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Relationship Between the Development of the Spinal Canal and the Etiopathogenesis of Lumbar Spinal Stenosis

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ABSTRACT

INTRODUCTION: The presence of a pre-existing narrow spinal canal may have an important place in the ethiopathogenesis of lumbar spinal stenosis. By consequence the study of the development of the spinal canal is crucial. The first goal of this work is to do a comprehensive literature search and to give an essential view on the development of spinal canal and its depending factors studied until now. The second goal is to give some considerations and hypothesize new leads for clinically useful researches.

MATERIALS AND METHODS: A bibliographical research was executed using different search engines: *PubMed*, *Google Scholar* ©, *Ovid* ® and *Web Of Science* ©. Free sources and available from the *University of Lausanne (UNIL)* and *Centre Hospitalier Universitaire Vaudois (CHUV)* were used. At the end of the bibliographic researches 114 references were found, 85 were free access and just 41 were cited in this work. Most of the found references are in English or in French.

RESULTS AND DISCUSSION: The spinal canal is principally limited by the vertebrae which have a mesodermal origin. The nervous (ectodermal) tissue significantly influences the growth of the canal. The most important structure participating in the spinal canal growth is the neurocentral synchondrosis in almost the entire vertebral column. The fusion of the half posterior arches seems to have less importance for the canal size. The growth is not homogeneous but, depends on the vertebral level. Timing, rate and growth potentials differ by regions. Especially in the case of the lumbar segment, there is a craniocaudal tendency which entails a greater post-natal catch-up growth for distal vertebrae. Trefoil-shape of the L5 canal is the consequence of a sagittal growth deficiency. The spinal canal shares some developmental characteristics with different structures and systems, especially with the central nervous system. It may be the consequence of the embryological origin. It is supposed that not all the related structures would be affected by a growth impairment because of the different catch-up potentials. Studies found that narrower spinal canals might be related with cardiovascular and gastrointestinal symptoms, lower thymic function, bone mineral content, dental hypoplasia and Harris' lines. Anthropometric correlations found at birth disappear during the pediatric age. All factors which can affect bone and nervous growth might be relevant. Genetic predispositions are the only factors that can never be changed but the real impact is to ascertain. During the antenatal period, all the elements determining a good supply of blood and oxygen may influence the vertebral canal development, for example smoking during pregnancy. Diet is a crucial factor having an impact on both antenatal and postnatal growth. Proteins intake is the only proved dietetic relationship found in the bibliographic research of this work. The mechanical effects due to locomotion changes are unknown. Socioeconomic situation has an impact on several influencing factors and it is difficult to study it owing to numerous bias.

CONCLUSIONS: A correct growth of spinal canal is evidently relevant to prevent not-degenerative stenotic conditions. But a "congenital" narrower canal may aggravate degenerative stenosis. This concerns specific groups of patient. If the size of the canal is highly involved in the pathogenesis of common back pains, a hypothetical measure to prevent developmental impairments could have a not-negligible impact on the society. It would be interesting to study more about dietetic necessities for a good spinal canal development. Understanding the relationship between nervous tissues and vertebra it might be useful in identifying what is needed for the ideal development. Genetic importance and the post-natal influences of upright standing on the canal growth remain unsolved questions. All these tracks may have a double purpose: knowing if it is possible to decrease the incidence of narrower spinal canal and consequently finding possible preventive measures. The development of vertebral canal is a complex subject which ranges over a wide variety of fields. The knowledge of this subject is an indispensable tool to understand and hypothesize the influencing factors that might lead to stenotic conditions. Unfortunately, a lack of information makes difficult to have a complete and satisfactory interdisciplinary vision.

INDEX

1. INTRODUCTION

- The importance of canal size
- Spinal stenosis and development
- Why has this subject been chosen?

2. MATERIALS AND METHODS

2b. ANATOMICAL REMINDER

3. RESULTS

- First embryological events.
- Main structures involved in the canal growth.
- The neurocentral synchondrosis.
- Closure of posterior arches.
- The pre-natal growth.
- The post-natal growth.
- Length and curvatures.
- Measurements and relationships.
- Atlas, axis, sacrum and coccyx.
- The cervical and thoracic canal.
- The lumbar canal.
- Lumbar levels and catch-up growth.
- The trefoil-shaped canal.
- A key element: the neuro-vertebral relationship.
- Movements and spinal canal.
- Vertebral growth impairment and others structures.
- The immune system.
- Obstetrical, antenatal and pediatric factors.
- Genetic considerations.
- Diet.
- Socioeconomic factors.
- Comparing with gorillas and chimpanzees.

4. DISCUSSION

- The mesodermal origin.
- Blood vessels and ossification.
- Why does the neurocentral synchondrose closes?
- The fusion of the half posterior arches.
- Mechanical effect on ossification and the price of the upright standing.
- Catch-up growth potential.
- The interaction between tissues.
- Trefoil-shape.
- Canal growth impairment associated with other structures.
- Smoking during pregnancy.
- Difference between ethnic groups.
- Diet is important but not so studied.
- The problem of retrospective studies.
- "Natural" prevalence of stenotic canals.
- Canal evolution.
- Prenatal versus postnatal: equally important?
- Aging and the relationship between congenital and degenerative stenosis.
- Limits of this work

5. CONCLUSION

6. REFERENCES

6b. FIGURE REFERENCES

1. INTRODUCTION

The importance of canal size

The selection of surgical candidates suffering from lumbar spinal stenosis is based on the severity of symptoms concurring with clinical and radiological signs. Patients in need of surgery have, on the average, a smaller spinal canal area at pedicle level compared to patients with an asymptomatic stenosis. The reduction of this area is not supposed to be caused by a degenerative progression. These observations suggest that the presence of a pre-existing narrow spinal canal may have an important place in the etiopathogenesis of lumbar spinal stenosis.

A study using ultrasound readings (15° oblique angle), suggested that a difference of only 2mm (a decrease in canal size about 15%) separates people with low back pain from people without symptoms (1). In a general practice randomized study it was found that patients with back pain have significantly smaller lumbar canals. Almost 2/5 of patients presenting clinical back pain have lumbar canals under the tenth percentile for the general population (2). Therefore a smaller vertebral canal has a clinical significance for back pain, a common symptom found not only in the patients diagnosed with lumbar spinal canal stenosis. The frontier between a smaller vertebral canal and the diagnosis of spinal stenosis is quite unclear: an individual borderline must be traced for each patient according to all the data collected by the physician. This diagnostic nuance may be seen in the severity of the symptomatology, from a simple low back pain to a neurogenic claudication, or even worse.

Spinal stenosis and development

The knowledge of development of the spinal canal and its influencing factors is undoubtedly a prerequisite to understand the etiology of pathologies like spinal stenosis. Most biomedical texts focus attention on specific parts of the development or on specific factors. References are sometimes just outdated and the “article-cites-article” chain makes the knowledge static. Trying to go into the subject in greater depth could be a tough task as it would take quite some time, more specifically if one wants only the useful information.

Why has this subject been chosen?

This Master Project started in April 2011 with goals that were not exactly the same at the end. At the beginning the first idea was to find some measurable structures that could be associated with smaller lumbar spinal canal. But to hypothesize a possible structure with developmental analogy or homology, it's necessary to know embryological, fetal and pediatric changes. Another condition to find new possible correlated structures is to know the

past studies undertaken until now. Hence, the principal objective changed: shifting from the initial idea to the creation of a text which could fulfill these necessities. Sometimes the bibliographical research was not always concentrated and clearly limited: to acquire background information was necessary to create new hypothesis.

The first goal of this work is to do a comprehensive literature search and to give an essential view on the development of spinal canal and its depending factors studied until now. Second, and mainly treated in the discussion, is to give some considerations and hypothesize new leads for clinically useful researches.

This work is globally not a guideline with standard sizes of vertebral canal. Important variations are present in the different populations depending on factors that will be elaborated in the following pages.

Note: a larger attention was given to the lumbar part of the canal, which were the most studied along with the cervical segment were the most studied and having more literary references.

2. MATERIALS AND METHODS

The bibliographical research was executed using different search engines: *PubMed*, *Google Scholar* ©, *Ovid* ® and *Web Of Science* ©. One first research was made during the month of April 2011. The keywords are listed in Table 1. To ensure this, different terms than the MeSH ones were looked for, even though there are synonyms which are theoretically included in the MeSH term.

It was considered that some terms are just synonyms with exactly the same meaning. For example, in this paper the antero-posterior diameter is the same as sagittal diameter. There are theoretically no misleading terms for the reader with some common sense.

It's really important to underline that just free references were considered, meaning that only free sources and available from the *University of Lausanne (UNIL)* and *Centre Hospitalier Universitaire Vaudois (CHUV)* were used.

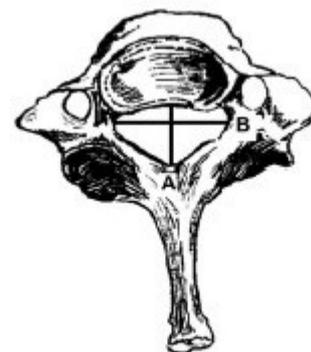
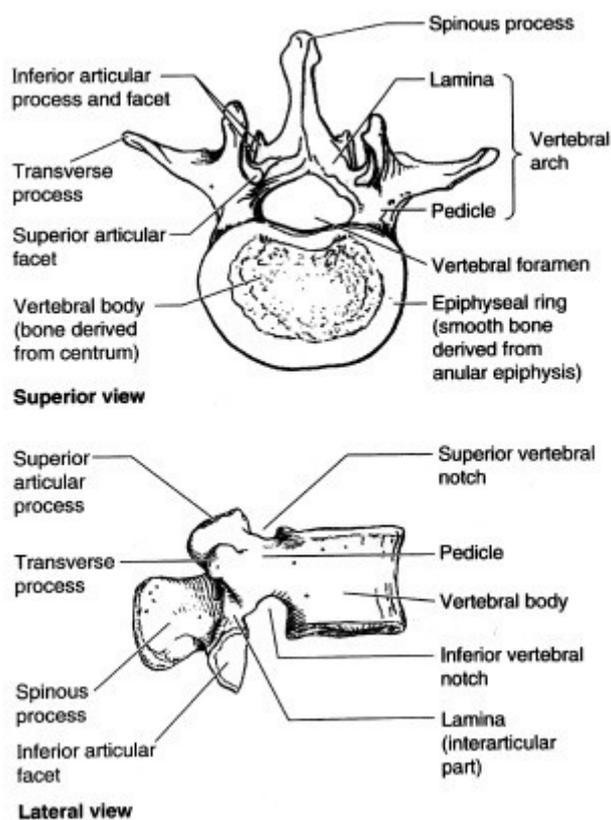
After reading the articles, a second research of the selected cross references was made. Then a summary of the most interesting parts was done, followed by the formulation of hypothesis. A first version of this text was elaborated and initial research was repeated to cover articles that appeared between April 2011 to February 2012. All of this was then followed by the writing of the thesis including only the structures judged important to understand spinal canal growth.

In the discussion data from the Dr. med. Schizas' study (3) were used to create hypothesis.

Keywords		+/- AND	+/- AND
vertebral / spinal / neural	- canal	morphogenesis	fetal
	- foramen / foramina	growth	embryonic
vertebral column / spine		development	antenatal
vertebra		embryology	pediatric
neurocentral	- synchondrosis		
	- junction		
neural arch			
pedicles			
catch-up			
trefoil-shape			

Table 1. Terms used for the bibliographical research.

2b. ANATOMICAL REMINDER



A: Canal Anterior-Posterior
B: Canal Transverse

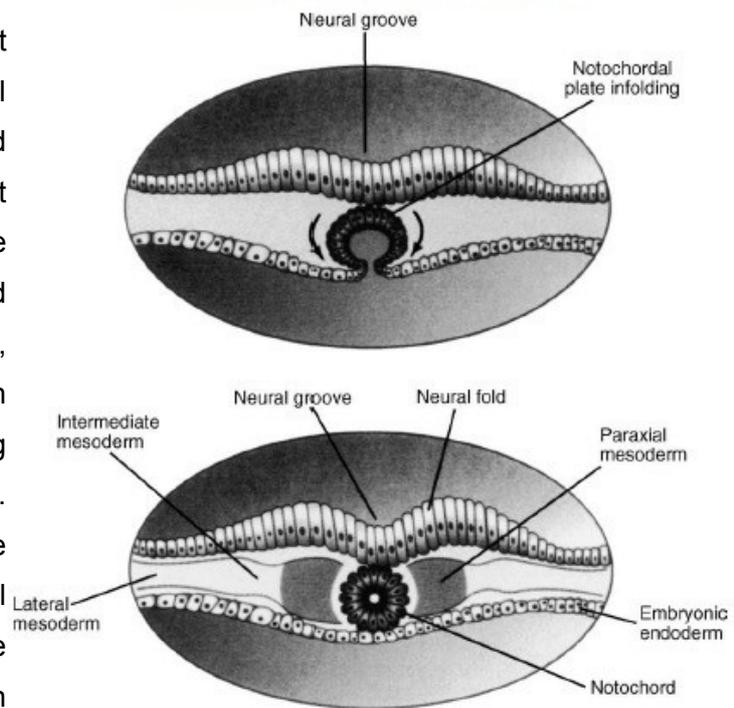
Figures 1 (left) and 2 (right).

3. RESULTS

At the end of the bibliographic researches 114 references were found, 85 were free access and just 41 were cited here. Most of the found references are in English or in French.

First embryological events

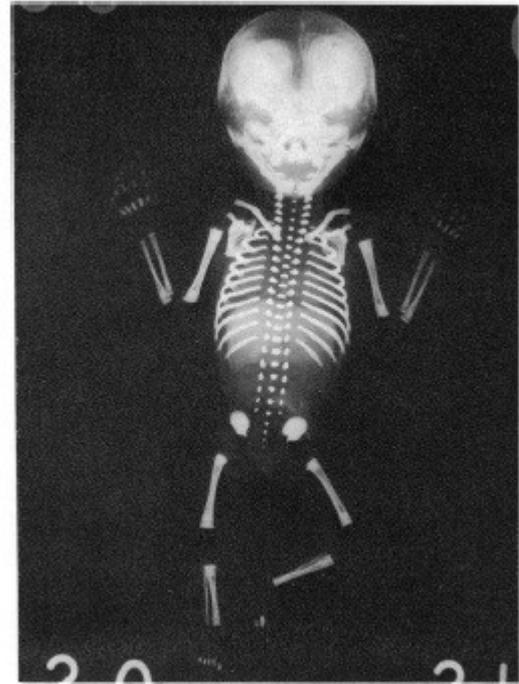
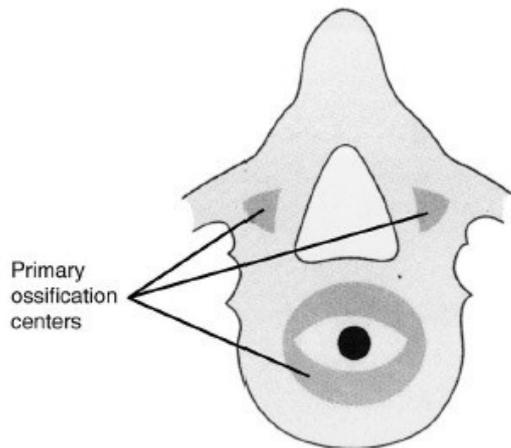
The development of spine begins at the third week of gestation. It's well recognized that somites and notochord are the most important embryonic structures involved in the vertebral development. The notochord derives from the notochordal process, a group of specialized cells which migrate from the primitive node during the third-fourth week of gestation. One of the principal roles of the notochord is to define the primordial longitudinal axis marking the future position of the vertebral bodies. On



top of that, notochordal cells induce the ectoblastic tissue in the course of the neural plate differentiation. On both lateral sides of notochord is placed the mesoblast which will differentiate in lateral, intermediate and paraxial. **(Figure 3.)**

During the fourth-fifth week of gestation the paraxial mesoderm forms 42 pairs of somites in a craniocaudal sense. The somites differentiate in sclerotome (future axial skeleton), myotome (striated muscles of the neck, trunk and extremities) and dermatome (subcutaneous tissues and skin). The sclerotome migrates toward and around the notochord and the neural tube. Consequently to some differentiations and fusions, the sclerotome forms the centrum (future vertebral body), the posterior arches and the primitives structures that will constitute the intervertebral discs (4). Each half posterior archi is formed by a pedicle, a lamina and an inferior articular apophysis, which is more important than the superior one (5). Throughout the course of the sixth week notochord and neural tube induce a chondrification of the future skeletal structure, followed by an ossification. During this lapse of time, notochord disintegrates.

At the third month the cartilaginous half posterior arches unite. Thanks to the development of blood vessels, three primary ossification centers are present by the end of embryonic period: one in the centrum and one at the each side of the posterior arch (4,5). The neural arch centers first appear in the upper cervical region and continue in a craniocaudal sense (6).



A typical anteroposterior radiograph of a 12 weeks fetus.

Figures 4 (left) and 5 (right). Primary ossification centers.

Main structures involved in the canal growth

The volume of spinal canal is limited by the vertebrae. In transversal plan the vertebral body grows only antero-laterally. Therefore the growth of the posterior arch determines the development of the spinal canal (7). A relative spinal canal stenosis can occur if there is an early closure of structures called neurocentral synchondroses. In the same way, an asymmetrical development of the neurocentral synchondroses may result in scoliosis (8). A study demonstrates that when pedicle screws are placed across the neurocentral synchondrosis in an immature porcine model, a narrow spinal canal with short pedicles is formed (9).

Drawings indicating the position of the NCS (arrows) in transverse and sagittal views. **a** Transverse view. **b** Sagittal view

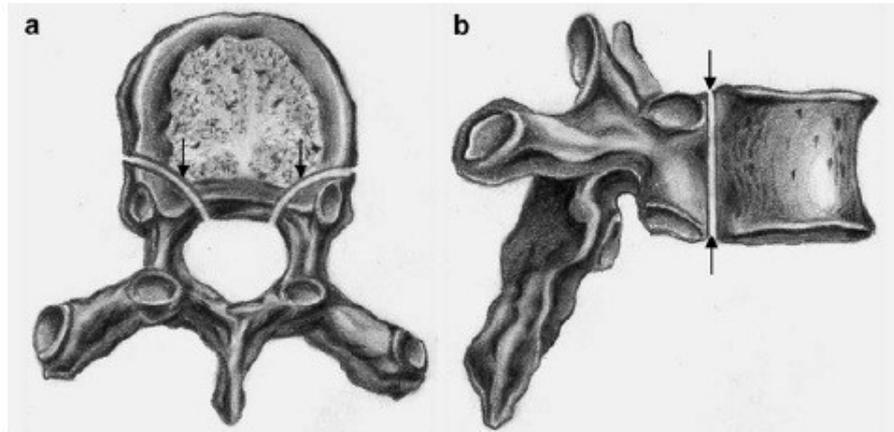


Figure 6. The neurocentral synchondrosis.

The neurocentral synchondrosis

Between the centrum and the neural arches lies the neurocentral synchondrosis (NCS) which contributes to the growth of one third of the vertebral body and one third of the posterior arch (10). A recent morphometric analysis using MRI demonstrates that the fusion of this neurocentral physis begins in the lumbar vertebrae around 4 years of age (~75% of the NCS no longer visible). After 5 years of age the middle-lower thoracic NCS begin to close. At 10 years the lumbar NCS are nearly 100% closed and the thoracic NCS closed by 50% (9). Another MRI study nearly agrees with these last observations: the closure occurs at 11-16 years of age between the T4 and L5 level. From 6 to 11 years of age the NCS closes in the C2-T3 region (11). These are the most ostensible found values. Other references reports closures between 5 and 8 years of age (4,8), or from 3 to 5-7 years of age (5,7). We considered that they were probably less reliable because of the technique of measurement: MRI seems to be more efficient than X-ray film. With MRI technique the cartilage of NCS is more visible and there is less risk of a bias of magnification. Furthermore the recent MRI studies have a bigger sample size than the past X-ray studies. It is essential to remember that the vertebral body grows just antero-laterally and not posteriorly, avoiding the encroachment on the lumen of the vertebral canal. Hence, the NCS is the most important structure for the growth of the spinal canal (7).

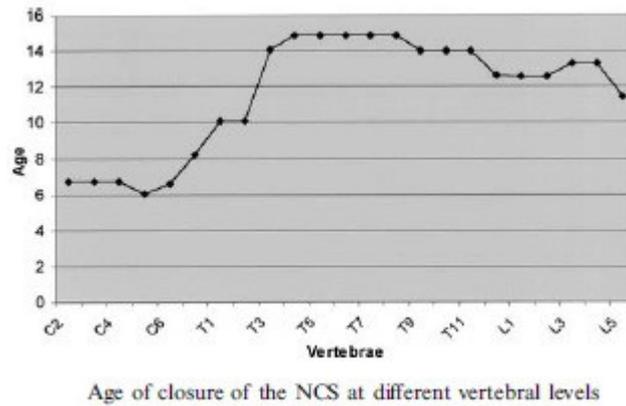


Figure 7.

Closure of posterior arches

From 1 to 6 years of age the neural cartilage between the two osseous parts of the posterior arch fuse disappear (4). The fusion begins from the dorsal region and progresses like a zipper. The complete closure of the sacral region is more tardive, as well as the cervical region: the atlas and the axis fuse at 2 respectively 4 years of life. The closure of sacrum doesn't occur before the age of 4 (5).

The pre-natal growth

The growth rate of the spinal canal is similar to the development of brain, spinal cord and cranial cavity (4).

The most rapid growth period of the vertebral canal is between 18 and 36 weeks of gestation. The lumbar and sacral regions develop with the same pattern until 14 weeks of gestation, followed by a faster growth for the lumbar canal than the sacral one. From the 30th week the same phenomenon happens respectively between the upper and the lower parts of the lumbar canal (12).

It was observed that between 6 and 26 weeks of gestation the antero-posterior and the transverse diameters of the cervical canal have the same growth rate (13).

The post-natal growth

Between childhood and adulthood maturity, the canal of the thoracic region changes more than the rest of spine (14). The area of the thoracic and lumbar spinal canal increases respectively by 22% and 15% from 0-3 to 4-7 years, and by only 1% and 0.3% from 4-7 to 8-10 years (9). These results match with previous data concerning the closure of the NCS. Generally the sagittal diameter of the canal reaches almost the adult size between 6 and 8 years of age. Thereafter only a little growth occurs (8).

The vertebral arch grows rapidly between the ages of 3 and 5 years, similarly to the cranium

cavity (10). Between 2-4 years and adulthood the sagittal and transverse diameters increase by 10% in the cervical region (15).

The pedicle width increases constantly until ~12 years of age. Then, the pedicle width grows with a slower rate. By 16 years of age pedicle growth appears complete in most children. It seems that this growth is slower in the lower than in the upper lumbar region (16).

Length and curvatures

The length of vertebral canal reflects the longitudinal growth of the spine. Obviously the canal curvature follows the vertebral one. During the fetal period the canal is kyphotic. During the infancy due to the gravity and the changing posture, cervical and lumbar lordosis appears (4).

Measurements and relationships

No linear relationship between (cervical) vertebral heights and any canal measurements was found (17). The anteroposterior and interpedicular diameters of the spinal canal are not necessarily associated with each other (1). The anteroposterior diameter was considered more important than transversal diameter in case of spinal stenosis (5) (but either could participate in the pathogenesis (1)). The reason is that spinal stenosis was more frequently observed when the anteroposterior diameter was affected.

The size of intervertebral foramen was largely related with midsagittal diameters (1). As it will be explained in the next paragraphs, it might simply be due to the effect of nervous mass size.

Atlas, axis, sacrum and coccyx

Due to the complexity of the subjects and since it is a less common vertebral stenosis condition, an exhaustive description of the vertebral canal growth of these structures was almost avoided.

The atlas has two lateral ossification centers which will constitute the future lateral masses. A third anterior center appears subsequently and is present in 20% of newborns; normally it cannot be visible up to one year of age. The canal diameter of the atlas is the biggest one in the cervical vertebrae. At 4 years of age the sagittal diameter is 80% of the adult size. The anterior arches are ossified in 33% of the children by three months, 81% by one year. Ossification was complete in all children by three years of age (18). An old study measuring the spinal canal of Australian Aborigine suggests that the vertebral foramen of atlas reaches 95% of the adult size by 6-7 years. After 14-15 years of age the canal not present other changes besides possible degenerative modifications (14).

The axis, which has different development than the atlas, has a NCS that disappears at 4 years of age (5). At this age we can presume that there is no more growth. Concerning the sacrum, from three months of gestation to the mid adult life 58 to 60 ossification centers can be identified. As many as eight ossifications centers were found in the coccyx (19).

The cervical and thoracic canal

In the cervical region the volume of spinal canal narrows from up to down. The sagittal diameter decreases slightly from the foramen magnum to C3, whereas in the rest of the cervical level it remains nearly constant (13). The cranial vertebrae reach the maturity first (20). At 3 years of life nearly 95% of its mature diameter is reached (18). The anteroposterior diameter seems to have the adult size at the age of 7-8 years. A cervical spine at the age of 8 has a configuration that reminds the adults' one. After this age, the transversal diameter continues to grow (5).

In infancy the thoracic canal is larger than the lumbar one (1). Between 2-4 years and adulthood the sagittal and transverse diameters increases of 5% and 12% respectively (15).

The lumbar canal

A study of a collection of fetuses indicated that the most rapid growth is between 12 and 32 weeks in utero (12). Using data from different studies Clark et al. observed that the lumbar spinal canal has a greater potential of postnatal growth than the thoracic segment. The same paper underlined that the canal size was approximately 65% of its total at birth and 90% at 5 years of life. Furthermore it appeared that the anteroposterior diameter reaches the adult size faster than the transversal diameter (1).

In the early 70's Tulsi had concluded to similar observations about a skeletal collection. In this osteological study the mean sagittal diameters of the spinal canal at 2-4 years of age correspond to the adult mean. By contrast, the transverse diameters follow the craniocaudal sequence of maturation. From 2-4 years to adulthood the transverse diameter of the lumbar spinal canal grows by 17% (15). According to Hinck et al., the total increase of the transverse diameter of lumbar vertebral canal was approximately the highest between 3 and 5 years of age (1).

Lumbar levels and catch-up growth

Studies on a collection of skeletons and a collection of fetuses conclude that some differences of spinal canal development are present between the lumbar levels (12,21). At birth the midsagittal diameter of L1-L4 is approximately 70% of adult dimension. The growth

is almost complete by one year of age, when the cross-sectional areas are similar to adult size. Differently, at birth the L5 midsagittal diameter is 50% of its adult size and probably grows until 5 years of age. By consequence if there is a poor growth in utero, L1-L4 levels will be more affected than L5, which has a bigger catch-up growth potential. Inversely if there is a problem of growth during the early infancy, the upper lumbar canal will be more “covered” than the lower part (12,21,22). The catch-up growth theory is based on the concept of the limited potential of growth of each organ during a limited range of time (23,24). Concerning the interpedicular diameter, it increases at L1 until 10 years and at the others lumbar levels until adulthood. Interestingly, this value is similar to the increase of L4-L5 canal perimeter until the age of 14 (21).

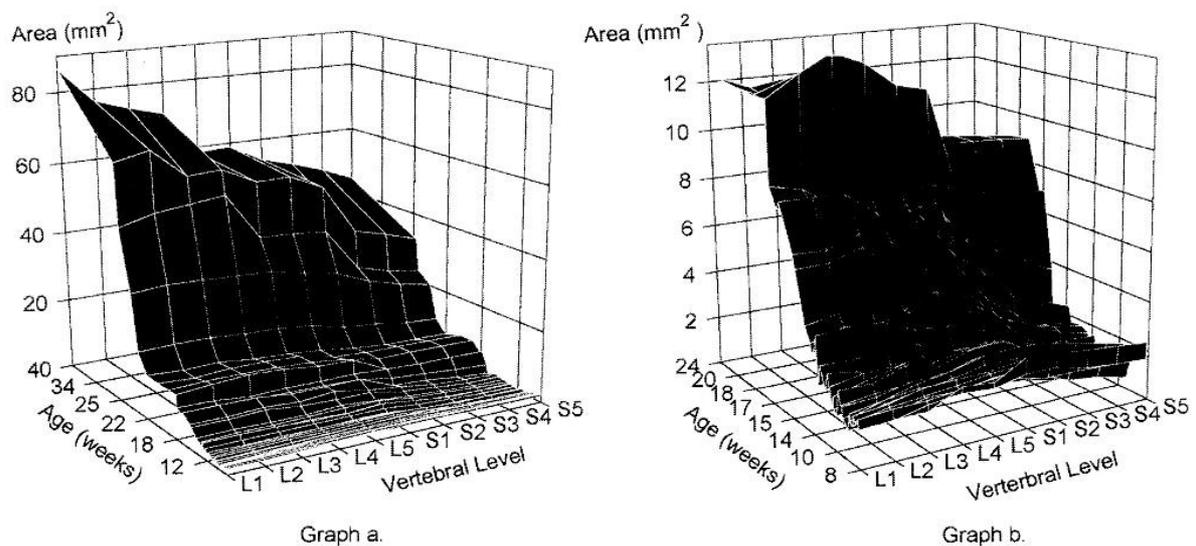
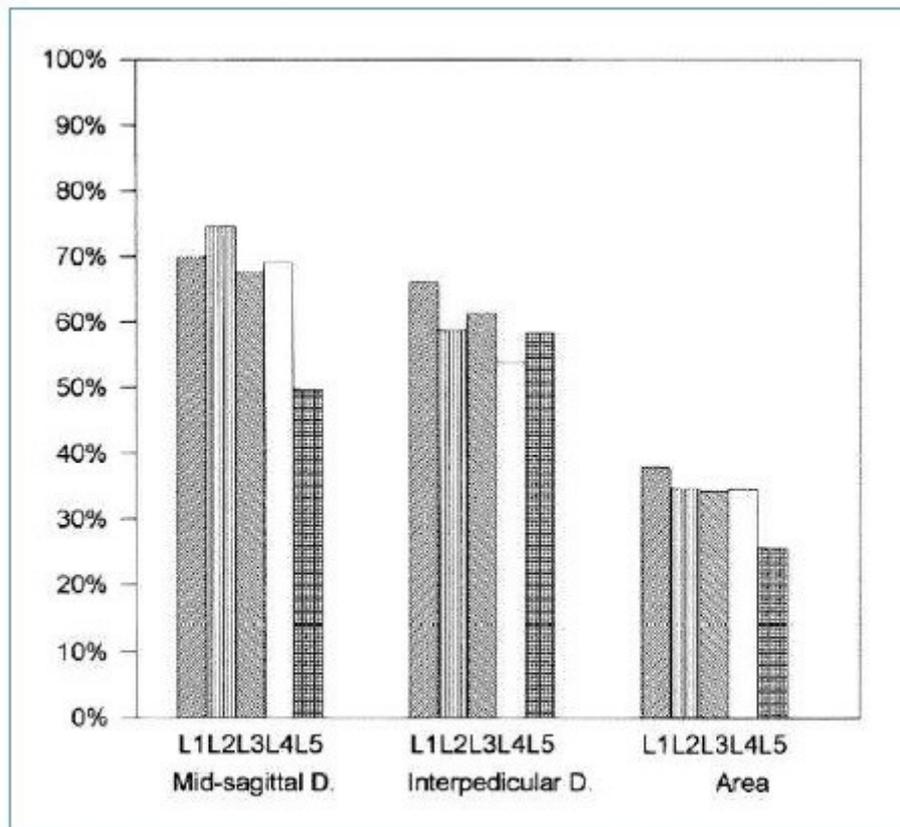


Figure 8. Prenatal growth of the spinal canal.

Graph a: 12th to 40th week of gestation. Graph b: 8th to 24th weeks of gestation.

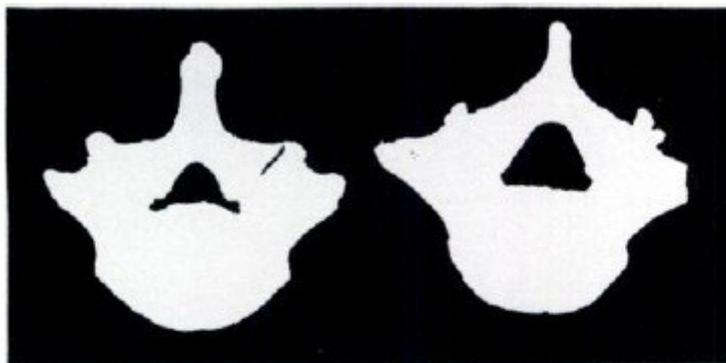


Vertebral canal parameters at birth compared with mean adult size vertebral canal parameters.

Figure 9.

The trefoil-shaped canal

Trefoil configuration is normally found at L5 level and generally does not appear until adulthood (25). An anatomico-archeological study demonstrates that the trefoil shape is not present before puberty (20). Trefoil-shaped canals are not observed in newborns because of the dome-shaped spinal canal (26).



The midsagittal diameter of the trefoil canal (left) is smaller than that of the normal canal (right).

Figure 10. The trefoil-shape.

The midsagittal diameter in the trefoil canals was found to be significantly smaller in stenotic canals than unaffected vertebral foramina (25). At 4 years of age, when the interpedicular diameter is still growing, the midsagittal diameter is almost larger than adult's one. Often, by the age of 6, the anteroposterior dimension begins to have a little decrease until the adult size. This reduction is related to the changing shape of the canal. One of the elements which contributes to the shape of the canal is the anterior border: it is concave in infancy and it becomes convex in the adult. Considering the increases of the interpedicular diameter and of the perimeter, the canal must change shape after the midsagittal diameter and the cross-sectional area have finished their growth (21).

Some studies suggest that there is a relation between trefoil spinal canal and symptoms of root compression: the trefoil spinal canal is a common finding in developmental spinal stenosis (26). Often radiologic findings of the trefoil shape are related to low back pain (21). In the case of trefoilness at level L5, some characteristics are present: smaller midsagittal diameter, lower recess depth, longer spinal nerve foramen, and shorter pedicles. The interpedicular diameter is similar to the one of not-trefoil canal, consequently less important to the development of trefoilness (20,26).

The trefoil shape is no more common in the spines of the elderly subjects. That is why it was supposed that the trefoil configuration of lumbar vertebral canal has developmental origin and is not a consequence of degeneration process (25). Considering that midsagittal diameter matures early and does not significantly modify during adulthood, it was suggested that patients with trefoil-shaped canals were born with sagittally smaller canals (21).

A key element: the neuro-vertebral relationship

At the fourth week of gestation the spinal cord is surrounded by its primary meningeal layer, undifferentiated mesenchymal cells. The differentiation of these cells occurs approximately during the sixth week, from the cervical region to the craniocaudal direction. The pia-mater and arachnoid begin to be recognizable. A "primary pavement" lines the vertebral canal: it's the rudiment of the dura-mater (or embryonic dura mater), present more or less at the seventh week. (27).



Separation of the primary meningeal layer of the spinal cord into two layers in a human embryo of 15 mm crown-rump length. 1) Vertebral body; 2) spinal cord; 3) zone of separation of mesenchyma into layers; 4) primary pavement of vertebral canal; 5) rudiment of pia mater of spinal cord. Sagittal section through spine, cervical segment. Hematoxylin and eosin. Objective $\times 8$; ocular $\times 7$.

Figure 11. Primitive structures of spinal canal.

During the embryonic and fetal periods the growth of vertebral column is impressive (28). At the beginning, during the embryonic period, the vertebral column and the neural tube grow in a synchronous way. It is from the fetal period that the vertebral column begins to grow faster than the spinal cord, this one initially ending in sacral position then in the lumbar region (5). The elongation engenders a longitudinal traction. Because of the force more pronounced dorsally, there is a complete dissociation within the embryonic dura mater in two different layers: parietal (external) and visceral (internal) dura mater. The parietal dura mater remains in contact with the vertebrae. In the middle of the two layers an interdural space containing the internal venous plexus takes place (28). The development of the dura-mater is coordinated with the vertebra, which in turn grows depending on the spinal cord (posterior arches) and the cord (vertebral bodies) (27).

Both vertebral canal and spinal cord have a slower development than other organs (heart, kidneys, skin and musculature) but they have a growth rate similar to the brain (13). For some authors it's obvious that the influence of the myelinating matter, the enlarging spinal cord, causes the change of shape of young malleable vertebral canal (29). There is experimental evidence that the vertebral growth depends on the nervous substance. The tight spinal canal appears to result from a failure of the latter neural function leading to overgrowth of the bony structures. The growing brain influences size and shape of the cranial vault and the same kind of relationship could be hypothesized for the spinal cord and the vertebral canal. The availability of space between the nervous and the bony tissues is a morphogenetic factor. The departure of the nerve roots of the cauda complex significantly reduces at L5 level. At the same time a pronounced braking effect of the massive L4 and L5 is present and it exerts a lateroventrally directed pressure contributing to the development of the triangular-trefoil shape (30).

In 1952 H. Holtzer observed that a reduction of the spinal cord mass in amphibian embryos provokes an increase of the number of surrounding precartilaginous cells (30). According to the works of Brain & Walton (1969) and Vassilopoulos & Spengos (1975) there is an association between atrophic spinal cord and narrow vertebral canal (13).

Ursu and Porter proposed another way to see the neuro-vertebral relationship. A conclusion of their study is that there is a close relationship between the sagittal diameter of the vertebral canal (in the study L1) and the diameter of the brain, which suggests that the vertebral canal is a permanent marker of the neural development (12).

Movements and spinal canal

The mid-sagittal diameter of the lumbar canal is greatest at L1 level. The lower end of lumbar enlargement of the spinal cord is located at the first lumbar vertebra level and this is the transitional site from the thoracic to the lumbar segment. L1 level coincides with the region of

functional transition between the relatively immobile thoracic spine and the mobile lumbar segment. By consequence, the diameter of vertebral canal at this level may not only be a reflection of the size of the neurological contents, but also an adaptation to the complex movements of this transitional region (31).

Vertebral growth impairment and others structures

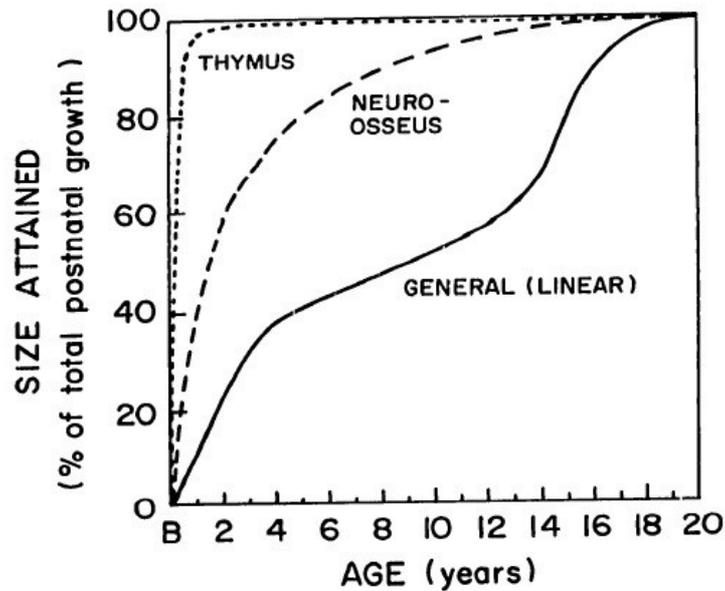
The mesoderm is also responsible for the development of dermis, connective tissues, skeletal muscles and bones. Furthermore it is involved in the formation of urogenital, pulmonary and cardiac systems. A defect of the vertebral development may be associated to other organ system impairments. It seems that the genitourinary system is the most frequently involved system with congenital spinal defects (4).

A study found that cardiovascular and gastrointestinal symptoms were more common in men and women with smaller canals, but there was no significant difference concerning respiratory systems. A relationship between the bone mineral content and the sagittal diameter of the lumbar canal in girls was established (32).

It was considered that the catch-up growth of the long bones (or simply the physiological postnatal growth) mask the presence of a narrow spinal canal: externally a person could be antropometrically not affected (24).

The immune system

The growth curves of thymus and central nervous system are comparable with the neuro-osseous development. By consequence an adverse environment could affect the immune and the neuro-vertebral structures. A study was designed to search a relationship between immune maturity and the anteroposterior diameter of the thoracic spinal canal. The result was a significant correlation of T7 sagittal diameter with the serum levels of thymosin- α 1, which let us suppose a lower thymic function. Thymosin- α 1 was considered a good predictor of immune maturity (24).



Thymus gland, neuro-osseous, and general (linear) growth from birth to adulthood (Scammon 1930; Steinman 1986).

Figure 12. The similar growth of thymus and neuro-osseous structures.

Obstetrical, antenatal and pediatric factors

Between 16 and 40/41 weeks of gestation the area and volume of the vertebral canal show a close correlation to the gestational age. In the same way a correlation could be found with femur length, abdominal and head circumferences (33,34). Like the spinal canal, the head circumference is particularly sensible to prenatal growth disruption (1).

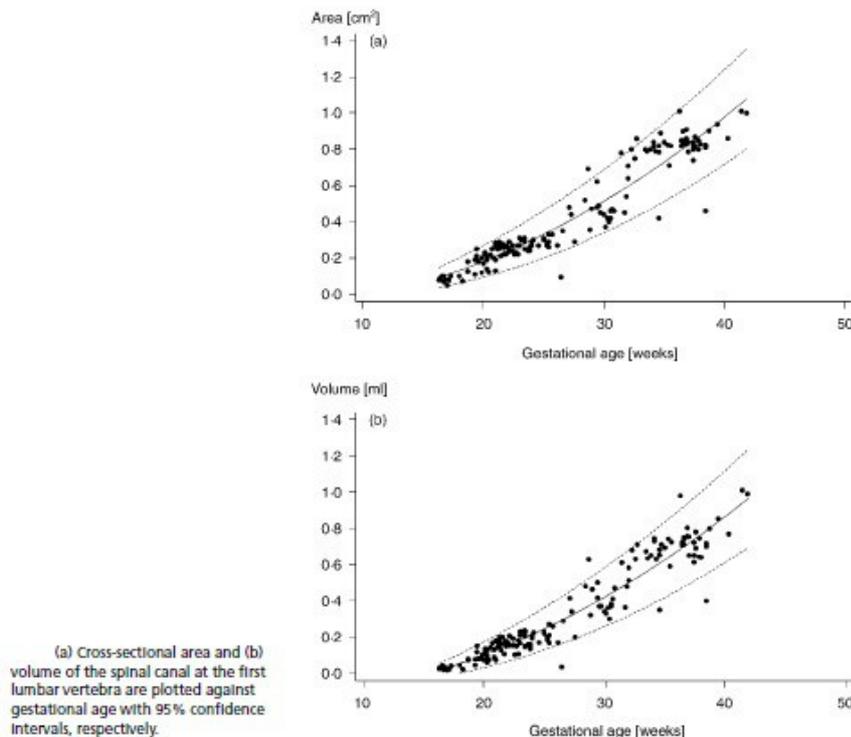


Figure 13. The growth of the spinal canal correlated with the gestational age.

Sagittal diameter and cross-sectional area are related with a low birthweight. In this case the growth retardation in utero is more influential than the length of gestation. Also low placenta weight and lower socioeconomic class of the family were considered related with a narrower canal (22). An older maternal age also seems to be significant (24).

Parity could be relevant in affecting the canal size: the first-born seems to have smaller canals than the subsequent brothers. Randomly or not, the birthweight of the newborns increases from the first to the second pregnancy (24). But not all studies agree with the influences of the parity.

Not surprising, smoking during pregnancy may reduce significantly canal perimeter and cross-sectional area.

Furthermore, no significant relationship was found with maternal height and age, child stature, maternal hypertension, vaginal bleeding, infection and anemia. In 10-years-old children no correlations were observed between smaller vertebral canal and the mean height, weight, head and middle upper arm circumferences (22). Considering the antenatal factors that may influence the vertebral canal size, it was noticed that L3 level (followed by L4 and L5) is the most affected by adverse antenatal factors. Lumbar spinal stenosis is particularly frequent at L4-L5, whereas for L4-L5 and L5-S1 disc protrusions are more common (24).

Genetic considerations

Morphological studies show differences between vertebral canal diameters of different races or populations. Significant differences in cervical canal dimensions are correlated to the ancestry and to the sexual dimorphism (17).

A genetic influence is always present, but is hard to know how strong it is. South African blacks have smaller canal diameters than Whites, but there is no difference in vertebral body size (1). White populations have the widest cervical canal and Japanese population the narrowest (35). The mean sagittal diameter of the lumbar spinal canal in the Korean population is smaller if compared to White and African populations, but there are no significant differences in the transverse diameter between the Korean, White, and African populations (31).

The size of the spinal canal is not necessarily related to the size of the vertebrae. However a tall stature was correlated with larger vertebral bodies and the presence of more spaced pedicles (36).

A recent genetic study performed on mice demonstrated that there are different pathways implied in the etiopathogenesis of the lumbar spinal stenosis. Activating mutations of the

fibroblast growth factor receptor 3 (FGFR3) cause different forms of pathologies, e.g. achondroplasia. Researchers discovered that by inactivating extracellular signal-regulated kinase (ERK) 1 and ERK2, pathways activated by FGFR3, they could improve the mice spinal canal size (37).

Diet

A study measuring magnetic resonance images by computerized analysis found that the perimeter measured by computerized analysis of the vertebral canal was considered the most sensitive vertebral measure to the environmental factors (24). An archeological study, comparing populations with different quantities of protein intake, found a significant decrease in canal size. The population with poor protein diet has a smaller vertebral canal. The sagittal diameter was more affected than the transversal, probably due to the minor catch-up growth potential. The lumbar segment was more affected than the thoracic one (1).

Dental hypoplasia and Harris' lines (transverse lines at the growing ends of bones considered a marker of illness) were associated with a smaller interpedicular diameter in the lumbar region. Dental hypoplasia is related to the nutrition state throughout the development of dentition. Therefore, the canal size could be a marker of a constant malnutrition during the pediatric age (20).

Socioeconomic factors

Past studies could not find an association between smaller vertebral canal and impairment of health or poor academic ability (22). A study tried to find a correlation between scholar performances and canal size and the authors reported a tendency suggesting that children with larger canals have better performances. But these results were not significant and apart from that, there might be several bias between scholar abilities, socioeconomic class, malnutrition, poor health and other factors which influence primarily or secondarily the neuro-vertebral growth (36).

The type of occupation determining bio-mechanical stress and the aging of the patients seem to have no significant influence on the size of canal without degenerative affections (1).

Comparing with gorillas and chimpanzees

A paper of comparative anatomy demonstrated a significant difference in size and shape of lumbar vertebral canals between gorillas, chimpanzees and humans. In the adult human spine, the lumbar canal area decreases from L1 to L4 and increases at L5. This last increase is not present in gorillas and chimpanzees, where there is just a proximo-distal decrease. Both primates spinal canal have interpedicular diameter and area that decrease. Still

considering the cranio-caudal direction, the midsagittal diameter reduces in gorillas, but increases in chimpanzees.

The two compared primates have a midsagittal diameter 50% greater than the interpedicular diameter, whereas in the human body the proportions are inverted (32).

4. DISCUSSION

The mesodermal origin

The spinal canal wall has a mesodermal origin which allow to hypothesize that if there is a growth impairment other mesodermal-related structures are might be affected too, orienting us logically to the VACTERL association: Vertebral, Anal, Cardiovascular, Tracheo-Esophageal, Renal-Radial and/or Limb anomalies.

The relationship between ectodermal and mesodermal tissues is very interesting. A little spinal cord entails a smaller vertebral canal. The shape of the canal depends on the size and position of the nervous tissues. This influence of ectodermal cells on the bone is not exclusive to the nervous system. It is well know that tooth enamel (or the crown of the dental follicle) has also an ectodermal origin and participates to the eruption process, which needs an osteoclastic effect.

Blood vessels and ossification

Primary ossification centers develop thanks to blood vessels which appear before the third month of gestation. Cartilaginous tissue needs less blood supply than bony tissue, but the potential final growth size is lower. These observations underline how important are oxygenation and nutrients for the growth of spinal canal. It seems obvious that all factors affecting blood composition or supply are determinant to the canal development.

Why does the neurocentral synchondrose closes?

The fact that the closure differs between the levels of vertebral column is compatible with the several growth potential. Differences between vertebrae are mainly due to genetic factors, as proven by all the discoveries regarding Sonic Hedgehog Homolog, Hox genes, etc. The ossification centers closures in the different bones are actually used to determine the age of a person. Bone age assessments are conducted even in case of malnutrition, which lets us suppose that it is not possible to extend the period of growth further on: the only possibility to

avoid some stenotic conditions is by preventing and to improving influencing factors during growth (always concordant with the catch-up theory).

A stenosis with a premature closure of NCS could be due to a physical trauma of the physis (e.g.: pedicle screws) or particular genetic conditions, like the Hunter disease (9,38). It might also be possible to include alimentary deficits, but they should seriously affect the biochemical pathways influencing the ossification.

The fusion of the half posterior arches

The importance of this event was more frequently related to the spina bifida disease. The role that it plays in the determination of the canal size is up to date not so clear and was considered less relevant than the role of the neurocentral junction.

Mechanical effect on ossification and the price of the upright standing

Shear stresses promote enchondral ossification, and intermittently applied hydrostatic compression inhibits or prevents cartilage degeneration and ossification (8,24). It was suggested that the pattern of ossification can be correlated with the muscular activity and fetal movements (6).

As previously seen in the anatomical comparative study there are important differences between canal parameters of semi-upright and upright beings. One possible explanation could be the position and size of the neural contents of the spine. Perhaps muscular traction or gravity have a bigger role. A child learns to stand up until 5 years of age, and under the influence of neurological maturation the vertebral curves develop. Consequently to holding the head straight, the cervical curvature appears at approximately 3 months of life. At 6 months the child keeps his trunk upright and the dorsal kyphosis appears when the lumbar lordosis begins to develop at age of 14-16 months, influenced by the upright standing (39). The upright standing implies a change of the forces applied on the vertebral column. By consequence it should be asked: "Could a precocious or late upright standing in child prevent or worsen a smaller spinal canal predisposition?". A recent study goes in the same direction observing that prolonged and repeated upright posture promotes the bone formation of rat lumbar vertebrae (40).

Another consequence of the development of spinal curvatures is the variation of the tractions and trajectories of spinal nerves. Variations on the symptomatology and radiological presentations in the population might be due to the different anatomical positions of the nerves which cannot be easily seen on radiological images.

Catch-up growth potential

It seems that the catch-up growth potential increases in a craniocaudal sense. The achievement of adult canal size can be observed soon in cervical, then thoracic and finally lumbar vertebrae. In the lumbar segment L5 more potential than L1-L4 can be observed. If we consider that this characteristic is merely genetic, the consequence is that, on the one hand we cannot prolong the period of growth of the canal to prevent stenotic conditions. On the other hand, trying to improve all the antenatal and postnatal factors could be more effective.

The interaction between tissues

The neuro-vertebral relationship is a seducing hypothesis but the actual knowledge is probably not sufficient enough to lead studies to strong conclusions. It would be interesting to have more information on histological and biochemical interactions among the cells of bone, periosteum, dura-mater, arachnoid, pia-mater and white/grey matter. The complexity surpasses the limit of this work but it makes no doubt that literature related to the subject can be found.

Trefoil-shape

Up to now, only a few researchers have spoken about the trefoil-shape. The shape is often associated with the development of smaller or stenotic spinal canal. But how could such information be clinically useful?

The trefoil-shape was associated with developmental stenosis, but it cannot be observed before the adult age. The development of the spinal canal is accomplished before this age, casting doubts in how the trefoilness could be related to a developmental stenosis. That is why we could rather say that the trefoil-shape is associated with smaller canals allow a better visible the change of shape. The “excavation” of the nerves in the bone is more evident when the canal is smaller. So trefoilness is an anatomical characteristic consequent to a lower potential of osseous growth inhibition or to a smaller nervous mass, which would clinically not help to diagnose lumbar spinal canal stenosis that much.

Canal growth impairment associated with other structures

In some cited studies it was attempted to find if there is an association between smaller spinal canal and other hypoplasias or hypofunctions. Knowing that diet or environmental factors are crucial to ensure a normal development, it is difficult to determine significance or relevance. In other words, the previously mentioned factors can have an effect on the entire human body, so the association might be considered without relevance.

Thinking about the fact that organs and tissues can have different moments and potentials of (catch-up) growth, a past impairment of the whole body can be hidden. That is perhaps the reason why some studies “failed” trying to find some association.

Smoking during pregnancy

It is recognized that smoking during pregnancy allows more chances to develop obstetrical or neonatal disturbances. As said in the previous paragraph, the effect of the presence or absence of a factor can have stronger general consequences than only one association. For example, in the case of smoking during pregnancy, we know that there are more probabilities to have low birth weight or premature births ostensibly caused by an insufficient oxygenation of the placenta.

Difference between ethnic groups

Sizes and heights differ depending on the genetic factors but there might be misleading circumstances. There is the necessity of all life conditions being equal during pregnancy and the pediatric age. Cited differences between South African blacks and Whites are surely possible but can we affirm that in the past diet or socioeconomic conditions were the same for all?

Diet is important but not so studied

There is a clear connection between protein intakes and the size of the spinal canal and, not surprisingly, proteins are very important to the brain development. But limiting it all to the protein intakes is unsatisfactory. Vitamins or other substances may be essential to a good neurological development. For an example Vitamin B1 is essential for the nervous system growth. This is also valid for the osseous development. An another example is Vitamin A, that may provoke an hyperostosis (without mentioning the teratogen effect).

The real problem is probably the difficulty to design a good study: measuring nutrients intakes and having delayed results complicate the task.

The problem of retrospective studies

Studying the factors influencing the spinal canal growth requires a long observation period. Therefore the majority of studies are performed retrospectively, limiting the possibilities to choose measures or anamnestic data. Creating a cohort is usually expensive and it might require a long-term collaboration between orthopaedic, neonatology, paediatric, radiology

specialities or other hospital services.

“Natural” prevalence of stenotic canals

The distribution of measured values of the spinal canal can be described by a Gaussian curve. If we consider the dimensions of spinal canal as a parameter like body height, developmental stenotic canals might be the lower extremity of the curve. Body height and measures of the vertebral canal are not clearly related but they might be the reflection of a non-pathological genetic condition.

Canal evolution

Socioeconomic, environmental or health situations change constantly. Concerning these conditions, there was great improvement of different human populations in the past. Perhaps the improvement of the factors influencing vertebral canal growth may have decreased the incidence of smaller developmental canals. If this hypothesis is true, in the close future, incidence of spinal canal stenosis would decrease too (except if we consider the phenomenon of overdiagnosis). No studies were found about this possibly recent evolution.

Prenatal versus postnatal: equally important?

According to past studies, the growth of spinal canal is more important and faster during the prenatal period. The consequence is that clinicians may find the effect of a prenatal growth impairment more relevant.

But by observing the data of a recent retrospective radiologic study concerning lumbar spinal stenosis (3) and thinking about the information collected in this work, the importance of the postnatal growth might be re-evaluated.

The sample of this study consisted of 93 patients divided in low back pain, conservatively treated (No Operated) and surgically operated groups. MRI measurements of the vertebral canal were effectuated at the pedicle level. The average of spinal canal areas at pedicle level were calculated [Table 2] and plotted in a chart [Figure 14].

Areas	L1 Average	L2 Average	L3 Average	L4 Average	L5 Average
Low Back Pain	2.51	2.75	2.44	2.21	2.14
No Operated	2.67	2.57	2.34	1.93	1.85
Operated	2.54	2.31	1.88	1.53	1.38

Table 2. The mean vertebral canal areas measured at the pedicle level.

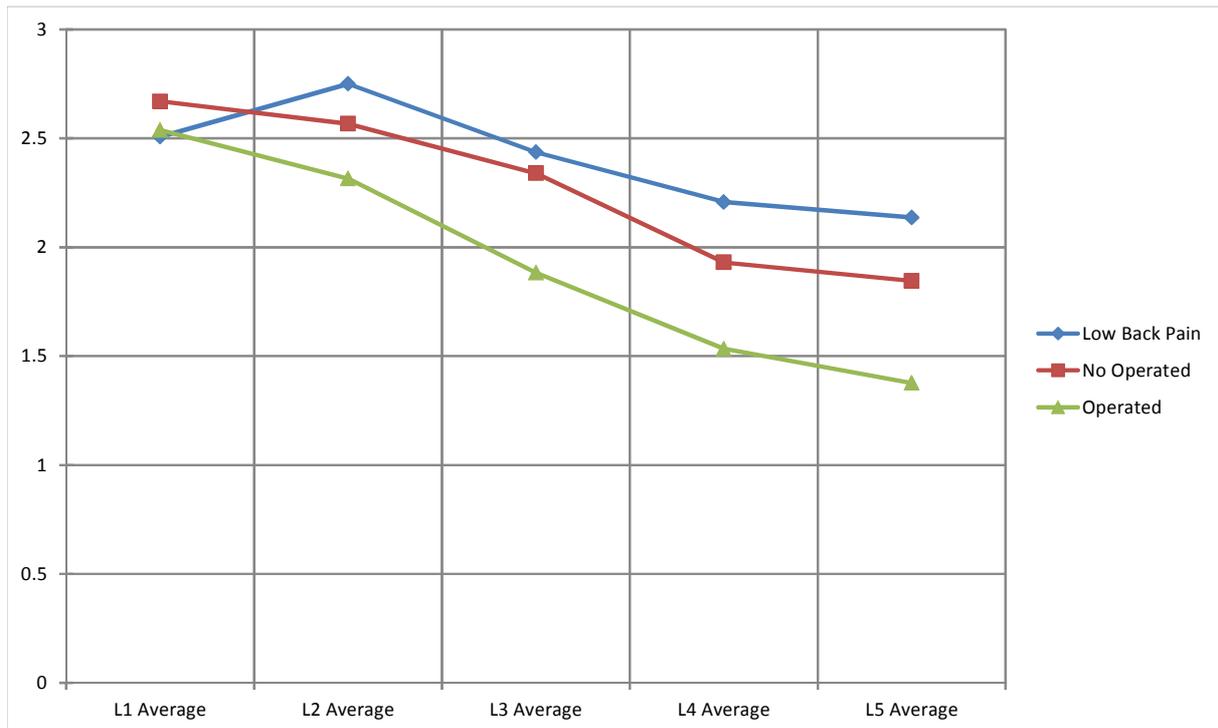


Figure 14. Average of the spinal canal areas. (to note that L1 Low Back Pain group area was calculated on a sample of only 4 patients which might explain the lower result.)

First of all, considering that surgically treated patients are generally more symptomatic than conservative treated patients, the chart shows a tendency: the more a person is clinically affected, the more lumbar spinal canal areas might be smaller. A second and more interesting consideration is that the stenotic tendency increases (almost constantly) in a cranio-caudal direction: the difference between the Low Back Pain group and the surgically treated group areas appears greater in the distal lumbar levels. The canal area at the pedicles at L5 is normally bigger than at level L4 enforcing the hypothesis of a cranio-caudal stenotic tendency (without a good statical analysis, it ought to be considered just an observation). During the first years of life the caudal levels have a greater catch-up growth potential but it seems though that they are the most affected. So what is the role of a post-natal growth impairment? Like semi-upright and upright primates, the volume narrows from up to down: is it a casualty or is it related to the locomotor development during the pediatric age?

At the same time one must remember that the caudal lumbar portion have other particularities which might explain (partially or not) the stenotic cranio-caudal gradient. For example it is well-known that the lower lumbar region is relatively more involved in mechanical-degenerative processes ("congenital" stenotic-smaller channels were never correlated to anamnesis of heavy works). As already said, another possibility is that all non-degenerative stenotic conditions of spinal canal were due to the individual genetic

particularities, which lessens expectations for a possible prevention.

Aging and the relationship between congenital and degenerative stenosis.

Degenerative spinal canal stenosis are widely more common than congenital stenosis, but logically a smaller vertebral canal (considering the spinal cord mass) offers more chances that degenerative presentations could be symptomatic. Briefly, a congenital narrow canal predispose to spinal stenosis.

With aging, the human body is submitted to different kind of changes. It would be appropriate to hypothesize that the relationship between nervous tissues and vertebral structures have a few modifications. For example, the physiological loss of nervous cells and mass might change the equilibrium of this relationship facilitating the expansion of other tissues. Following the same reasoning, there might exist a genetic predisposition which allows a higher osseous growth comporting narrower vertebral canals and pathologic osseous growth. Another hypothesis is that mechanical traumas breaks this neuro-osseous equilibrium. Another consideration about the aging is the changes of postures and gait. It is reasonable to hypothesize that people with pediatric locomotor troubles are more submitted to changes of posture and gait during their life. With or without mechanical stresses, an effect on the vertebral column and his contents is shown. This can be easily understood by imagining that nerves pass through a stretch canal resulted from years of "excavation-inhibition". A minimal change in orientation of the nerves or of its vertebral container position could press the content. This hypothesis suggests that during the pediatric age incorrect posture and gait unfavorably model the spinal canal, getting caught the nerves in a narrow situation. With aging and with worsening posture and gait, it is no longer possible to change the shape of the canal, which will consequently affect more the nerves.

Limits of this work

As already mentioned, the data collection for this work was limited by the availability at free sources and access of *University of Lausanne (UNIL)* and *Centre Hospitalier Universitaire Vaudois (CHUV)*. The lack of exhaustive information about specific subjects may lead to wrong or at least unprecise hypothesis or conclusions. Moreover, in the selected literature, there was a great variability of methods (different study designs, patient population, etc.). This might increase the incertitude of some considerations, since it is very difficult to draw a conclusion with observations coming from different, heterogeneous sources.

5. CONCLUSIONS

The spinal canal is principally limited by the vertebrae which have a mesodermal origin. The nervous (ectodermal) tissue significantly influences the growth of the canal. The most important structure participating in the spinal canal growth is the neurocentral synchondrosis in almost the entire vertebral column. The fusion of the half posterior arches seems to have less importance for the canal size.

The growth is not homogeneous but, depends on the vertebral level. Timing, rate and growth potentials differ by regions. Especially in the case of the lumbar segment, there is a craniocaudal tendency which entails a greater post-natal catch-up growth for distal vertebrae. Trefoil-shape of the L5 canal is the consequence of a sagittal growth deficiency.

The spinal canal shares some developmental characteristics with different structures and systems, especially with the central nervous system. It may be the consequence of the embryological origin. It is supposed that not all the related structures would be affected by a growth impairment because of the different catch-up potentials. Studies found that narrower spinal canals might be related with cardiovascular and gastrointestinal symptoms, lower thymic function, bone mineral content, dental hypoplasia and Harris' lines. Anthropometric correlations found at birth disappear during the pediatric age.

All factors which can affect bone and nervous growth might be relevant. Genetic predispositions are the only factors that can never be changed but the real impact is to ascertain. During the antenatal period, all the elements determining a good supply of blood and oxygen may influence the vertebral canal development, for example smoking during pregnancy. Diet is a crucial factor having an impact on both antenatal and postnatal growth. Proteins intakes is the only proved dietetic relationship found in the bibliographic research of this work. The mechanical effects due to locomotion changes are unknown. Socioeconomic situation has an impact on several influencing factors and it is difficult to study it owing to numerous bias.

A correct growth of spinal canal is evidently relevant to prevent not-degenerative stenotic conditions. But a "congenital" narrower canal may aggravate degenerative stenosis. This concerns specific groups of patient. If the size of the canal is highly involved in the pathogenesis of common back pains, a hypothetical measure to prevent developmental impairments could have a not-negligible impact on the society.

It would be interesting to study more about dietetic necessities for a good spinal canal development. Understanding the relationship between nervous tissues and vertebra it might be useful in identifying what is needed for the ideal development. Genetic importance and the post-natal influences of upright standing on the canal growth remain unsolved questions.

All these tracks may have a double purpose: knowing if it is possible to decrease the incidence of narrower spinal canal and consequently finding possible preventive measures.

The development of vertebral canal is a complex subject which ranges over a wide variety of fields. The knowledge of this subject is an indispensable tool to understand and hypothesize the influencing factors that might lead to stenotic conditions. Unfortunately, a lack of information makes difficult to have a complete and satisfactory interdisciplinary vision.

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