EMBRYOLOGIC DEVELOPMENT AND KNEE MALFORMATIONS

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EMBRYOLOGIC DEVELOPMENT AND KNEE MALFORMATIONS. REVIEW OF LITERATURE DATA (Abstract) : The embriologic development of the lower limb, including here the development of the knee, it is known to be between 6-8 weeks postovulatory when we can identify the differentiation of the main joint cavities (synovial, cartilaginous, fibro-cartilaginous). During chondrogenesis proteoglicans like versican, tenascin C, aggrecan and hyaluronic acid play a major role and they are well represented in pericondrum. I followed to present the very important stages of the knee development and the same for the malformations of the lower limb. Studying some dissections of human embryos classified with Carnegie (Streeter) stages, and some scientific publications we try to understand better the main cavitation mechanism of the lower limb and the knee, anatomic element structured with the developpement of the femur, patella, tibia and fibula. The developpement disorders of these structures imply congenital patellar syndrome without significant changes in the static of the lower limb, proximal focal femoral deficiency, congenital short femur, tibial/peroneal hemimelia, congenital bowing of the knee. **Key words :** JOINT, KNEE, EMBYOS, MALFORMATIONS

INTRODUCTION

The knee joint is a synovial joint (1). In the embryological development process, between 6-8 weeks of intrauterine life, joint differentiation (synovial, cartilaginous, fibrous) occurs alongside other processes(2). Synovial joints are formed by differentiating mesenchyme. From the central part of it is formed the articular cavity, from the peripheral part results the capsular ligament and other ligaments, from the related structures resulting the synovial membrane (2). In the chondrogenesis process an important role is played by tenascin C and versican markers, the first one being present at the level of the perichondrium of the tibia and femur, while versican is identified at the level of the joint surface and the perichondrium at the level of the tibia. Tenascin C is better represented in the perichondrium of a long bone than versican. The proteoglycan called aggrecan is considered to be a specific marker for differentiated cartilage (3). Studies (4) raise the role of hyaluronic acid in morphogenesis, this glycosaminoglycan being identified in the area between the tibia and the femur in Streeter stage 37 (Carnegie), while the cavitation process is also occurring (4). Hyaluronic acid and its CD44 receptor, glycosaminoglycan in high concentration due to very intense metabolic processes, has a particular role in the cavitation process (5).

The mechanisms of development of the inferior limb and especially of the knee are of a complex nature, involving numerous factors and structures.

DEVELOPMENT OF THE INFERIOR LIMB

The lower limb buds can be highlighted at the end of the 4th week of embryonic development. The first to begin to develop is the inferior limbs for 1-2 days to start the process at the upper ones. The limb buds are formed from mesenchymal tissue derived from the lateral mesoderm, the parietal foil, whereby connective tissue and bones are formed. The distal ectoderm by thickening forms the ectodermal

apical crest. The development of the limbs occurs from the proximal to the distal. The terminal portion of the limb buds is presented in week 6 with a flattened appearance, then the proximal portion undergoes a division process from where two segments result, with the main parts of the extremities easily visible. Chondrocytes form the first types of hyaline cartilage sketching the future bone structures of the extremities. At the cartilaginous condensation level, the joints are formed, the cells in this area increasing in density and number, and cell death has a contributory role in the formation of the articular cavities. The joint capsule is formed by differentiating the surrounding cells. Ossification centers are present from the 12th week of development in the long limb bones. The ossification at the level of the bones of the lower limbs is generally complete at birth, the epiphytes being of the cartilaginous type, the ossification centers at their level appearing in a short time after birth (6).

Next, I will present knee development stages as well as some of the more common malformations of the knee joint structures, malformations involving changes in the femur, patella, tibia and fibula, which in turn cause changes in the static of the inferior limb and changes of walking in adult life.

By studying numerous dissections performed on embryos at different stages of development, significant data were extracted to understand the formation of different knee structures, as well as the main knee malformations. The Carnegie criteria were used to delineate the knee development periods as accurately as possible, taking into account the age of the embryo expressed in postovulatory weeks, as well as the size of the embryo.

KNEE DEVELOPMENT ASPECTS

The chondrification process starts at 5 weeks at the level of the lower limb skeletal parts. At 6 weeks, the chondrification process begins in the fibula, the tibia and the femur, structures that are in the form of a condensation of the mesenchyme, the knee joint presenting as a condensation of the blastic cells (7).

The patellar ligament is in the process of differentiation and can be identified in embryos, the chondrification process being more advanced. At this stage of development, the peroneum and the femur are relatively close to each other (7).

Around the age of 7 weeks (46 days postovulatory), the femoral condyles are formed, between the tibia and the femur being a homogenous blastemal interzone. The formation of the fibular collateral ligament in the form of a cellular condensation is noted, and in some embryos at the same stage of development, the tendon of the popliteal muscle is evident. The patellar ligament can be seen in all Streeter 19 embryos (7).

Fibula is even closer to the femur. The cruciate ligaments formation is observed by a slight cellular condensation (7).

Also around 7 weeks of age, tibial and femoral condyles are observed, in some embryos, these structures fuse with the area between the two structures that form the knee joint. When condyles are in the process of chondrification, the inter-zone between the tibia and the femur is better defined. The lateral tibial zone in the process of conditioning can be seen better between theperoneum and the femur. The patella is highlighted as a cellular condensation, having a characteristic form. At the same time, fibular collateral ligament, tibial collateral ligament and popliteal muscle tendon are formed. The lateral meniscus as well as cruciate ligaments can be noted. The patellar retinaculum can be seen in all embryos at this stage of development (7).

Around 7 1/2 weeks (51 days postovulatory), the tibial and femoral condyles are well defined and have a cartilage structure. The interzona is presented as having three layers. The patellar retinaculum appears at the same time as the patella which undergoes the chondrificationprocess. The development of the tibial collateral ligament is difficult to distinguish due to its smaller dimensions, instead, the fibular collateral ligament and the popliteal muscle tendon can be readily studied. Simultaneously with blood condensation, blood vessels in the periphery of the knee can be observed (7).

In 8-week embryos (53 days postovulatory), the tibia, femur and fibula are cartilaginous, well represented. The layers of the area between the femur and the tibia, chondrogenic structures, begin to unite. The knee joint begins to resemble that of an adult, it is vascularized, the tendons have cellular structure and are well differentiated, the cruciateligaments have cellular structure, both meniscus can be identified, the lateral meniscus cells being better oriented. The collateral ligaments are present in the form of cellular condensation (7).

In embryos at 56 post-delivery days, the knee joint is increasingly similar to that of the adult, both as an arrangement and as a form (7).

In the 9th week continues the process of formation of the meniscus, the cavities of the meniscotibial and femuromeniscal joints are finalized, along with these structures being identified a few connective tissue tracts. The patella is disposed differently from the above-mentioned elements, and is articulated with the side condyle. The triangular space formed under the patella is occupied at this stage of mesenchymal tissue, being the first stage of adipose tissue formation at this level. Meniscus are attached to the capsule by means of meniscal ligaments (8).

Week 10 and 11 show slight changes from week 9a. The first to form at this stage is the upper tibiofibular articular cavity, with a link between it and the meniscus-tibial lateral cavity. Continuing the development of the medial meniscus, which causes new changes in the femoral-meniscal and menisc-tibial joints. On the antero-superior surface of the tibia is attached the anterior horn of the medial meniscus. The lateral meniscus is fairly well differentiated, its formation also influencing the position of the meniscotibial and femuromeniscal joints (8).

Weeks 12 and 13 are evidenced by the fact that the knee has an articular cavity that resembles that of the adult, the communication between the superior tibiofibular cavities and the lateral meniscotibial cavity disappears. The ossification process begins at the epiphyseal level during the 13th week, the most obvious being in the upper portion of the tibia and in the inferior part of the femur. The pericardial zone of the condyles is invaded from superficial to deep cartilaginous channels, which at the femoral level penetrate through the deep portion and through the edges of the intercondylar notchof the femur. At the level of the tibia they penetrate the edges from the upper and the anterior (8).

At week 14, the onset of the patella ossification has been observed, with cartilaginous canals penetrating through the superior and anterior joint surfaces (8).

DEVELOPMENTAL KNEE DISORDERS

In terms of knee development disorder, we discuss the congenital abnormalities of the femur : coxo-femoral dysplasia, short congenital femur, tibial / peroneal hemimelia, congenital tibial curvature, congenital defects of the knee, all of these disorders having an impact on knee functionality.

Coxo-femoral dysplasia represented by lack of acetabular cavity or femoral head. From the clinical point of view, the segment of the thigh is shortened, the leg being rotated laterally and abducted, hip and knee flexion often irreductible as age is more advanced (9). The Aitken classification is the most used to express degrees of severity :

A. The acetabular cavity is normal, the femoral neck and head are present, a small portion of the proximal femur is missing (10).
B. The acetabular cavity is normal or has a minimal degree of dysplasia, the femoral neck and head are present, and a larger portion of the proximal femur is missing (10).
C. The acetabular cavity has severe dysplasia, the cervix and the femoral head are missing or have severe hypoplasia, even a large portion of the femur is missing, the proximal portion of the femur being tapered (10).
D. The most severe form, the acetabular cavity, the head and the femoral neck are missing, and the remaining femur portion is very short, deformed and often fused with the tibia (10).

In Forms A and B, the coxa vara and femoral neck retracing occur frequently, coxa vara being often a progressive form, while femoral head retracing is confused with congenital hip dysplasia. Femoral states may have a flattened, hypoplasic appearance (10).

The most commonly used methods of investigation are MRI and ultrasound, which can show the type of tissue (cartilaginous, fibrous, fibro-cartilaginous) as well as the loss of continuity, un-structured structures and other structural defects (10).

Congenital shortened femur

From a clinical point of view it is considered that the affected foot is not as shortened as in the coxo-femoral dysplasia, it is abdus and rotated laterally in relation to the hip and the knee flexed. The deformities of flexion are not so severe and resolve after the first year of life. Deviations in the ankle and anteroposterior laxity of the knee are observed, the ligament laxity at its level becoming more apparent as the

flexure is reduced. The acetabular cavity often has a normal appearance. The femoral head and head show retroversion and deviation in var, the radiological image leaving the impression of a congenital hip dislocation. Around the age of 2 years, the proximal portion of the femur suffers an ossification process, which shows some degree of coxa vara and the very good development of the great trohanter. In these patients, the length of the femur is between 40-60% of the normal femur, so some will not have significant knee and hip flexion, which will allow the extension of the foot and thus as close as normal (9).

What can be noticed is the difficulty in achieving the medial knee rotation. Surely the most affected will be children whose femur length is 40% of the normal value, and it is necessary to use an orthosis to help the full knee extension, which is made harder by the excessive distance between the leg and the support surface (9).

Congenital patellar syndrome

The patella is considered to be the largest sesamoid bone in the thickness of the quadriceps muscle tendon that has the role of protecting the knee joint's cartilage during extension and to facilitate the quadriceps muscle extension function. Congenital patellar syndrome is a rare, non-disabling disorder. The frequency of this syndrome is 1 per 10000 births, although it is difficult to tell this at birth because the patella has a cartilaginous structure at birth and the ossification process takes place after 2 years (11).

The congenital absence of the patella without other bone abnormalities is often accompanied by lateral dislocation of the extensor mechanism or quadriceps muscle agenesis. Lack of development occurs in trisomy 8 or is caused by mutation in a single gene (11).

Dorso-ventral asymmetry of the inferior limb is explained by the interaction between mezenchim and ectoderm with the Lmx1b gene expressed in the dorsal mesenchyme, Wnt7a expressed in dorsal ectoderm. Ent7a induces Lmx1b expression that results in the formation of distal and proximal structures at the dorsal level of the limb such as the nail bed and the patella. The expression of the Lmx1b gene was identified in the patellar mesenchyme where the patellar tendon and the patella are formed. Mutations of these genes result in lower limb malformations such as shorter metatarsal, absence of patella, and others (11).

The patellofemoral joint is a structure that provides stability to the knee. The treatment is surgical intervention by the release of tissue tension, correction osteotomy, alignment procedures, quadriceps muscle plasty. The recovery physician intervenes postoperatively to prevent possible vicious positions and retractions (11).

Tibial hemimelia

Malformed tibia, shortened and in some cases even absent. The literature also shows tibial-hemimelia accompanied by other malformations such as abdominal hernia, cranioschisis-especially at the frontal level where meningocele originates, defects of the reproductive apparatus, lack of fusion of pubic symphysis (12).

Tibialhemimelia has also been identified in Langer-Giedion syndrome, the TRPS II gene being in contiguity with the gene involved in limb development, undergoes mutations that lead to tibialhemimelia (13). The most commonly proposed treatment is amputation, but in cases where it is not desired to use the Lizarov external fixator (for type 1 tibialhemimelia) as well as synostosis of the fibula and tibia followed by elongation of the femur (for type 2 tibialhemimelia) (14). When tibial malformations are accompanied by fibular hemimelia, following the elongation procedures, a tibial growth deficit was observed which demonstrates the difficulty of predicting the efficacy of the tibial elongation method (15).

DISCUSSION

The present study is a synthesis of data in the literature on knee development, from cell differentiation, from limb formation to formation of an adult-like joint. The period in which the limbs are formed in the embryo is between 3 and 6 weeks after fertilization (6-8 postovulatory). The study of knee joint formation by understanding the phenomenon allows visualization of variations in embryo formation. The biochemical data presented show the implication of specific proteoglycans with a role in chondrogenesis : versican, tenascin C, aggrecan and hyaluronic acid, quite well represented in the perichondrium. We followed the presentation of the main stages of knee development as well as the most important malformations resulting from this complex process involving

both individual and environmental factors. We understand that impairment of the metabolism of these proteoglycans is the basis for the occurrence of congenital malformations of the knee, malformations represented by the absence of a round, most of the time without resonance in the stale of the lower limb, absence of proximal femur or short congenital femur and other disorders tibia and perone : tibial / femoral hemimelia, curved tibia.

BIBLIOGRAPHY

1. *Gray's Anatomy*, *The Anatomical Basis of Clinical Practice*, Thirty-ninth edition, Elsevier LTD 2005, ISBN : main edition 0 443071683, pag 1471.
2. *Embriologia Clinica*, El Desarollo Del Ser Humano, K.Moore, T.V.N. Persaud, 7th Edition, Elsevier Espana, 2004, pag 385-386.
3. Masahito Yamamoto, Hiromasa Takada, Takeshi Takayama. *Cartilage attachment morphology of the fetal cruciate ligaments of the knee : an immunohistochemical study using human fetal specimens*, Okajimas Folia Anat. Jpn., 93(2) : 67-72, August, 2016
4. Fiona M. Craig, Michael T. Bayliss, George Bentley and Charles W. Archer „A role for hyaluronan in joint development", *J. Anat.* (1990), 171, pp.17-23, with 2 figures, printed in Great Britain.
5. J.C.W. Edwards, L.S. Wilkinson, H.M. Jones "The formation of human synovial joint cavities : a possible role for hyaluronan and CD44 in altered interzone cohesion", *J. Anat.* (1994), 185, pp. 355-367, with 10 figures, printed in Great Britain.
6. T.W. Sadler, *Langman's Medical Embriology,* Twelfth Edition, 2012 Lippincott Williams and Wilkins, ISBN 978-1-4511-1342-6, pag 151.
7. Ernest Gardner and Ronan O'Rahilly, "The early development of the knee joint in staged human embryos", *J. Anat.* (1968), 102, 2, pp. 289-299, with 16 figures, printed in Great Britain.
8. Juan A. Merida-Velasco, Indalecio Sanchez Montesinos, Joaquin Espin-Ferra, Jose F. Rodrigues-Vazques, Jose R. Merida-Velasco and Juan Jimenez-Collado,"Development of the human knee joint", *The Anatomical Record* 248 : 269-278 (1997).
9. R. Gillespie, I.P.Torode, „Classification and management of congenital abnormalities of the femur", *The Journal of Bone and Joint Surgey*, vol.65-B, No.5, November 1983.
10. A. Bergere, E. Amzallag-Bellenger, G. Lefebre, „Imaging features of lower limb malformations above the foot", *Diagnostic and Interventional Imaging* (2015) 96, 901-914.
11. J. Terrence Jose Jerome, M. Varghese, B. Sankaran, „Congenital patellar syndrome", *Romanian Journal Of Morphology and Embryology* 2009, 50(2) : 291-293.
12. J.-M. Lapointe, S. Lachance, and D.J. Steffen, "Tibial hemimelia, Meningocele, and Abdominal Hernia in Shorthorn Cattle", *Vet. Pathol* 37 : 508-511 (2000).
13. Cathy A. Stevens , Cynthia A. Moore, "Tibial hemimelia in Langer-Giedion syndrome-possible gene location for tibial hemimelia at 8q, *Am. J. Med. Genet* 85 : 409-412, 1999-Wiley-Liss, Inc.
14. Hosny, Gamal Ahmed, "Treatment of tibial hemimelia without amputation : preliminary report", *Journal of Pediatric Orthopaedics B* : July 2005-volume 14-issue 4-pp 250-255
15. Sharma, Mukut M.D, Mackenzie, William G.M.D, F.R.C.S (C) ; Bowen, J. Richard M.D, "Severe tibial growth retardation in total fibular hemimelia after limb lengthening", *Journal of Pediatric Orthopaedics* : July/August 1996-volume 16-issue 4-pp 438-444.

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