On the deep side of the supraspinatus tendon, a triangular fold displayed strong immunoreactivity for vimentin (Fig. 6). This fold appeared to correspond to the posterior part of the glenoid labrum and/or the superior glenohumeral ligament extending toward the biceps tendon insertion.

The intertubercular sulcus was very deep at 12 and 15 weeks (Figs. 4A and 5E). However, no specific fibrous component was evident at the bottom of the sulcus in the humeral head. The sulcus, in the course, might correspond to a part of the anatomical neck, but the neck was clearly identified in the more distal or inferior side (out side) of these figures. Ossification of the humeral head was initiated at 12 weeks (Fig. 4), followed by ossification of the glenoid (Fig. 5B). A well-developed venous plexus was evident in the space between the supraspinatus tendon and the coracohumeral ligament (Fig. 5E), the latter being established at 9 weeks and beyond (Fig. 2D). We also found a fibrous connection between the acromion and the infraspinatus tendon (Fig. 1C) or the glenoid (Fig. 5A).

## Discussion

The superior glenohumeral ligament is one of the major components of the

rotator interval because it is most likely to check and support the biceps long tendon<sup>10</sup>. However, on the basis of the present observations, we hypothesized that a primitive form of the glenohumeral ligament is present as collateral ligaments lining the joint capsule internally to, or on the humeral side of the rotator cuff tendons and the biceps long tendon. This primitive form is consistent with macroscopic observations<sup>11</sup>. Thus, the glenohumeral ligament, especially the superior part, seems to undergo later modification or restructuring as a result of mechanical demands from the subscapularis tendon and biceps long tendon. The presence of a vimentin-positive fold, possibly corresponding to the posterior part of the glenohumeral ligament, also suggested that this area was subjected to stress from the biceps long tendon. Gardner and Gray (1953)<sup>12</sup> also noted specific fibers in this fold with the aid of silver impregnation, but they considered that this might be one of the original sites for vascularization or synovium formation.

Arai et al. (2009)<sup>3</sup> clearly demonstrated the morphology of the superior glenohumeral ligament, wrapping around the biceps long tendon to support its distal or inferior aspect. A change in position from the inner side of the subscapularis tendon to the outer aspect at 15 weeks seems to account for the winding form of the superior glenohumeral ligament in the adult. However, because of the passive

change effected by the strong subscapularis tendon, we speculate that the morphology of the superior glenohumeral ligament varies between individuals, and is easily influenced by age-associated degeneration. In this context, the role of the strong subscapularis tendon is noteworthy, but we did not find any evidence to suggest that the subscapularis tendon is responsible for formation of the anterior concavity of the glenoid<sup>4</sup>. In contrast, the intertubercular sulcus was very deep at 12 and 15 weeks.

The coracohumeral ligament, another major component of the rotator interval<sup>3, 13</sup>, seems to form at an early stage in accordance with the approach of the biceps long tendon to the glenoid; the extending tendon seems to involve and accompany some mesenchymal tissue around the coracoid process at 7 weeks, before joint cavitation has occurred. Thus, we agree that the coracohumeral ligament definitely provides structural support for the biceps long tendon. However, in the present fetuses, the coracohumeral ligament was clearly separated from the superior glenohumeral ligament. A complex of the coracohumeral and glenohumeral ligaments<sup>14, 15</sup> seems to be established after 15 weeks, in contrast to the situation in the early stage described by Gardner and Gray (1953)<sup>12</sup>.

The bursa-like structure for the biceps long tendon may also originate from the mesenchyme around the coracoid process. It is not a false bursa (i.e., a slit-like tissue space without a synovial lining<sup>16</sup>). The biceps long tendon seems to reach the glenoid before joint cavitation occurs. Thus, the so-called intra-articular course of the tendon is formed at the later stage. The glenoid labrum is continuous with the biceps long tendon as far as the ventral glenoid notch, and is supplemented by a connecting band between the superior and inferior glenohumeral ligaments. However, the latter band might not have been formed in present specimens we examined. Finally, Mochizuki et al. (2008)<sup>17</sup> described the detailed laminar architecture of the supraspinatus and infraspinatus tendons in the adult rotator cuff. The present observations also support their contention that the infraspinatus tendon sandwiches the supraspinatus tendon. However, more strictly, the supraspinatus tendon may insert between the coracohumeral ligament and infraspinatus tendon at the early stage.

In contrast to the coracohumeral ligament, which develops in the fetal period, the superior glenohumeral ligament seems to form as a result of secondary functional demands imposed by the subscapularis and biceps long tendons. Because of the significant modification that appears to occur, anatomical reconstruction after

rotator cuff tears should not be based on the “ideal” anatomy of the superior glenohumeral ligament but on individual requirements.

## **Conclusions**

The early development of the coracohumeral ligament suggests that it is a primitive and basic structure. However, mechanical demands from the subscapularis tendon and biceps long tendon are likely to change the primitive form of the rotator interval to the adult morphology, including the superior glenohumeral ligament. The significant modification evident during early fetal development suggests that anatomical reconstruction after rotator cuff tears should not be based on the “ideal” anatomy, especially that of the superior glenohumeral ligament, but on individual requirements.

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### **Figure legends**

Common abbreviations:

A, acromion

CL, clavicle

BB, biceps brachii muscle

CP, coracoid process

DL, deltoideus muscle

G, glenoid of the scapula

H, humerus

PM, pectoralis major muscle

SS, supraspinatus muscle

++ all figures, black and white

**Figure 1. Shoulder without the joint cavity at 7 weeks of gestation.**

Horizontal sections. Panel A (D) is the most superior (inferior) in the figure. Intervals between panels are 0.1 mm (A-B), 0.2 mm (B-C) and 0.2 mm (C-D), respectively. Joint cavitation has not yet occurred. The biceps long tendon is cut longitudinally (arrows in panels A and B). Notably, between the tendon and humeral head (H), a slit-like tissue space is evident (arrowhead in panels A and B; a bursa-like space). The biceps tendon is accompanied by mesenchymal tissue (clear star in panel B; the primitive coracohumeral ligament) from the coracoid process (CP). Asterisk indicates the infraspinatus tendon. For other abbreviations, see list of common abbreviations.

**Figure 2. Start of shoulder joint cavity formation at 8 weeks of gestation.**

Frontal sections. Panel A (F) is the most anterior (posterior) in the figure. Intervals between panels are 0.5 mm (A-B), 0.5 mm (B-C), 0.2 mm (C-D), 0.1 mm (D-E) and 0.2 mm (E-F), respectively. The joint cavity (arrowheads) appears between the humeral head (H) and the glenoid (G). However, no communication is evident between the early joint cavity and the bursa-like space along the biceps long tendon (arrow). The biceps long tendon inserts to the glenoid in the section next to panel E: the insertion corresponds to the site encircled by dots in panel F. The primitive coracohumeral ligament (clear star) appears to connect with the insertion of the infraspinatus muscle (IF) as well as with the infraspinatus tendon (asterisk). BP, brachial plexus; SSC, subscapularis. For other abbreviations, see list of common abbreviations.

**Figure 3. Extension of the shoulder joint cavity at 10 weeks of gestation.**

Horizontal sections. Panel A (E) is the most superior (inferior) in the figure. Intervals between panels are 0.2 mm (A-B), 0.2 mm (B-C), 0.5 mm (C-D) and 0.3 mm (D-E), respectively. The joint cavity (arrowheads) extends along the humeral head in panels B-E, but is still separated from the bursa-like space along the biceps long tendon (arrows) by a membrane (arrow in panel B). The biceps long

tendon inserts to the glenoid in a section near panel B: the insertion corresponds to the site encircled by dots in panel C. The primitive coracohumeral ligament (clear star) connects with the infraspinatus tendon (asterisk). The infraspinatus tendon receives the tendon of the supraspinatus (SS) in panel D. In panels D and E, a black star indicates the subscapularis tendon. In panel E, the glenoid issues membranous structures (small arrows; the future glenohumeral ligament) to cover the humeral head and, notably, these are located deeply to, or on the humeral side of the rotator cuff tendons (black star and asterisk). For other abbreviations, see the list of common abbreviations.

**Figure 4. Appearance of the rotator cuff interval at 12 weeks of gestation.**

Horizontal sections. Panel A (E) is the most superior (inferior) in the figure. Intervals between panels are 0.5 mm (A-B), 0.4 mm (B-C), 0.2 mm (C-D) and 0.3 mm (D-E), respectively. In panel C, the joint cavity (arrowhead) communicates with a bursa-like space along the biceps long tendon (arrows). The biceps long tendon inserts to the glenoid in a section next to panel C: the insertion corresponds to the site encircled by dots in panel D. In panels C and D, the infraspinatus tendon (asterisk) receives the tendon of the supraspinatus (SS) and connects with

the coracohumeral ligament (clear stars). The subscapularis tendon (black star) is evident between the glenoid (G) and the coracoid process (CP). For other abbreviations, see the list of common abbreviations.

**Figure 5. Extension of the rotator cuff interval at 15 weeks of gestation.**

Horizontal sections. Panel A (F) is the most superior (inferior) in the figure. Intervals between panels are 0.6 mm (A-B), 0.4 mm (B-C), 0.4 mm (C-D), 0.2 mm (D-E) and 0.4 mm (E-F), respectively. The biceps long tendon (arrows in panels D-F) connects with the glenoid labrum (“lip” in panel C). The rotator cuff has become thick: the infraspinatus tendon (asterisk) receives the supraspinatus tendon (triangle) in panels D-F, and the subscapularis tendon (black star) has become attached to the glenoid labrum in panel B. The primitive superior glenohumeral ligament (small arrows) extends to the lateral or inner side of the subscapularis tendon (star) in panel A, whereas the ligament switches its position to extend to the medial or outer aspect of the tendon in panels B and C. The coracohumeral ligament (clear stars) covers the rotator interval from the dorsal side. For other abbreviations, see the list of common abbreviations.

**Figure 6. Vimentin immunohistochemistry of the glenohumeral ligament at 15 weeks of gestation.**

Horizontal sections. A section adjacent to that shown in Fig. 5D. A triangular fold (indicated by a circle) displays extremely strong immunoreactivity for vimentin. This fold is likely to correspond to the posterolateral part of the coracohumeral ligament. Arrow indicates the biceps long tendon. An asterisk indicates the infraspinatus tendon. H, humeral head in which ossification has started.

Figure.1

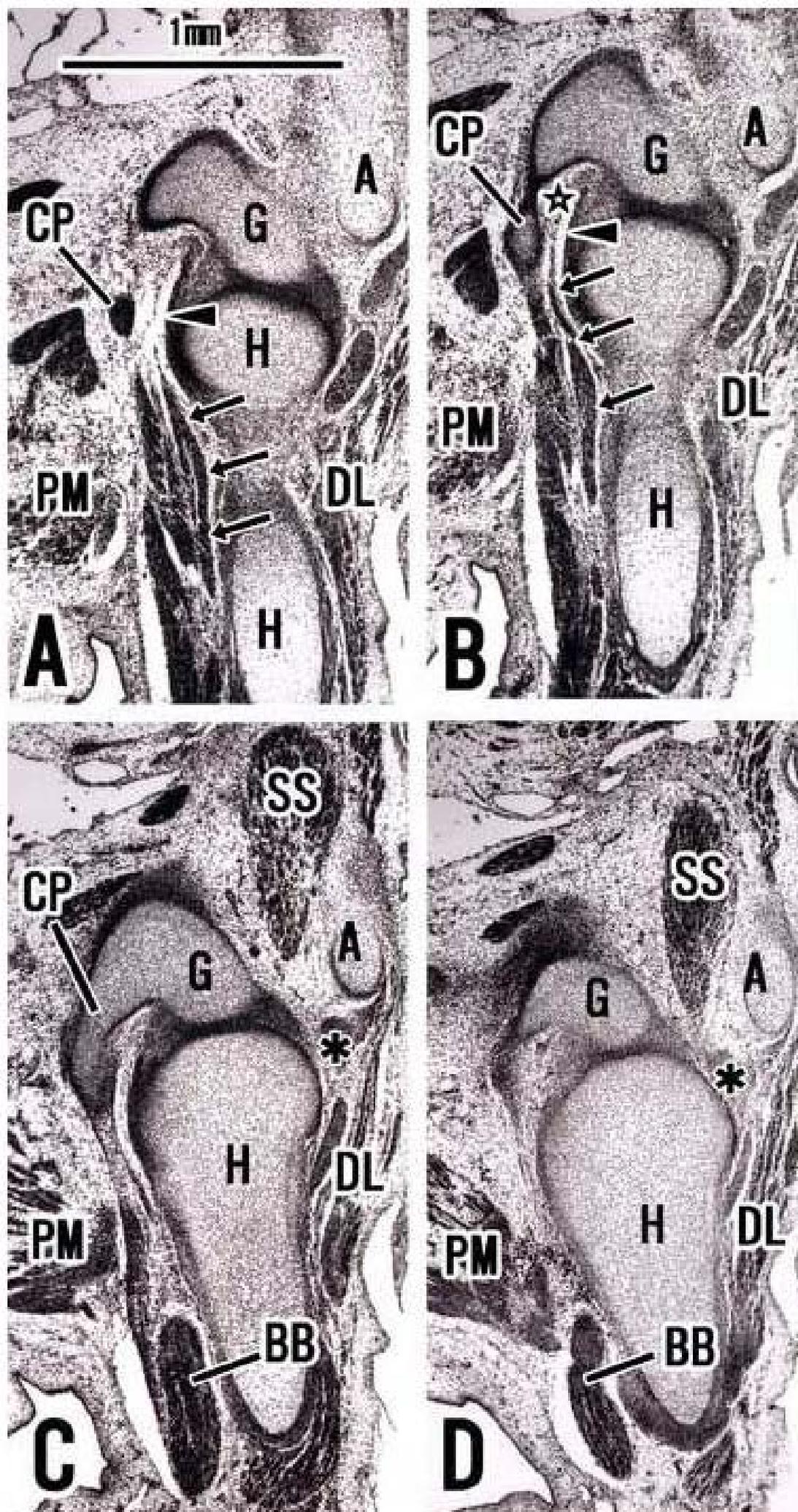


Figure.2

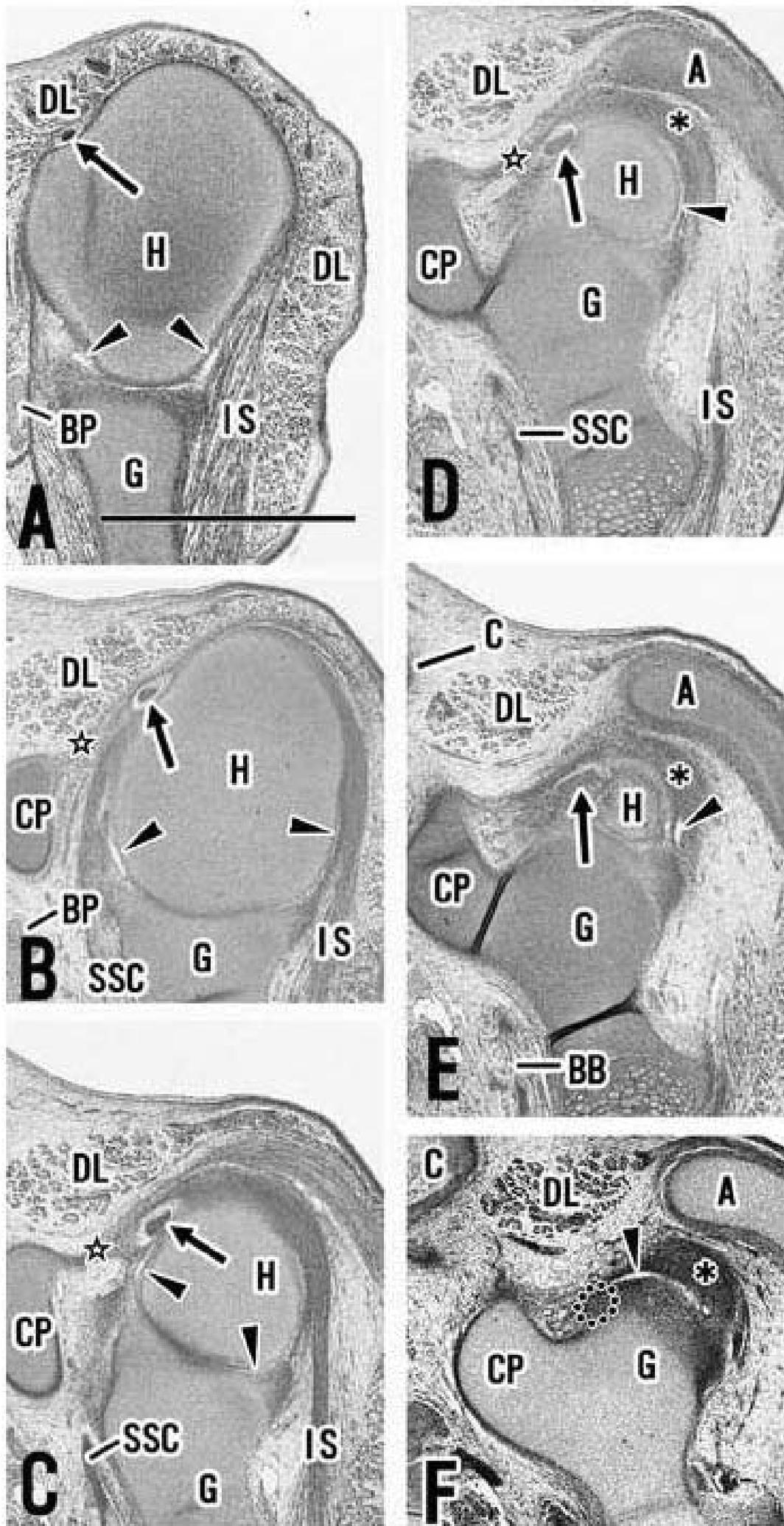


Figure.3

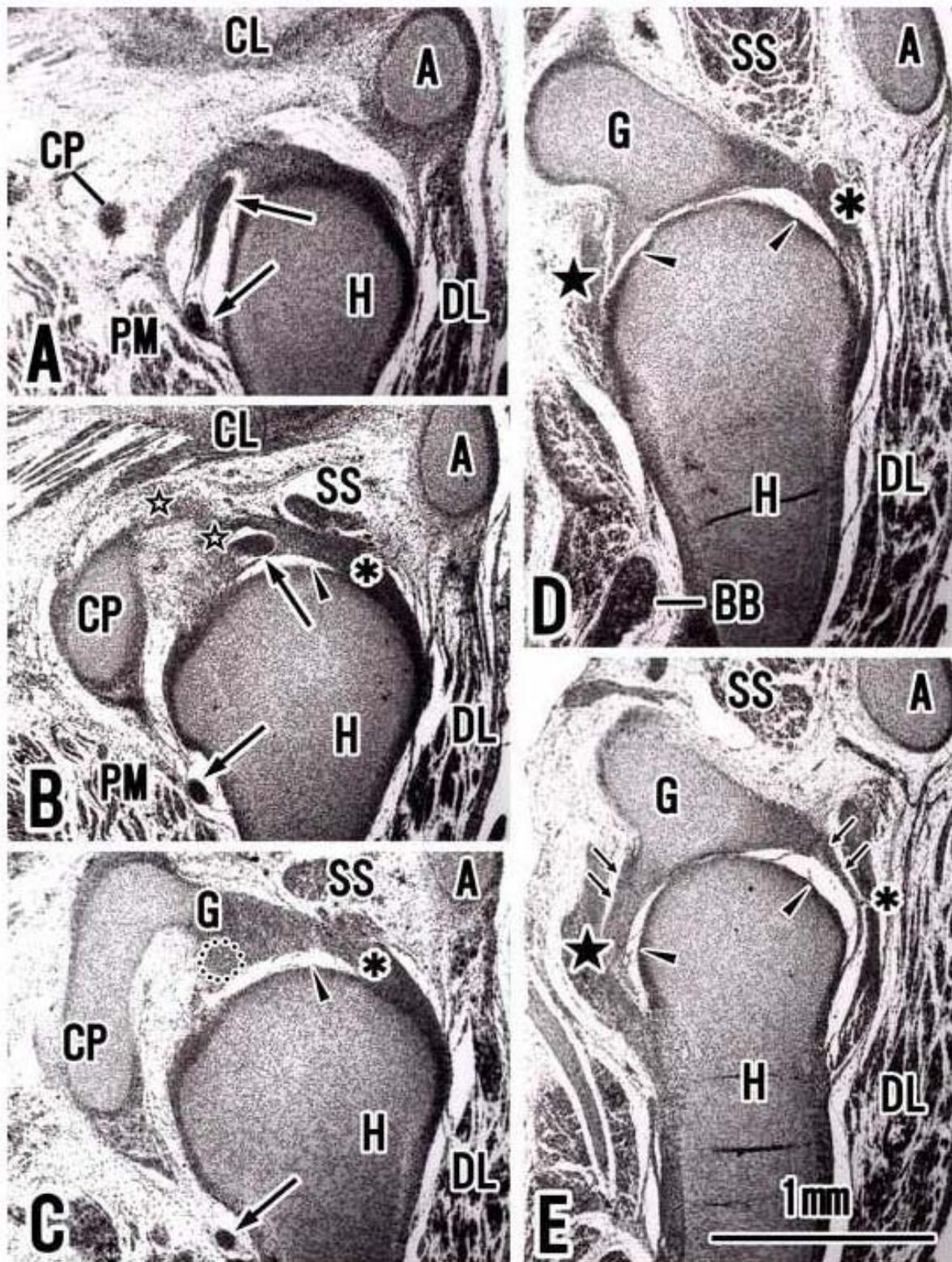


Figure.4

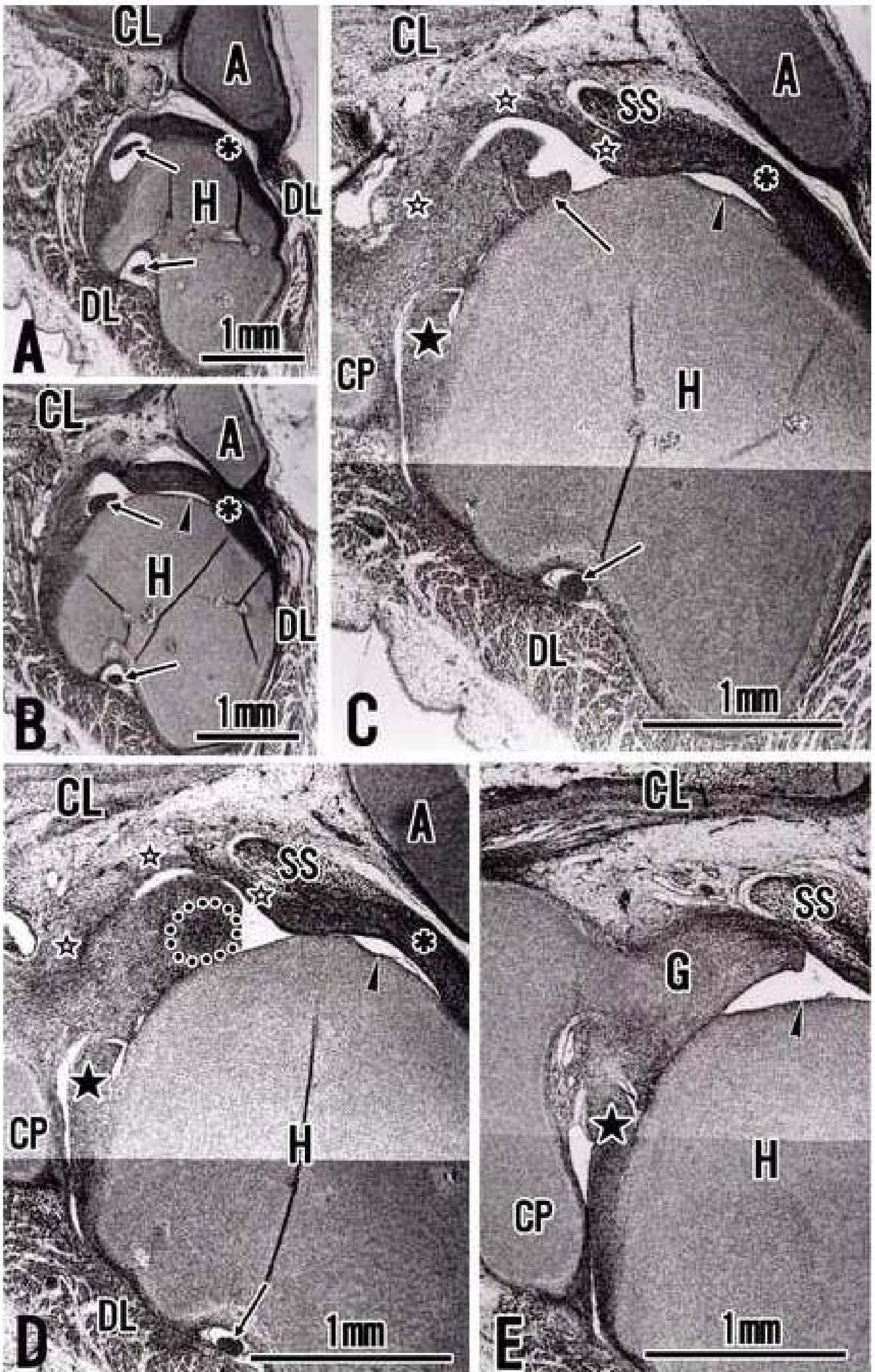


Figure.5

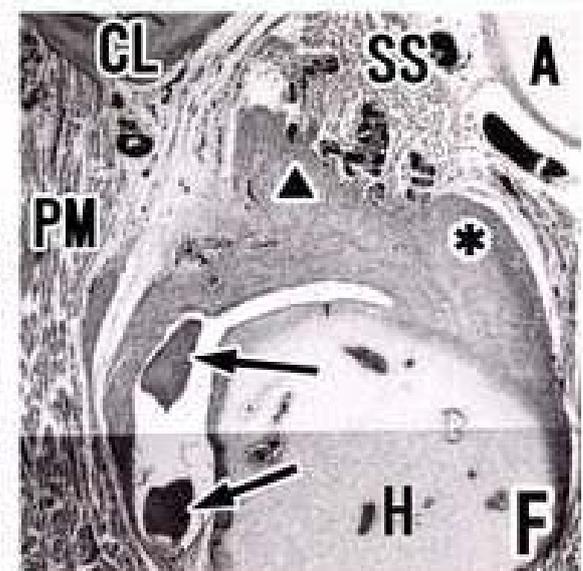
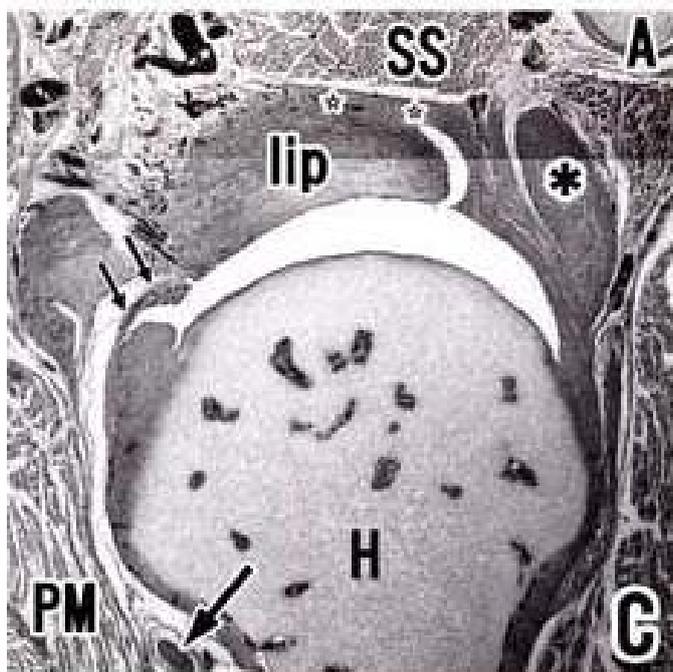
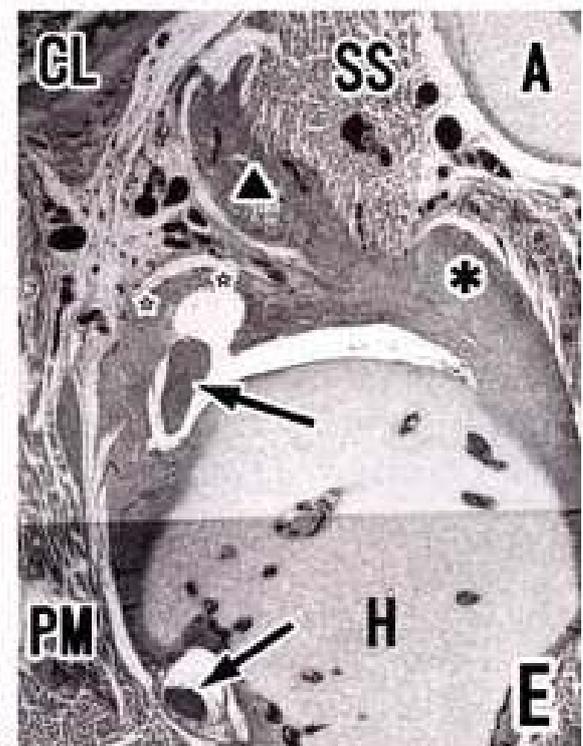
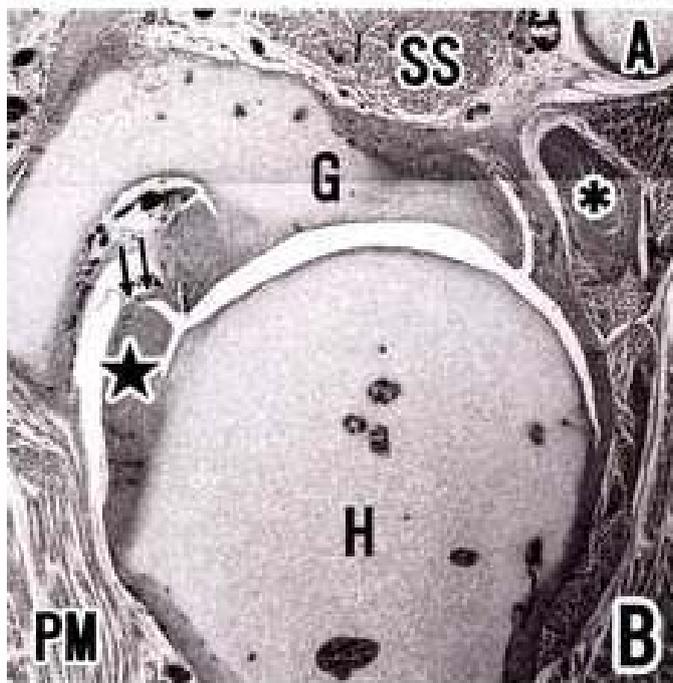
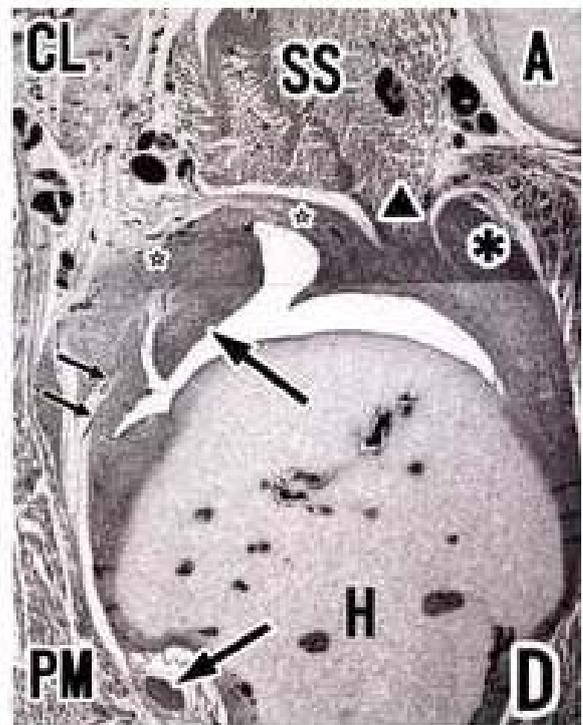
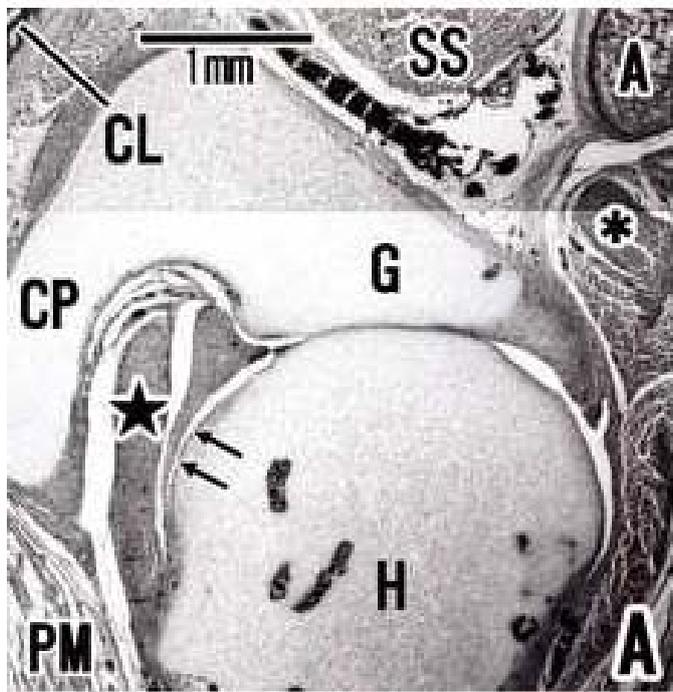


Figure.6

