Prenatal traces of aberrant neurofacial growth

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The interrelation between the development of the brain/peripheral nerves and that of the surrounding bone tissue is termed neuro-osteology. In orthodontic and pediatric practice the development of the hard tissues is evaluated radiographically, but the development of the neural tissue within the bone tissue is not evaluated. In this review the emphasis is placed on two neuro-osteologic interrelations that can be observed on profile radiographs and orthopantomograms, respectively. One is the connection between the pituitary gland of the central nervous system and the sella turcica (profile radiograph), and the other is the association between the peripheral nerves and the development of the dentition (orthopantomogram). Pituitary gland/sella turcica: The correlation between prenatal malformation in the pituitary gland/sella turcica and the postnatal morphology of the sella turcica in holoprosencephaly, spina bifida/myelomeningocele, and cri-du-chat syndrome is demonstrated. Peripheral nerves/dentition: The prenatal innervation of the dentition is presented. Agenesis and tooth malformation occur in constant patterns within the dental arch fields that share the same innervation. The findings demonstrate that in postnatal diagnosis of the cranium and the teeth, traces of prenatal aberrations can be found that are important for neurofacial growth. □ *Brain; cranium; dentition; development; pituitary gland; radiography*

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Neuro-osteology is a new discipline concerned with the interrelations between nerve tissues and hard tissues. Neuro-osteology can be illustrated as the connection between a hand (nerve tissue) and a glove (bone tissue). The hand and glove fit together; the glove protects the hand in the same way as, for instance, the cranium protects the brain. In this metaphor neurologists are the 'hand' specialists, and osteologists and radiologists are the 'glove' specialists. Neurologists are not usually concerned with the bony tissue that surrounds the nerves, and radiologists do not automatically relate the radiographic contours to neurologic conditions. Recent research suggests that specialists may be obliged to overstep narrow disciplinary boundaries, such as those between neurology and osteology/orthodontics.

I. Postnatal pituitary gland/sella turcica malformations

A clinical example of a neuro-osteologic interrelation is the pituitary gland in its sella turcica. Radiologists are concerned with the structures of the sella turcica as shown, for instance, on a profile radiograph of a child (Fig. 1a). The neurologist looks at the pituitary gland as part of the brain (Fig. 1b). The neuro-osteologist links the sella turcica and the function and morphology of the pituitary gland, as illustrated in Fig. 1c, and in normal conditions the pituitary gland fits into the sella turcica like a hand in a glove. When the shape of the sella turcica deviates from the normal (Fig. 1d), orthodontists have problems. For instance, are the conditions shown in Figs. 1e, 1f, and 1g merely differences within the normal range of variation, or are they pathologic? Do these differences mean that the pituitary glands are maldeveloped? And, finally, are these conditions important for the endocrine function of the pituitary gland? All these questions are neuro-osteologic.

Orthodontists have been looking at sella turcica deviations for years without being able to explain them. The problem has been how to approach this matter scientifically. As the deviations appear on radiographs of even very young infants, and hence must necessarily be congenital, the key to the explanation must be found prenatally.

Theoretical neuro-osteology

Neuro-osteology: normal embryology

The fetus develops around the notochord—a primitive cell streak—which acts like a master key from the sacral region to the pituitary gland region, inducing the development of both the brain/spinal cord (CNS) and the skeleton (axial skeleton) (1). This is illustrated in Fig. 2. The left-hand drawing shows a fetus at the age of about 7 weeks, with the notochord indicated by arrows. Figs. 2Aa–c show different developmental stages before the 7th fetal week. The sketches are horizontal sections from the region marked A in the left-hand drawing, and they show the close anatomic relation between the ectodermally derived structures (neural plate/neural groove/neural tube), from which the CNS develops, and the mesodermally derived

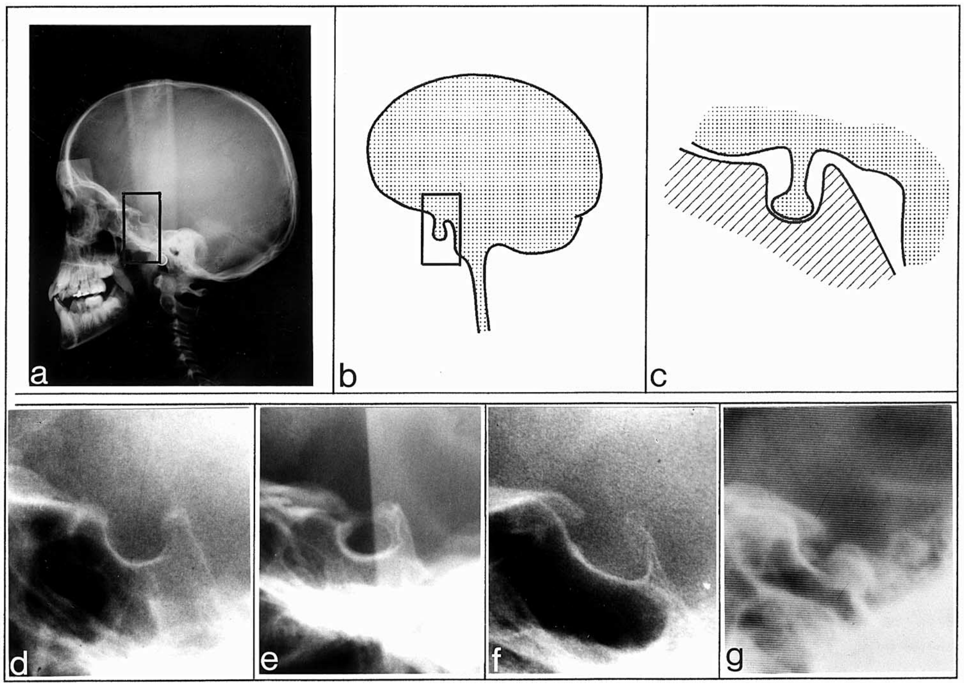

Fig. 1. The upper row shows in lateral projection a) the radiologist's view of the pituitary gland region of a 13-year-old boy (sella turcica area outlined on profile radiograph); b) the neurologist's view of the region in the same patient (outlined area), and the neuro-osteologist's linkage; and c) the neurologist's view of the morphology of the sella turcica and pituitary gland in the same patient. The lower row shows d) the sella turcica region of an 11-year-old girl; e) the overgrown sella turcica of an 8-year-old girl with holoprosencephaly; f) a sella turcica with an oblique anterior wall in a 15-year-old boy with lumbosacral myelomeningocele; g) irregular sella turcica contour and a voluminous dorsum sellae in a 13-year-old girl with cri-du-chat syndrome.

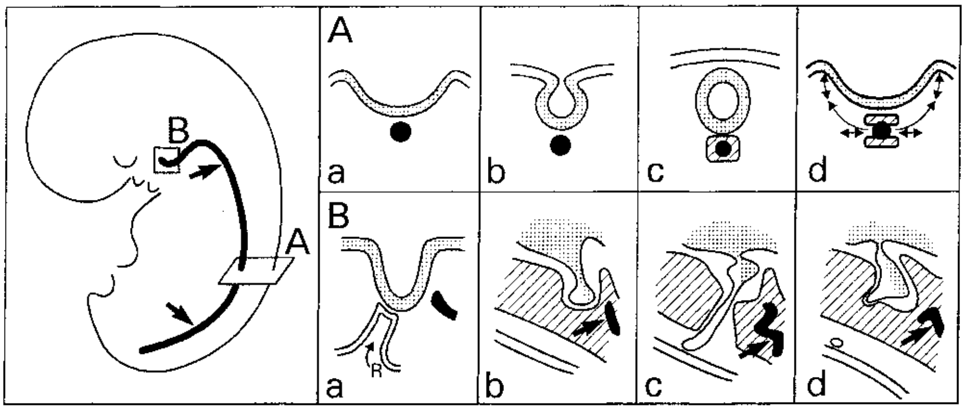

Fig. 2. The left-hand drawing shows an embryo (age, about 7 weeks) in the midsagittal plane. The thick black line marks the course of the notochord from the sacral to the pituitary gland region. The development of the area marked A (horizontal section of the thoracic region) and of the area marked B (sagittal section of the pituitary gland region) is shown in the upper- and lower-right rows of sketches, respectively. Aa, b, and c show different developmental stages, before the 7th fetal week, of the CNS (dotted) and of the axial skeleton (hatched). Ad shows defective neural tube closure and malformation of the vertebral body (hatched). The arrows indicate the normal directions of notochord signaling to ectoderm and scleroderm. Ba and b show different developmental stages, before the 10th fetal week, of the pituitary gland and sella turcica and the notochord (arrow in Bb). In Ba, R indicates the location of Rathke's pouch. Bc (trisomy 18) and d (myelomeningocele) show examples of malformed pituitary glands, sella turcica, and notochord (arrows).

structures (somites/vertebral bodies and cranial base), from which the axial skeleton develops.

The lower-right portion of Fig. 2 shows how the pituitary gland and sella turcica develop before the 10th fetal week in front of the cranial end of the notochord (Figs. 2Ba,b).

The pituitary gland consists of two parts, the adenopituitary and the neuropituitary. The adenopituitary originates in the pharyngeal mucosa, and the neuropituitary (infundibulum) in the neuroectoderm. Tissue from these two different regions are connected on the inferior aspect of the brain. The adenopituitary tissue is 'drawn up' through the submucosa that supports the brain, and later cartilage is formed. This drawing up is presumably regulated by the notochord. When the notochord has fulfilled its function in this respect, it becomes enveloped in cartilage in exactly the same way as the notochord in the vertebral column is enveloped in the cartilage forming the later vertebral bodies. The cranial end of the notochord can be seen in the rear wall of the sella turcica, the dorsum sellae (the black structure indicated by the arrow in Fig. 2Bb). Below the pituitary gland a dish-shaped sella turcica is formed, first in cartilage and later in bone. The notochord disappears in the course of the fetal period, both in the sella turcica and in the vertebral bodies. During its period of functioning the notochord is considered to be the 'crank' for the normal and synchronous development of the axial skeleton and CNS—it is the alpha and omega of the human body axis. It determines the development of the CNS, and it controls when, where, and how the skeleton develops. It is the common denominator of the interrelation between CNS development and the development of the bone tissue that surrounds the CNS, the spinal cord, and the cranium.

The timing of the normal development of the skeletal parts of the spinal cord and the cranial base is extremely precise. There is also a constant morphology and a well-defined positioning of the individual bony components. If the developmental patterns along the notochord are disturbed, this will become manifest both in the nerve tissue (the hand) and in the skeleton (the glove). It is the notochord that is the common denominator of maldevelopment—whether due to faulty genetic information, toxic action, and/or ectopic location.

Two different examples will be given to illustrate what happens when the notochord does not function normally and normal axial tissue interactions fail. The two examples, which manifest themselves in both nerve and bone tissue, are shown on the extreme right of Fig. 2.

Prenatal spina bifida/myelomeningocele malformations

The neural tube is not closed normally in spina bifida (Fig. 2Ad). Studies have shown that in spina bifida and myelomeningocele there is a correlation between the degree and type of malformations in the CNS and the spinal column (2). The bony malformations are observed in the region in the vertebral body where the notochord was located (Fig. 2Ad). This morphologic sign seemingly indicates that the notochord has not signaled correctly either to the neuroectoderm or to the scleroderm (see arrows in Fig. 2Ad).

Prenatal pituitary gland/sella turcica malformations

The second example concerns malformation of the pituitary gland/sella turcica. If the adenopituitary is not 'drawn up' normally, but remains partly in the pharyngeal submucosa, the pituitary gland and the cranial base will both be malformed (3). The pituitary gland may thus form an elongated mass of tissue in the cranial base, and the sella turcica may form a canal around the mass of tissue instead of a bowl below it (Fig. 2Bc). There are various other types of pituitary gland abnormalities, and a variety of different sella turcica anomalies are observed in association with the gland abnormalities (e.g. Fig. 2Bd). Recent research has shown that there are pronounced variations in the shape of the cranial portion of the notochord in the dorsum sellae in various types of malformation (4) (see examples of a twisted notochord in Fig. 2Bc and of a hook-shaped notochord in Fig. 2Bd).

Sella turcica diagnosis and etiology

The three sella turcica malformations presented in the introduction and illustrated in Fig. 1 are comparable to the types of prenatal malformations shown in Fig. 2. The three different types of sella turcica malformations in children, shown in Fig. 1, will now be dealt with in more detail.

Overgrown sella turcica (Fig. 1e). This type of bony change, with a small sella turcica, has been described in patients whose hemispheres are not separated normally (holoprosencephaly). Also, in this group of patients the anterior cranial fossa and the maxilla are not normally developed in the median axis. In other words, there is a neuro-osteologic defect that extends from the palate through the facial skeleton to the brain (5). Children with these malformations have a shorter final stature than other children (6).

Oblique anterior wall in the sella turcica (Fig. 1f). This type of bony change in the sella turcica has been described in a group of patients with myelomeningocele/spina bifida (7). These children have a shorter final stature than other children (8).

Malformed dorsum sella (Fig. 1g). This type has been described in a group of patients with cri-du-chat syndrome (9). Cerebellar hypoplasia has recently been documented by computed tomography in this group of patients. They have a subnormal final stature (10).

Studies show that children with the illustrated malformations in the sella turcica have brain defects and growth problems. Comparing these findings with those of prenatal studies, it is probable that the patients have maldeveloped pituitary glands (11). Fetuses with holo-

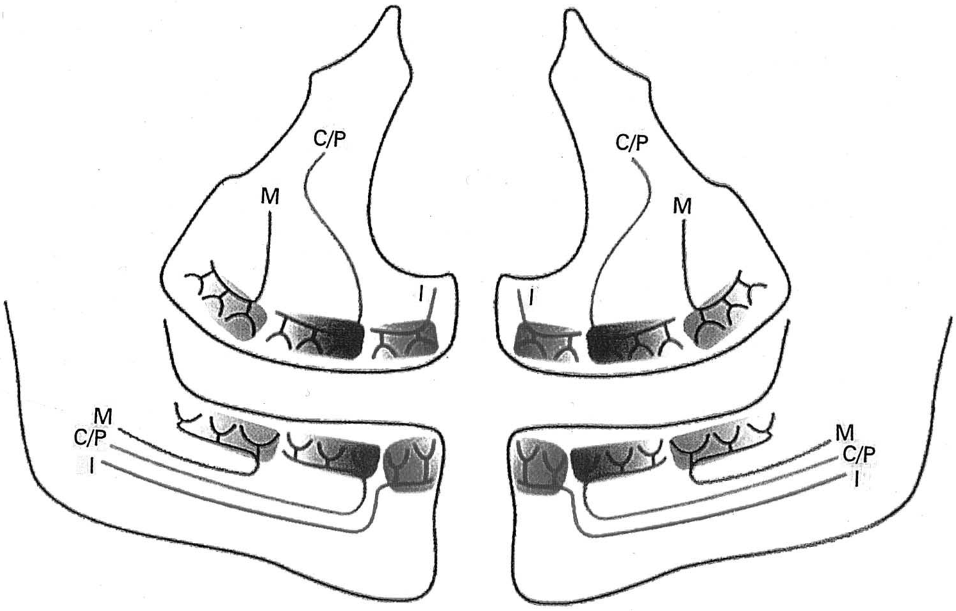

Fig. 3. Schematic drawing of the innervation of the individual tooth groups in the maxilla and mandible. I = incisors (red); C/P = canines/premolars (green); and M = molars (blue). The reproduction of the jaws and dentition corresponds to that seen on an orthopantomographic radiograph of the jaws and dentition.

prosencephaly, for example, have a sella turcica floor and a pituitary gland that resemble the condition shown in Fig. 2Bc, and abnormalities in the anterior wall of the sella turcica are seen not only postnatally but also prenatally in myelomeningocele (2). In both abnormalities of the pituitary gland/sella turcica, adenopituitary tissue is partly located ectopically.

II. Postnatal deviations in the dentition

Deviations in the permanent dentition are well known. These include, for example, agenesis and tooth malformations. It is characteristic that these deviations, which are predominantly diagnosed on orthopantomographic radiographs, are located in specific regions: those of the second premolar and third molar, and in the front lateral incisor in the maxilla and the central incisor in the mandible. It has always been a mystery why these regions are subject to 'weakness' in a developmental sense.

Prenatal development of the innervation of the jaws

The embryonic development of the peripheral nervous system in the jaws has revealed that the individual tooth groups are innervated separately. Hence, the maxillary incisors, canines, and molars are innervated by different peripheral nerves, and the first bony tissue in the maxilla forms in close association with the courses of these different peripheral nerves (12). Likewise in the mandible there are different peripheral nerve branches to the different tooth groups (13). In conclusion, the innervation of the jaws can be illustrated schematically, as in Fig. 3.

Dentition, diagnosis, and etiology

When the locations of the deviations in the dentition are compared with the diagram of the innervation of the maxilla and mandible (Fig. 3), it is remarkable that those regions that exhibit developmental 'weakness', such as agenesis, are the ones innervated last. Consequently, it must be presumed that the innervation, or rather the factors affecting the outgrowth of the peripheral nerves, play a part in tooth formation and tooth shape. This cannot be the only factor involved, however. Surface ectoderm deviations also play a part (14).

III. Conclusion

The correlation between certain malformations in the CNS and in the peripheral nervous system have been described and related to findings in the hard tissues.

This line of research started in 1990 (12), and this hypothesis was gradually developed: Behind a malformed craniofacial bone there exists a malformed brain/nerve structure (15). Concerning the sella turcica the hypothesis was as follows: A malformed sella turcica encloses a malformed pituitary gland. Since the defect had arisen prenatally, it was necessary to tackle the problem by first analyzing the skeletal development of fetuses with brain defects. Fetuses with congenital malformations in the CNS (required autopsy including the CNS) were examined, and the results were then compared with the skeletal findings on radiographs of children with the same type of congenital malformations in the CNS. In other words, the long-term aim has been to improve radiographic diagnosis of profile and orthopantomogram exposures in clinical practice by means of the autopsy investigation of fetal material.

Autopsy studies have shown that the development of the pituitary gland is closely linked to that of the entire CNS, and the development of the sella turcica is closely related to that of the entire body axis, that is, the axial skeleton.

An example of defective neural tube development is given, namely, myelomeningocele/spina bifida. This particular example was chosen because it has been demonstrated that fetuses with myelomeningocele not only have defective neural tube closure but also exhibit abnormalities in the pituitary gland/sella turcica region. The signaling from the notochord has 'failed' not only lumbosacrally but also cranially. The sella turcica region therefore must be seen in relation to the entire body axis, and the pituitary gland in relation to the entire CNS. This correlation is extremely important for children born with neural tube defects. It was earlier known that these children had endocrine disorders, but without knowing the etiologic background for this clinical observation. There is now much evidence to suggest that the endocrine disorders are caused by pituitary gland defects that can be observed as suspicious from profile radiographs.

Abnormalities in the peripheral nerves are difficult to study histologically. As the permanent teeth are first laid down at a late stage in the prenatal period or in the postnatal period, it is difficult to demonstrate neuro-osteologic interrelations in the dentition in the same manner as in the pituitary gland/sella turcica region. The conditions show that there are traces from the prenatal period of aberrant developmental course that can be read postnatally and that influence neurofacial growth.

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