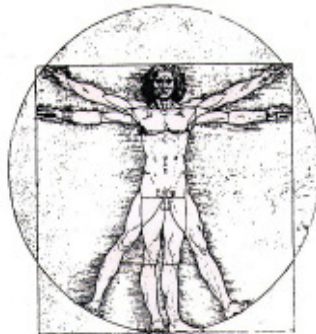


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СОДРЖИНА

9. Анатомија и варијации во издвојувањето на arteria vertebralis. Живадиновиќ Јулија, Папазова М, Матвеева Н, Додевски А, Зафирова Б
14. Варијации во нивото на влез на жрбетната артерија во напречниот отвор. Додевски Аце, Лазареска М, Чадиловска Е, Алији В, Јаневски П
18. Значење на антропометријата на надлактот кај деца на возраст од 7 години од урбана средина и македонска националност во процена на нутритивниот статус. Зафирова Билјана, Наќева Н, Трпковска Б, Чадиловска Е, Живадиновиќ Ј
24. Свиткувачки бразди. Елизабета Чадиловска, Додевски А, Бојациева Б, Зафирова Б, Трпковска Б
28. Улогата на некои антропометриски параметри на фетусот во проценка на гестациската старост. Трпковска Билјана, Лазарова Д, Зафирова Б, Чадиловска Е, Папазова М
32. Покривање на дефекти на преден абдоминален ѕид-приказ на случаи. Новески Лазо, Џонов Б, Мостров И, Мирчевска Е
36. Комплетен подмускулен слој како крајно решение за компликации при аугментација на дојки. Џонов Боро, Даскалов О, Новески Л, Мостров И, Мирчевска Е
42. Ганглион во предел на колениот зглоб - приказ на случај. Џолева-Толевска Розе, Попоска А, Самарџиски М, Георгиева Д, Стефановска Е
45. Yolk sac тумор на овариумот со конкомитантен матурен цистичен тератом кај нулипара: приказ на случај. Стојовски Марјан, Тантуровски Д, Лазарова А, Тантуровски М
48. Хируршки зони на повреди на екстензорни тетиви на шака-современи принципи на хируршкиот третман. Џокиќ Ѓорѓе, Ѓоргиевска Ј, Пејкова С, Тренчев В, Милошевска-Мијалковска М
54. Реконструкција на очните капаци и периорбиталната регија со резанки. Мостров Илија, Новески Л, Џонов Б, Гиноска Т, Росо И
59. Прогностички фактори за појава на метастази кај малигни меланом на екстремитети. Новески Лазо, Џонов Б, Мостров И, Мирчевска Е
64. Употреба на ултрасонографски параметри во разликувањето на конгениталната опструктивна и неопструктивна хидронефроза кај децата. Петровски Миле, Трајковски З, Димов А, Тодоровиќ Л, Симеонов Р, Чадиловски В
71. Третман на фрактури на тибија кај деца со флексибилни ендер-ови клинови. Тодоровиќ Лазар, Петровски П, Петровски М, Димов А, Симеонов Р, Камилоски М
76. Евалуација на функционални и радиолошки резултати после конзервативен третман на скршеници на дисталниот крај на радиусот. Игор Кафтандчиев, Трпески С, Пејкова С, Пендовска Б
81. Аголна корекција со користење конзервативен третман на фрактури на торако-лумбалниот сегмент на рбетот. Трпески Симон, Кафтандчиев И, Митев К, Неделковска М, Каев А
86. Симптоматска епилепсија кај постари лица. Чепреганова-Чанговска Татјана, Лазарова С, Таравари А, Стојчев С

-
90. Вредност на рН на вагина кај пациентки со спонтано предвремено породување. Трајкова Корнелија, Адамова Гордана, Јовчевски Саша, Лазарова Стојовска Александра
96. Радиоизотопен метод за одредување на желудочен транзит на цврста храна. Угринска Ана, Васкова О, Андоновски Б
101. Надополнување на различни днк методи во идентификација на човечки остатоци. Јанкова-Ајановска Рената, Јаковски З, Јанеска Б, Чакар З, Дума А
105. Прогностичка моќ на нормална спект миокардна перфузиона томосцинтиграфија кај пациенти со и без коронарна артериска болест. Вавлукис Марија
111. Гломеруларни болести кај деца во република македонија документирани со бубрежна биопсија. Наунова Тимовска Силвана, Кузмановска Д, Шахпазова Е
117. ИНФОРМАЦИИ ЗА АВТОРИТЕ

CONTENT

9. Anatomy and variations in the origin of vertebral artery. Zhivadinovik Julija, Papazova M, Matveeva N, Dodevski A, Zafirova B
14. Variation in level of entry of the vertebral artery into the transverse foramen. Dodevski Ace, Lazareska M, Cadikovska E, Aliji V, Janevski P
18. The meaning of the upper arm anthropometry at the 7 years -old-children, from urban area and macedonian nationality for assessment of the nutritional status. Zafirova Biljana, Nakeva N, Trpkovska B, Chadikovska E, Zhivadinovik J
24. Flexion creases. Cadikovska Elizabeta, Dodevski A, Bojadzieva B, Zafirova B, Trpkovska B
28. The role of some anthropometrical parameters of the fetus in estimation of gestational age. Trpkovska Biljana, Lazarova D, Zafirova B, Chadikovska E, Papazova M
32. Coverage of anterior abdominal wall defects: case reports. Noveski Lazo, Dzhonov B, Mostrov I, Mirchevska E
36. Total sub muscular plane as final solution for the complications in breast augmentations (case reports). Dzhonov Boro, Daskalov O, Noveski L, Mostrov I, Mirchevska E
42. Ganglion cyst of the knee – case report. Dzoleva-Tolevska Roza, Poposka A, Samardziski M, Georgieva D, Stefanovska E
45. Yolk sac tumor of the ovary with a concomitant mature cystic teratoma in a nulliparous patient: a case report. Stojovski Marjan, Tanturovski D, Lazarova A, Tanturovski M
48. Surgical zones of the extensor tendon injuries of the hand- principals of surgical treatment. Dzokic Gjorgje, Gjorgievska J, Pejкова S, Trenchev M, Milosevska-Mijalkovska M
54. Reconstruction of eyelid and periorbital area with flaps. Mostrov Ilija, Noveski L, Dzhonov B, Gjinoska T, Roso I
59. Prognostic factors for onset of metastases in malignant melanoma of the extremities. Noveski Lazo, Dzhonov B, Mostrov I, Mirchevska E
64. Ultrasonographic parameters in the differentiation of congenital obstructive and non-obstructive hydronephrosis in children. Petrovski Mile, Trajkovski Z, Dimov A, Todorovic L, Simeonov R, Chadikovski V
71. Management of tibial fractures in children with flexible intramedullary ender nailing. Todorovik Lazar, Petrovski P, Petrovski M, Dimov A, Simeonov R, Kamiloski M
76. Evaluation of functional and radiologic outcome after conservative treatment of distal radius fractures. Kaftandziev Igor, Trpeski S, Pejкова S, Pendovska B
81. Angulation correction using conservative treatment of compression fractures of the thoraco-lumbar spine. Trpeski Simon, Kaftandziev I, Mitev K, Nedelkovska M, Kaev A
86. Symptomatic epilepsy in the elderly. Cepreganova-Cangovska Tatjana, Lazarova S, Taravari A, Stojcev S
90. Vaginal pH value in women with spontaneous preterm delivery. Trajkova Kornelija, Adamova G, Jovcevski S, Lazarova Stojovska A
96. Radionuclide technique for the assesment of gastric transit of solid meal. Ugrinska Ana, Vaskova O, Andonovski B

-
101. Complementation of different DNA methods in identification of human remains. Jankova-Ajanovska Renata, Jakovski Z, Janeska B, Cakar Z, Duma A
105. Prognostic power of normal spect muocardial perfusion tomoscintigraphy in patients with and without significant coronary artery disease. Vavlukis Marija
111. Biopsy-proven childhood glomerular disease in Republic of Macedonia. Naunova Timovska Silvana, Kuzmanovska D, Shahpazova E
117. INFORMATION FOR AUTHORS

Списанието АСТА MORPHOLOGICA во целост е достапно на:



АНАТОМИЈА И ВАРИЈАЦИИ ВО ИЗДВОЈУВАЊЕТО НА ARTERIA VERTEBRALIS

Живадиновиќ Јулија, Папазова М, Матвеева Н, Додевски А,

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Извадок

A.vertebralis вообичаено се опишува како прва гранка на истостраната a. subclavia, но во литературата се публикувани бројни варијации во нејзиното издвојување.

Испитувањето е направено на 110 неселектирани хумани срца без патоанатомски промени, добиени по аутопсии на новородени, фиксирани во 10% формалин. За анализа на издвојувањето на a. vertebralis од аортниот лак користени се стандардните анатомски методи инспекција и дисекција.

Анализата покажа дека 102 препарата (92,7%) имаат вообичаен изглед и топографски соодноси на аортниот лак и неговите гранки. Кај три од препаратите (2,7%) a. vertebralis sinistra се издвојува помеѓу a. carotis communis sinistra и a.subclavia sinistra. Кај еден препарат a. vertebralis sinistra се издвојува како четврта гранка помеѓу a. carotis communis sinistra и a. subclavia sinistra, а постои и петта гранка на лакот која се издвојува дистално од a. subclavia sinistra.

Клучни зборови: вертебрална артерија, анатомија, ембриологија, варијации

ANATOMY AND VARIATIONS IN THE ORIGIN OF VERTEBRAL ARTERY

Zhivadinovik Julija, Papazova M, Matveeva N, Dodevski A, Zafirova B

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Abstract

The vertebral artery (a. vertebralis, VA) is classically described as the first branch of the ipsilateral subclavian artery (a. subclavia), but multiple variations in the origin of that vessel have been reported in the literature.

This examination was made on 110 unselected human hearts without pathoanatomical changes, obtained after autopsy of newborns, fixed in 10% formaldehyde. Standard anatomical methods, inspection and dissection were used for the analyzing of the origin of a. vertebralis.

The analysis showed that 102 of the specimens (92.7%) had the usual pattern of the aortic arch and its branches, with the usual topographic relations. In three of the specimens (2.7%) a. vertebralis sinistra had a separate origin between a. carotis communis sinistra and a.subclavia sinistra. In one specimen a. vertebralis sinistra had a separate origin as the fourth branch between a. carotis communis sinistra and a. subclavia sinistra and there was a fifth branch originating distal to a. subclavia sinistra.

Key words: vertebral artery, anatomy, embryology, variations

Introduction

The vertebral artery (a. vertebralis, VA) is classically described as the first branch of the ipsilateral subclavian artery (a. subclavia). Eventhough, multiple variations in the origin of this vessel have been reported in the literature, a. vertebralis can arise from the aortic arch (arcus aortae); from the common (a. carotis communis), internal (a. carotis interna), or external carotid (a. carotis externa) arteries; or from subclavian branches, such as the thyrocervical trunk (truncus thyrocervicalis). Also, a. vertebralis may have duplicate origins, generally from the aortic arch and a. subclavia (1, 2, 3).

Diagnosis of these abnormalities in cases of vascular diseases such as arteriovenous malformations or aneurysms, before cerebral angiography, is important to avoid wrongly interpreted nonopacification of a. vertebralis as a blockage or stenosis that may prove dangerous during the endovascular surgeries in the head and neck region (2).

Material and methods

The examination was made on 110 unselected human hearts without pathoanatomical changes, obtained after autopsy of newborns, fixed in 10% formaldehyde. The hearts were taken with the aortic arch, proximal part of thoracic aorta and lig. arteriosum.

Standard anatomical methods, inspection and dissection, were used for analyzing the origin of the a. vertebralis.

Results

The analysis of the 110 heart specimens showed that 102 of them (92.7%) had the usual pattern of the aortic arch and its branches, with the usual topographic relations.

In three of the specimens (2.7%) a. vertebralis sinistra had a separate origin between a. carotis communis sinistra and a.subclavia sinistra (Fig. 1, 2).

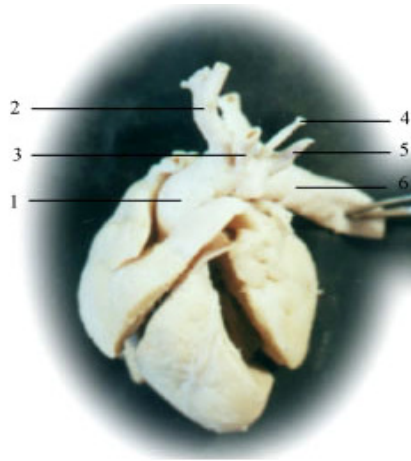


Fig. 1. Separate origin of a. vertebralis sinistra between a. carotis communis sinistra and a. subclavia sinistra. 1. aorta ascendens, 2. truncus brachiocephalicus, 3. a. carotis communis sinistra, 4. a. vertebralis sinistra, 5. a. subclavia sinistra, 6. ductus arteriosus

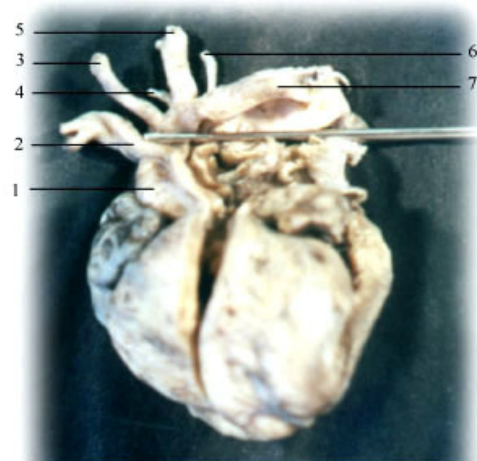


Fig. 3. Separate origin of the a. vertebralis sinistra as the fourth branch between a. carotis communis sinistra and a. subclavia sinistra, and a fifth branch originating distal to a. subclavia sinistra. 1. aorta ascendens, 2. truncus brachiocephalicus, 3. a. carotis communis sinistra, 4. a. vertebralis sinistra, 5. a. subclavia sinistra, 6. branch of truncus costocervicalis, 7. ductus arteriosus.



Fig. 2. Separate origin (ostium) of the a. vertebralis sinistra between a. carotis communis sinistra and a. subclavia sinistra. 1. aorta ascendens, 2. ostium of truncus brachiocephalicus, 3. ostium of a. subclavia sinistra, 4. ostium of a. vertebralis sinistra, 5. ostium of a. subclavia sinistra, 6. ductus arteriosus

One of the specimens had an aortic arch with five branches, with separate origin of the a. vertebralis sinistra as the fourth branch between a. carotis communis sinistra and a. subclavia sinistra, and a fifth branch originating distal to a. subclavia sinistra, probably branch of truncus costocervicalis (Fig.3).

Discussion

Anatomy of a. vertebralis

A. vertebralis is the first branch of the a. subclavia, and it arises from the upper and posterior part of the first portion of the vessel. It is surrounded by a plexus of nerve fibers derived from the inferior cervical ganglion of the sympathetic trunk, and ascends through the foramina in the transverse processes of the upper six cervical vertebrae. Then, it winds behind the superior articular process of the atlas and, entering the skull through the foramen magnum, unites, at the lower border of the pons, with the vessel of the opposite side to form the basilar artery (a. basilaris) (3, 4).

A. vertebralis may be divided into four parts: the *first part* runs upward and backward between the m. longus colli and the m. scalenus anterior. In front of it, there are internal jugular (v. jugularis interna) and vertebral veins (vv. vertebrales), and it is crossed by the inferior thyroid artery (a. thyroidea inferior); a. vertebralis sinistra is also crossed by the ductus thoracicus. Behind it, there are the transverse processes of the seventh cervical vertebra, the sympathetic trunk and its inferior cervical ganglion. The *second part* runs upward through the foramina in the transverse processes of the upper six cervical vertebrae, and it is surrounded by branches from the inferior cervical sympathetic ganglion and by a plexus of veins which unite to form the vertebral vein at the lower part of the neck. It is situated in front of the trunks of the cervical nerves, and pursues an almost vertical course as far as the transverse process of the atlas, above which it runs upward and lateralward to the foramen in the transverse process of the atlas. The *third part* issues from the latter foramen on the medial side of the m. rectus capitis lateralis, and curves backward behind the superior articular process of the atlas, the anterior ramus of the first cervical

nerve being on its medial side; it then lies in the groove on the upper surface of the posterior arch of the atlas, and enters the vertebral canal by passing beneath the posterior atlantooccipital membrane. This part of the artery is covered by the *m.semispinalis capitis* and is contained in the suboccipital triangle (*trigonum suboccipiale*) — a triangular space bounded by the *m.rectus capitis posterior major*, *m. obliquus superior*, and *m. obliquus inferior*. The first cervical or suboccipital nerve lies between the artery and the posterior arch of the atlas. The *fourth part* pierces the dura mater and inclines medialward to the front of the medulla oblongata; it is placed between the *n. hypoglossus* and the anterior root of the first cervical nerve and beneath the first digitation of the *lig. denticulatum*. At the lower border of the pons it unites with the vessel of the opposite side to form *a. basilaris* (3, 4).

The branches of the *a. vertebralis* may be divided into two sets: those given off in the neck, and those within the cranium.

Spinal branches (rami spinales) enter the vertebral canal through the intervertebral foramina, and each divides into two branches. Of these, one passes along the roots of the nerves to supply the medulla spinalis and its membranes, anastomosing with the other arteries of the medulla spinalis; the other divides into an ascending and a descending branch, which unite with similar branches from the arteries above and below, so that two lateral anastomotic chains are formed on the posterior surfaces of the bodies of the vertebrae, near the attachment of the pedicles. From these anastomotic chains branches are supplied to the periosteum and the bodies of the vertebrae and others form communications with similar branches from the opposite side; from these communications small twigs arise which join similar branches above and below, to form a central anastomotic chain on the posterior surface of the bodies of the vertebrae (3,4).

Muscular branches are given off to the deep muscles of the neck, where the *a. vertebralis* curves around the articular process of the atlas. They anastomose with the occipital, and with the ascending and deep cervical arteries.

The meningeal branch (*ramus meningeus; posterior meningeal branch*) springs from the *a. vertebralis* opposite the foramen magnum, ramifies between the bone and dura mater in the cerebellar fossa, and supplies the falx cerebelli. It is frequently represented by one or two small branches.

The *posterior spinal artery (a.spinalis posterior; dorsal spinal artery)* arises from the *a. vertebralis*, at the side of the medulla oblongata; passing backward, it descends on this structure, lying in front of the posterior roots of the spinal nerves, and is reinforced by a succession of small branches, which enter the vertebral canal through the intervertebral foramina; by means of these it is continued to the lower part of the medulla spinalis, and to the cauda equina. Branches from the posterior spinal arteries form a free anastomosis around the posterior roots of the spinal nerves, and

communicate, by means of very tortuous transverse branches, with the vessels of the opposite side. Close to its origin each gives off an ascending branch, which ends at the side of the fourth ventricle.

The *anterior spinal artery (a. spinalis anterior; ventral spinal artery)* is a small branch, which arises near the termination of the *a. vertebralis*, and, descending in front of the medulla oblongata, unites with its fellow of the opposite side at the level of the foramen magnum. One of these vessels is usually larger than the other, but occasionally they are about equal in size. The single trunk, thus formed, descends on the front of the medulla spinalis, and is reinforced by a succession of small branches which enter the vertebral canal through the intervertebral foramina; these branches are derived from the *a. vertebralis* and *a. cervicalis ascendens* of the *a. thyroidea inferior* in the neck; from the *aa. intercostales* in the thorax; and from the *aa. Lumbales*, *aa. iliolumbales*, and *a. sacralis lateralis* in the abdomen and pelvis. They unite, by means of ascending and descending branches, to form a single anterior median artery (*a. mediana anterior*), which extend as far as the lower part of the medulla spinalis, and is continued as a slender twig on the *filum terminale*. This vessel is placed in the pia mater along the anterior median fissure; it supplies that membrane, and the substance of the medulla spinalis, and sends off branches at its lower part to be distributed to the cauda equine (3, 4).

The *posterior inferior cerebellar artery (a. cerebelli inferior posterior)*, the largest branch of the *a. vertebralis*, winds backward around the upper part of the medulla oblongata, passing between the origins of the *n. vagus* and *n. accessorius*, over the inferior peduncle to the under surface of the cerebellum, where it divides into two branches. The medial branch is continued backward to the notch between the two hemispheres of the cerebellum; while the lateral supplies the under surface of the cerebellum, as far as its lateral border, where it anastomoses with the anterior inferior cerebellar and the superior cerebellar branches of the *a. basilaris*. Branches from this artery supply the choroid plexus of the fourth ventricle (3, 4).

The *medullary arteries (bulbar arteries)* are several minute vessels, which spring from the vertebral artery and its branches and are distributed to the medulla oblongata.

Embryology of a. vertebralis

Embryologically, the *a. vertebralis* is formed by the development of longitudinal anastomoses that link the cervical intersegmental arteries. The intersegmental arteries eventually regress except for the seventh, which becomes the proximal subclavian artery and which includes the point of origin of the *a. vertebralis* in adults (1,3) (Fig.4).

During the normal embryologic development, the aortic sac (*AS*) is connected with the left and right dorsal aortas (*DA*) via the aortic arches [the first (*I*), second (*II*), third (*III*), and fourth (*IV*)]. The segment of the *DA* located between the third and fourth aortic arches is called the

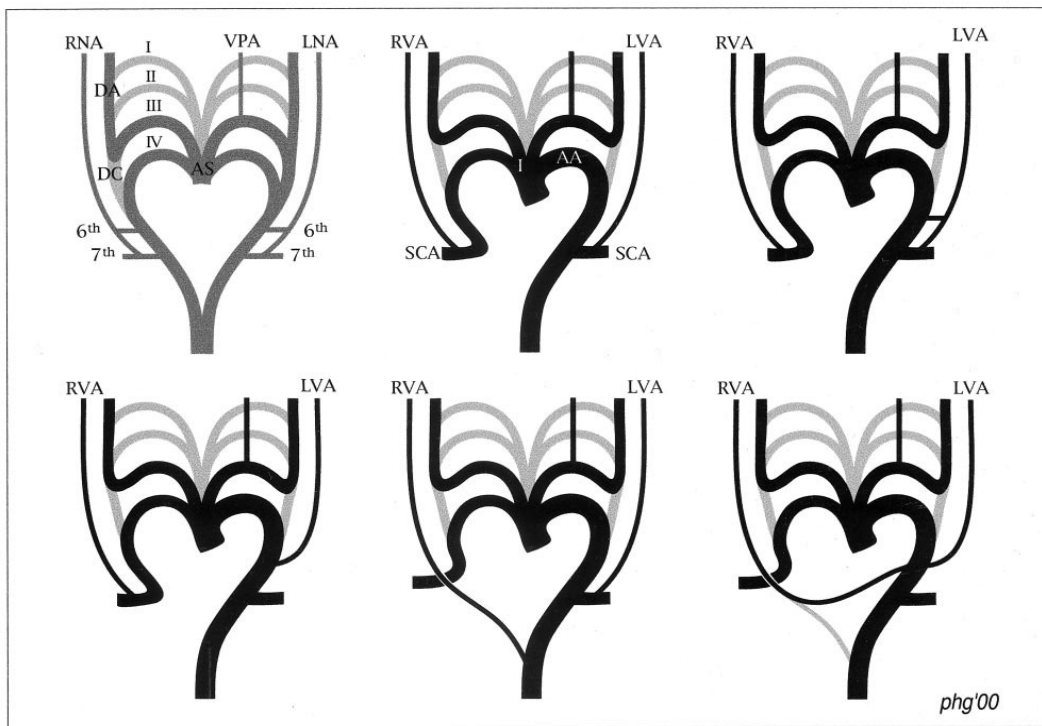


Fig. 4. Schematic representation of the embryologic mechanism underlying anatomic variants of the VA origin (according to Albayram S, Gailloud Ph and Wasserman B)

ductus caroticus (*DC*). The left neural axis (*LNA*) and right neural axis (*RNA*), which later become the vertebral arteries, result from the formation of longitudinal connections linking the intersegmental arteries (only the sixth and seventh intersegmental arteries are depicted here). The ventral pharyngeal artery (*VPA*) arises from the third aortic arch. It later constitutes the trunk of a. carotis externa (1, 3).

In adults, bilateral regression of the *DC* separates the a. carotis communis from the a. subclavia on the right side and from the aortic arch on the left side. A. vertebralis sinistra (*LVA*) and a. vertebralis dextra (*RVA*) arise from the ipsilateral a. subclavia (*SCA*), which are derived from the seventh intersegmental arteries. The *AS* has evolved into the innominate artery (truncus brachiocephalicus, *I*) and aortic arch (*AA*). On each side, the third aortic arch and the distal dorsal aorta constitute the carotid axis, which is divided into the a. carotis communis and a. carotis interna by the origin of the a. carotis externa from the third arch.

If both the sixth and seventh intersegmental arteries persist, the *LVA* has a double origin from the a. subclavia sinistra and aortic arch. A similar mechanism on the right side usually results in a double origin of the *RVA* from the a. subclavia dextra (1).

If the sixth intersegmental artery persists instead of the seventh, the *LVA* has a single origin from the aortic arch, between the a. carotis communis sinistra and a. subclavia sinistra.

Aortic origin of the a. vertebralis dextra (aberrant *RVA*) involves the persistence of the proximal right dorsal aorta, which links the *RVA* to the thoracic aorta distal to

the a. subclavia sinistra. If the right fourth aortic arch involutes as well, the a. subclavia dextra stays connected to the descending thoracic aorta (aberrant a. subclavia dextra or arteria lusoria).

In bilateral arch origin of the *Vas*, the *LVA* arises from the arch because of the persistence of the sixth intersegmental artery instead of the seventh. The *RVA* arises from the arch proximal to the a. subclavia sinistra by means of a hypothetical mechanism that involves the initial origin from the descending thoracic aorta distal to the a. subclavia sinistra, which is followed by proximal migration of the *RVA* origin between the a. carotis communis sinistra and a. subclavia sinistra (1,3).

Variations at the origin of a. vertebralis

According to Gray's anatomy (3) the a. vertebralis sinistra may arise between the a. carotis communis sinistra and a. subclavia sinistra or rarely (0.2%) distal to a. subclavia sinistra.

An analysis made by Saadon Kadir showed that 70% of population had the usual pattern of the aortic arch. About 6% of analyzed cases had separate arising of the a. vertebralis sinistra (5).

A. vertebralis sinistra not infrequently arises from the aortic arch, with reported prevalences of 2.4–5.8% (1, 2, 3, 6). When it originates from the arch, it usually enters the transverse foramen of the fourth or fifth cervical vertebra rather than of the sixth (2). On the other hand, an aortic origin of the a. vertebralis dextra is a rare anatomic variant. In such instances, the artery generally arises distal to the supra-aortic trunks. In a literature review performed in 1999, Lemke et al (2) found only nine cases in which the

a. vertebralis dextra originated from the arch. In those cases, the a. vertebralis dextra arose between the a. carotis communis sinistra and a. subclavia sinistra (one case), between the a. subclavia dextra and a. carotis communis dextra in the absence of a formed innominate artery (truncus brachiocephalicus) (one case), or distal to the a. subclavia sinistra (seven cases). A bilateral aortic arch origin of the a. vertebralis represents an exceptional anatomic variant (1). Sait Albayram et al. presented a case of bilateral origins of a. vertebralis from the aortic arch in which both arteries arose proximal to the left subclavian artery (1). To our knowledge, this anatomic configuration has not been previously reported in the literature. In other reported cases with anomalous origin of the a. vertebralis sinistra, the artery arose between the origins of the a. carotis communis sinistra and a. subclavia sinistra (6, 7, 8). The aberrant right a. vertebralis arose from the descending aorta distal to the origin of the a. subclavia sinistra (1, 2, 9).

Anomalous origins of the vertebral arteries represent a potential pitfall at diagnostic cerebrovascular imaging. One or both arteries may be wrongly assumed to be occluded or diseased, either by eluding catheterization during angiography or by lying outside the region of interest during noninvasive studies such as CT angiography, MR angiography, or Doppler sonography. Finally, knowledge of potential VA origin variants appears to be mandatory for planning aortic arch surgery or endovascular interventions.

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ВАРИЈАЦИИ ВО НИВОТО НА ВЛЕЗ НА `РБЕТНАТА АРТЕРИЈА ВО НАПРЕЧНИОТ ОТВОРДодевски Аце,¹ Лазареска М,² Чадиќовска Е,¹ Алији В,² Јаневски П²¹Институт за анатомија, Медицински факултет, Универзитет "Св. Кирил и Методиј", Скопје, Р. Македонија; ²Ј.З.У. Универзитетска Клиника за радиологија, Универзитет "Св. Кирил и Методиј", Скопје, Р. Македонија**Извадок**

Целта на оваа студија е да се прикажат анатомските варијации на нивото на влез на `рбетната артерија во напречниот отвор.

За таа цел во оваа студија беа анализирани 40 снимки од КТ ангиографија.

Резултатите покажаа дека кај 38 пациенти (95%) артеријата навлегува во напречниот отвор на шестиот вратен прешлен. Кај два (5%) пациенти артеријата има абнормално ниво на влез, и тоа кај еден пациент навлегува на ниво на четврти, и кај еден пациент на ниво на петти цервикален прешлен.

Варијабилно ниво на влез на `рбетната артерија е релативно честа појава. Оваа потенцијално опасна состојба треба да биде детектирана преоперативно, со цел да се избегнат јатрогени повреди на жрбетната артерија за време на хируршките интервенции.

Клучни зборови: анатомија, `рбетна артерија, напречен отвор, `рбетен столб, хирургија.

VARIATION IN LEVEL OF ENTRY OF THE VERTEBRAL ARTERY INTO THE TRANSVERSE FORAMENDodevski Ace,¹ Lazareska M,² Cadikovska E,¹ Aliji V,² Janevski P²¹ Institute of Anatomy, Medical Faculty, "Ss. Cyril and Methodius" University, Skopje, R. Macedonia; ² University Institute of Radiology, "Ss. Cyril and Methodius" University, Skopje, R. Macedonia**Abstract**

The aim of this study was to analyze the variable level of entrance into the transverse foramen and to point the risks of injury of the vertebral artery during accomplishing surgical procedures.

For that purpose we examined 40 patients with CT angiography and analyzed the level of entrance into the transverse foramen.

The vertebral artery entered the C6 transverse foramen in 38 (95%) patients. Abnormal level of vertebral artery entrance was observed in two (5%) patients, with entrance into the C4 and C5 transverse foramen. The vertebral artery entered the C6 transverse foramen in 96.25% of specimens (77 out of 80 courses). An abnormal level of entrance was observed in 3.75% of specimens (3 courses), with a level of entrance into the C4 or C5 transverse foramen, respectively, in 2.5% and 1.25%.

The incidence of abnormal level of entrance into the transverse foramen is relatively frequent, and this potentially dangerous condition should be detected on preoperative imaging in order to avoid vertebral artery injury.

Key words: anatomy, vertebral artery, transverse foramen, cervical spine, surgery.

Introduction

Despite the complexity of their embryologic development, the course of the vertebral arteries appears relatively constant. The vertebral artery usually arises from the upper posterior surface of the subclavian artery and is the most proximal and largest branch of the subclavian artery. For descriptive purposes the vertebral artery may be divided into four segments. The first segment of the vertebral artery extends from its origin to its point of entrance into the foramen of the transverse process of a cervical vertebra, usually the sixth. The second segment extends from C6 to C2 transverse process, the third from C2 to the foramen magnum, and the fourth from the foramen magnum dura to vertebrobasilar junction [1]

The anatomic variations of the vertebral arteries are numerous [2]. Variations of the pretransverse segment

of the vertebral arteries have been described extensively, concerning origin of the vertebral arteries, tortuosity in its course, and size of the vertebral arteries [2]. The two vertebral arteries are usually different in caliber, with the left being more often larger or dominant [3]. The most important variation is the level of entrance of the vertebral artery into the transverse foramen. Most commonly the artery enters the transverse foramen of sixth cervical vertebra. But in variable percentage of cases, the vertebral artery enters the C7, C5, C4, or even the C3 and C2 transverse foramen. In case of entrance above C6, the vertebral artery runs anteriorly to the C6 transverse process, between the longus colli muscle and the anterior branch of the C6 transverse process. The vertebral artery is thus unprotected by bony structures and at risk of injury when the muscle is divided. Thus, recognizing this anatomic variation on preoperative investigations is important to avoid any inadvertent damage [4].

The objective of this study was to describe the variable level of entrance into the transverse foramen and to point the risks during accomplishing surgical procedures.

Material and methods

Forty patients from the University Institute for Radiology in Skopje, R. Macedonia were investigated during a period of 8 months, from February 1st 2010 to September 30ⁱⁿ 2010. For the purpose of this study 17 females and 23 males, ranging in age between 19 and 75 years, mean age of 54.1 ± 12 years, were examined.

This was an anatomical analysis of CTA images realized for medically justified goal. Patients were investigated with computed tomography angiography (CTA). CTA was performed with CT scanner Somatom, Volume Zoom, Simens, multislice 4. Contrast material was injected by using intravenous catheter placed in the peripheral vein, a total of 100 ml. at a rate of 3 ml/s with a pressure injector. After the contrast medium was injected, by use of bolus tracking software, scanning was carried out automatically. The data were transferred to a workstation for post-processing. Reconstruction included the following: maximum intensity projection-MIP; four-dimensional CTA with volume rendering; reformatted multiplanar reformation-MPR.

By using the CTA we received 40 high quality images, which satisfied the requirements of our study. For conducting these study 80 vertebral arteries of 40 patients were analyzed for the level of entrance of the vertebral artery into the transverse foramen of the vertebrae.

Results

The vertebral artery entered the C6 transverse foramen in 95% of the patients (38 out of 40 patients). An abnormal level of entrance was observed in 5% of the cases, (2 out of 40 patients).

The vertebral artery entered the C6 transverse foramen in 96.25% of specimens (77 out of 80 courses). An abnormal level of entrance was observed in 3.75% of specimens (3 courses), with a level of entrance into the C4 or C5 transverse foramen, respectively, in 2.5% and 1.25%. One patient (2.5%) out of 40 had a unilateral anomaly and one (2.5%) had a bilateral anomaly. Two abnormalities were on the left side (66.6%) and one was on the right side (33.4%).

Discussion

In anatomy, surgery, angiography and in all non-invasive procedures it is very important to know the exact course of the artery and the possible variations [5].

Until now, several studies reporting the incidence of anatomic variations of the vertebral artery have been published in the literature. According to the available data from these studies vertebral artery shows variable level of entrance into the transverse foramen.

Matula et al. found level of entry of the vertebral artery into the transverse foramen at C6 in 91% of their cases. They also found two cases of the vertebral artery entering at C4 and C5 and two cases of vertebral artery entering at the level of C7 [5].

In the study conducted by Kajimoto et al. 37 of 40 dissected vertebral arteries entered the transverse foramen at the sixth cervical vertebra (C6-92.5%) and three (7.5%) of them through C7 transverse foramen [6].

Bruneau et al. found that in 93% of all specimens vertebral artery entered the transverse foramen of C6 vertebrae. An abnormal level of entrance was observed in 7% of the specimens, with a level of entrance into the C3, C4, C5, or C7 transverse foramen, respectively, in 0.2%, 1%, 5% and 0.8%. Seventeen abnormalities were right-sided and eighteen (18) were left-sided. Thirty one out of 250 patients had a unilateral anomaly and two had a bilateral anomaly [7].



Fig. 1. CT angiography showing normal entrance of the vertebral artery into the C6 transverse foramen on the left and right side

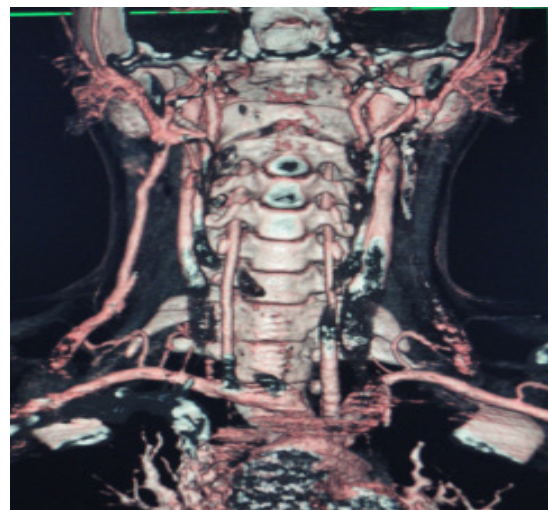


Fig. 2. CT angiography showing abnormal entrance of the vertebral artery into the C4 transverse foramen on the left and right side

Hong et al. in their study found that the vertebral artery entered the C6 transverse process in 94.9% of the specimens. Abnormal vertebral artery entrance was observed in 5.1% of the specimens, with entrance into the C4, C5, or C7 transverse foramen 1.6%, 3.3%, and 0.3%, respectively [8].

There is a correlation between the artery entering into the foramen at an unusual level and a variation in its origin from the subclavian artery. Based on the findings of Yamaki et al. the right and left vertebral arteries that arose from the subclavian arteries had the most common entrance at the transverse foramen of C6. The right and left vertebral arteries that arose from other than the subclavian artery had a high frequency of entrance at C3, C4 or C5 [9].

It is important to know anatomic variations of the vertebral artery and to look for them systematically on preoperative investigations to avoid inadvertent tearing during anterior or lateral approach to the cervical spine. These anatomic variations of the entrance level can be detected easily on MRI and contrast enhanced CT scans. These variations could be missed on a noninjected CT scan, but should be suspected nevertheless if a transverse foramen appears to be small. When facing a small transverse foramen, the differential diagnoses are a hypoplastic or aplastic vertebral artery or an unfilled foramen because of the upper level of entrance. In such a case, MRI or CT scan is mandatory if surgery is performed in the vertebral artery vicinity [7].

Anterior cervical decompressive surgery is performed for a variety of reasons. The indications for surgery in cervical spine region include spondylosis, degenerative disc disease, benign and malignant bone tumors, infection, and trauma. With each of these surgical indications, there is the potential for damage to the vertebral artery during the extent of the decompression. Thus, an understanding of the anatomy of vertebral arteries and the surrounding bony anatomy is essential to prevent iatrogenic vertebral artery injuries [10].

Iatrogenic vertebral artery injuries can occur from posterior cervical surgery in the spine; however, these injuries are rare [10].

The true incidence of vertebral artery injury during anterior cervical spine surgery is unknown because of underreporting of such occurrences [11]. Considering unrecognized and underreported cases, the true incidence of vertebral artery injury will probably remain unknown and underestimated, and will increase with the increasing popularity of cervical instrumentation techniques [12].

In 1992 Smith et al. on a retrospective review on 1195 anterior cervical spine operation reported an incidence of vertebral artery laceration in 0.5%. Five patients had postoperative neurological deficits, four being a direct complication of the arterial injury [13].

Burke et al. in a retrospective study over a 7-year period, included a total of 1976 patients who had undergone anterior cervical spinal procedures, and in six cases (0.3%) iatrogenic vertebral artery injury was identified [14].

Based on a retrospective analysis of 1215 anterior cervical operations Golfinos et al reported that four (0.3%) patients sustained vertebral artery injuries [15].

Consequences of vertebral artery injury are often unpredictable, with a wide spectrum of symptoms. Although some patients may remain asymptomatic due to adequate collateral circulation, other patients may sustain devastating vertebrobasilar ischemia or fatal bleeding [12].

Laceration of the vertebral artery is the most challenging of surgical dilemmas during anterior cervical spine surgery, as ganging control of the massive hemorrhage from a ruptured vertebral artery is difficult and could possibly result in an uncertain neurologic morbidity. The vertebral arteries comprise the posterior circulation of the brain, which includes the occipital lobes, the brain stem, and the labyrinthine branches to the inner ear. Therefore, even though the bleeding from the artery can be controlled, ischemic neurologic consequences may occur in some individuals. The potentially devastating complications of vertebral artery injury with its supply of the cerebellum, brainstem and spinal cord are well known: brain stem infarction or central respiratory dysfunction [16].

When a vertebral artery laceration occurs, there is disagreement as to the optimal method to manage this potentially devastating complication. The various options available include direct ligation, use of thrombostatic agents, endovascular techniques, etc. After vascular control of a vertebral artery laceration, it is mandatory to obtain radiographic imaging confirmation of the adequacy of the repair or ligation. CT angiography or MR angiography is necessary to exclude a growing pseudoaneurysm [10].

There is no doubt that prevention of the problem is the best treatment. Careful preoperative planning is essential in cases with unusual anatomy of the vertebral arteries and helps avoiding potentially life threatening complications [2, 8, 10, 12, 13, 16].

Conclusion

In conclusion, excellent knowledge of the vertebral artery anatomy and variations is absolutely necessary. In 5% of the patients in our study we noticed abnormal level of entrance. When entering is above C6, the pre-entry course of the vertebral artery is at risk for injury during surgery. Vertebral artery anatomy and variations are interesting from anatomical aspect, but they are clinically important. Solid knowledge about vertebral artery anatomy and variations finds clinical application during surgical procedures on the spine in order to prevent vertebral artery injury.

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ЗНАЧЕЊЕ НА АНТРОПОМЕТРИЈАТА НА НАДЛАКТОТ КАЈ ДЕЦА НА ВОЗРАСТ ОД 7 ГОДИНИ ОД УРБАНА СРЕДИНА И МАКЕДОНСКА НАЦИОНАЛНОСТ ВО ПРОЦЕНА НА НУТРИТИВНИОТ СТАТУС

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Извадок

Целта на трудот беше детекција на полово-специфичните разлики на нутритивните антропометриски параметри на надлактот кај деца на возраст од 7 години и нивното значење во процена на нутритивниот статус.

Во студијата беа вклучени 224 здрави деца на возраст од 7 години (112 машки, 112 женски), од македонска националност, од различни урбани региони на Македонија. Антропометриските мерења беа вршени според ИБП со стандардна техника и опрема за мерење. Пресметани и изведени се следните индекси: телесна маса-за-возраст (ТМ), телесна висина-за-возраст (ТВ), ВМІ и нутритивните параметри на надлактот: TUA-вкупната површина, UMA-мускулната површина, UFA-масната површина и AFI-масниот индекс.

Резултатите покажаа постоење на сигнификантна полово-специфична разлика само за ТМ во корист на момчињата. За останатите параметри (ТВ, ОНАД, ВМІ) разликите не се значајни, со исклучок на кожните дупли кои беа значајно повисоки кај девојчињата. Граничните вредности за 5^{от} и 85^{от} перцентил кај момчињата изнесуваа: 20.3 и 33 kg за ТМ, 118.07 и 131.39 cm за ТВ, односно 14.16 и 20.07 kg/m² за ВМІ. Соодветните вредности кај девојчињата изнесуваа: 20 и 31.75 kg за ТМ, 117 и 130.08 cm за ТВ, 13.58 и 19.4 kg/m² за ВМІ. Вредностите за 50^{от} перцентил на нутритивните параметри кај момчињата изнесуваа: 26.96 cm² TUA, 18.68 cm² UMA, 7.60 cm² UFA, односно 29.41% AFI. Девојчињата имаа вредности од: 28.44 cm² TUA, 19.33 cm² UMA, 8.78 cm² UFA, односно 30.76% AFI.

Се препорачува овие вредности да најдат примена како значајни критериуми во евалуацијата на нутритивниот статус кај деца на 7 годишна возраст во Р.Македонија.

Клучни зборови: антропометрија на надлактот, детска популација, нутритивен статус.

THE MEANING OF THE UPPER ARM ANTHROPOMETRY AT THE 7 YEARS-OLD-CHILDREN, FROM URBAN AREA AND MACEDONIAN NATIONALITY FOR ASSESSMENT OF THE NUTRITIONAL STATUS

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Abstract

The aim of this study was to evaluate the sex-specific characteristics of the nutritional parameters of the upper arm in 7 years-old children and the importance of these parameters in nutritional assessment.

In this study 224 healthy 7 years-old-children were examined (112 male, 112 female) of Macedonian nationality, from different regional urban areas in R. of Macedonia. Anthropometric measurements were done according to the methodology of IBP with standard technique and equipment of the measurements. A few anthropometric indexes were calculated: body weight-for-age (BW), body height-for-age (BH), BMI, and nutritional parameters of upper arm: TUA – upper arm area, UMA-upper arm muscle area, UFA-upper arm fat area and AFI- arm fat index.

Results showed significant sex-specific differences only in BW in favor of the boys. For other anthropometric parameters (BH, MUAC, BMI) differences were not significant, with exception of the skin folds that were significantly higher in girls. Border values for 5th and 85th percentile as cut off points in boys were as follows: 20.3 and 33 kg for BW, 118.07 and 131.39 cm for BH, 14.16 and 20.07 kg/m² for the BMI. The values of these parameters in girls were: 20 and 31.75 kg for BW, 117 and 130.08 cm for BH and 13.58 and 19.4 kg/m² for BMI. The values of the 50th percentile for the nutritional parameters in boys were as follows: 26.96cm² TUA, 18.68cm² UMA, 7.60 cm² UFA and 29.41% AFI and in girls were: 28.44cm² TUA, 19.33cm² UMA, 8.78 cm² UFA and 30.76% AFI.

It is recommended that these results can be used as important criteria for nutritional assessment in 7 years-old-children in R of Macedonia.

Key words: upper arm anthropometry, child population, nutritional status.

Introduction

Overweight is one of the most common serious health problems of today. This trend of increasing body weight is becoming even more common in childhood (1). This is supported by the fact that in the last 30 years obesity in childhood has increased by almost three times (2). Namely, the prevalence of obesity among children aged 6 to 11 years increased from 6.5% in 1980 to 19.6% in 2008 (2). Children who become overweight or obese in childhood usually remain overweight as adults, i.e. approximately 80% of the children who are overweight at the age of 10-15 are also overweight or obese adults by the age of 25 (3, 4). Obesity is an important risk factor for a lot of cardiovascular and endocrine diseases; different dyslipidemias; sleep disorders; psychic and orthopedic disorders; etc. Research done on a sample of children at the age of 5 - 17 shows that 70% of the obese children have had at least one of the risk factors for cardio-vascular diseases (CVD-risk factors) such as: high blood pressure, high cholesterol, abnormal glucose-tolerance test. In 39% of the overweight children two or more CDV risk factors were registered (5). In order to reduce the growing trend of obesity or overweight, we need to observe the state of nutrition (6). The anthropometric examinations, which are fast, economical and easily-applicative, play an important role in the evaluation of the nutritional status, especially at an early age (7). Different anthropometric indexes provide assessment and evaluation of the nutritional status as well as detection of possible health risks (1,7,8). In order to better evaluate the level of nutrition, Frishanko points out that the muscular and mass area of the upper-arm should be determined, and he starts from the fact that the upper-arm and its constituents (muscular, subcutaneous fat, and bone mass) are cylindrical. This author uses the mass of the skin fold triceps and the mid upper arm circumference in the construction of the so called nutritional parameters of the upper-arm. He also derives formulas to calculate those parameters and works out standard values (9).

Aim

To evaluate sex-specific differences of nutritional parameters of the upper-arm and their significance in the evaluation of the nutritional status of 7 years-old children of Macedonian nationality, from different urban areas in R. Macedonia.

Examinees and methods

Examinees

The study included a sample of examinees defined as population of 7-years-old school children of Macedonian nationality from various urban areas of R. Macedonia. The sample was chosen randomly. The total number of examined children (n= 224) was divided into two groups according to sex criterion.

Anthropometry

The following anthropometric parameters were measured: body weight (BW), body height (BH), mid upper-arm circumference (MUAC), skin folds scapula ad

triceps (SS Fand TSF) and they were measured following the methodology of IBP (International Biological Program) with standard equipment and measuring technique. The following standard anthropometric instruments were used: anthropometer by "Martin" for measuring of body height with reading precision of 1 mm ; medical decimal scales for measuring of body weight with precision of 0.1 kg; elastic plasticized band for circumference with precision 0.1 mm, caliper "John – Bull" for determination of skin folds with precision of 0.1mm.

The following indexes were also drawn: weight for age, height for age and BMI (as a relation between the weight and the height of a square). The nutritional parameters of the upper arm were also calculated: the total (TUA), the muscle (UMA), the mass area (UFA) as well as the mass index (AFI) using formulas created by Frishanko (8):

$TUA = UAC^2 / 4 \times 3,14$; TUA - the total area of the upper-arm (cm²); UAC- circumference of the upper-arm (cm),
 $UMA = [UAC - (TSF \times 3,14)]^2 / 4 \times 3,14$, UMA-muscle area of the upper-arm (cm²),

TSF -skin fold triceps,

$UFA = TUA - UMA$; UFA - fat area of the upper-arm (cm²),
 $AFI = (UFA / TUA) \times 100$; AFI - fat index of the upper-arm.

According to several authors, the following percentile ranks are recommended for defining the anthropometric indicators of the upper-arm:

15th to 85th percentile normal distribution; 5th – 15th percentile points to under average values which still can't categorize the child in the group of underweight; as opposed to this, the values under the 5th percentile, especially for the parameter UMA, with a bigger possibility point to underweight ; children with values between the 85th and 95th percentile for the parameters weight/age, are defined as overweight and these children run the risk of becoming obese; the values over the 95th percentile for weight for age or the 85th percentile for UFA and AFI point to the category of obese children (6-12).

Statistical analysis

The gathered data for the relevant variables were analyzed with descriptive statistics presented with measures of central tendency and deviation (arithmetic mean \pm standard deviation) along with ranges expressed in percentiles. Testing of sex differences was done with analysis of variance for large, independent samples-ANOVA. Differences for $p < 0.05$ were considered significant.

Results

The mean values, and standard deviations of the examined anthropometric parameters, as well as the significance of their differences, are shown in table 1.

There is statistically significant difference only in terms of weight in favor of the boys, whereas body height, mid-upper arm circumference and BMI differences were insignificant. Only skin folds were significantly higher in girls ($p < 0.05$).

Sex-specific percentiles of the indicators weight-for-age, height-for-age and BMI are shown in table 2.

Table 1. Values of the anthropometric parameters in 7 years-old-children from Macedonian nationality.

| | <i>Body weight (kg)</i> | <i>Body height (cm)</i> | <i>BMI (kg/m²)</i> | <i>Mid upper arm circumf (cm)</i> | <i>Skinfolds (mm)¹ Scapula</i> | <i>Triceps</i> |
|--------------|-----------------------------|-----------------------------|-----------------------------------|---------------------------------------|---|----------------|
| Boys | | | | | | |
| X | 27.93 | 125.79 | 17.55 | 18.64 | 6.23 | 9.55 |
| SD | ± 5.78 | ± 5.07 | ± 2.96 | ± 2.5 | ± 1.45 | ± 2.23 |
| Girls | | | | | | |
| X | 26.46 | 124.64 | 16.93 | 19.09 | 6.93 | 10.17 |
| SD | ± 5.35 | ± 5.61 | ± 2.54 | ± 2.22 | ± 1.8 | ± 2.21 |
| (p) | P<0.05 | P>0.05 | P>0.05 | P>0.05 | P<0.05 | P<0.05 |

¹All values are means ± standard deviations;

² p; significance of the sex differences (ANOVA)

Table 2. Sex -specific percentiles of the indexes: Weight-for-age, Height-for-age and Body Mass Index in 7-years-old children from Macedonian nationality.

| | Percentiles | | | | | | | | | | |
|---------------------|-------------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | X | SD | 5 | 10 | 15 | 25 | 50 | 75 | 85 | 90 | 95 |
| Boys (N=112) | | | | | | | | | | | |
| Weight-for-age | 27.93 | ±5.78 | 20.30 | 21.00 | 23.00 | 25.00 | 27.00 | 30.00 | 33.00 | 35.00 | 38.95 |
| Height-for-age | 125.79 | ±5.07 | 118.07 | 119.00 | 119.55 | 122.00 | 125.90 | 128.70 | 131.36 | 133.36 | 135.18 |
| BMI-for-age | 18.64 | ±2.96 | 14.16 | 14.68 | 14.85 | 15.70 | 16.94 | 18.75 | 20.07 | 20.95 | 23.40 |
| Girls(N=112) | | | | | | | | | | | |
| Weight-for-age | 26.46 | ±5.35 | 20.00 | 20.75 | 21.40 | 22.38 | 26.00 | 29.00 | 31.75 | 33.50 | 38.00 |
| Height-for-age | 124.64 | ±5.61 | 117.00 | 117.50 | 118.40 | 120.00 | 125.00 | 128.43 | 130.08 | 132.65 | 133.83 |
| BMI-for-age | 16.93 | ±2.54 | 13.58 | 14.26 | 14.53 | 15.26 | 16.38 | 18.52 | 19.40 | 20.38 | 21.95 |

Table 3. Values of the nutritional parameters of upper arm: TUA-upper arm area, UMA-upper arm muscle area, UFA-upper arm fat area and AFI arm fat index in 7 years-old-children from Macedonian nationality.

| | <i>TUA (cm²)</i> | <i>UMA (cm²)</i> | <i>UFA (cm²)</i> | <i>AFI (%)</i> |
|--------------|-----------------------------|-----------------------------|-----------------------------|----------------|
| Boys | | | | |
| X | 28.17 | 19.82 | 8.35 | 29.38 |
| SD | ± 7.84 | ± 5.38 | ± 2.86 | ± 4.59 |
| Girls | | | | |
| X | 29.4 | 20.36 | 9.04 | 30.04 |
| SD | ± 6.95 | ± 4.57 | ± 2.76 | ± 4.34 |
| (p) | P>0.05 | P>0.05 | P>0.05 | P>0.05 |

¹All values are means ± standard deviations;

² p; significance of the sex differences (ANOVA)

For these indicators, we calculated the values for the 5th and 85th percentile. Body weight, body height and BMI on the 5th percentile were 20.3 kg; 118.07cm and 14.16 kg/m² for boys, and for girls 20,0 kg, 117.0 cm and 13.58 kg/m².

Table 3 shows mean values, standard deviations of the nutritional parameters of the upper-arm, as well as the significance of their differences. The mean values of the nutritional parameters of the upper-arm are higher in girls, but sex differences are insignificant.

Table 4. Sex specific percentile of the nutritional parameters of upper arm: TUA–upper arm area,UMA-upper arm muscle area, UFA-upper arm fat area and AFI arm fat index in 7-years- old children from Macedonian nationality.

| | | <i>Percentiles</i> | | | | | | | | | |
|------------------------|----------|--------------------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Boys(N=112) | X | SD | 5 | 10 | 15 | 25 | 50 | 75 | 85 | 90 | 95 |
| TUA (cm ²) | 28.17 | ± 7.84 | 18.25 | 19.88 | 22.20 | 23.28 | 26.96 | 32.49 | 37.73 | 40.31 | 44.54 |
| UMA (cm ²) | 19.82 | ± 5.38 | 13.12 | 14.19 | 15.69 | 16.45 | 18.68 | 21.812 | 4.83 | 28.30 | 30.08 |
| UFA (cm ²) | 8.35 | ± 2.86 | 4.64 | 4.84 | 5.49 | 6.41 | 7.60 | 10.00 | 11.61 | 12.20 | 13.53 |
| AFI (%) | 29.38 | ± 4.59 | 20.68 | 22.89 | 24.81 | 26.85 | 29.41 | 32.64 | 34.54 | 35.39 | 36.17 |
| Girls (N=112) | X | SD | 5 | 10 | 15 | 25 | 50 | 75 | 85 | 90 | 95 |
| TUA (cm ²) | 29.4 | ± 6.95 | 19.69 | 22.07 | 23.76 | 24.94 | 28.44 | 32.49 | 36.80 | 39.24 | 42.39 |
| UMA (cm ²) | 20.36 | ± 4.57 | 13.91 | 15.79 | 16.56 | 17.55 | 19.33 | 22.85 | 25.24 | 26.31 | 28.65 |
| UFA (cm ²) | 9.04 | ± 2.76 | 4.80 | 5.36 | 6.20 | 7.15 | 8.78 | 10.59 | 11.72 | 12.52 | 14.07 |
| AFI (%) | 30.4 | ± 4.34 | 23.01 | 24.06 | 25.19 | 27.97 | 30.76 | 33.76 | 35.24 | 35.72 | 37.15 |

Sex-specific percentiles of the nutritional parameters of the upper-arm for 7-year-old male and female examinees are shown in table 4.

The muscle area of the upper-arm in boys has a average of 19.82 ± 5.38 cm², and in girls 20.36 ± 4.57 cm², whereas UFA – mass area is 9.04 ± 2.76 cm² in girls and 8.35 ± 2.86 cm² in boys.

Discussion

Several anthropometric parameters were examined in our study. Those parameters are used for assessment of the nutritional status in children.

The obtained values allow comparison of our values with the corresponding anthropometric examinations performed on children from different regions in other countries, as well as different regions from our country. Namely, Todorovska L. (1997) in her vast anthropometric study of school children at the age of 7-15 also includes the age of 7 which was examined in our study.

On the 50th percentile the values of the indexes body weight and height-for-age in our male examinees were 27 kg and 125.9 cm i.e. 26 kg and 125.0 cm for female examinees. These values are slightly higher compared to the ones in Todorovska's study, whereas according to the information from the NCHS-referent population our male examinees weigh 1.2 kg more and are 0.7 cm shorter and the girls have approximately the same values with the referential ones, which are 25.7 kg and 124.4 cm (13).

Figure 1 shows the values of BMI on the 50th percentile in children in our study (MKD 2009) compared to the corresponding value of BMI in children from other areas and populations (Spain, Mexico, NHANES/CDC, WHO, Todorovska MKD-97,) (10-15).

Figure 2 shows border values, i.e. cut-off points for BMI o the 85th and 95th percentile in our male and female examinees and the corresponding values obtained from the representative international referential sample of Cole et al (16).

Based on this information, which is used to identify individuals who run the risk of becoming overweight and obese, we can notice that the cut-off points

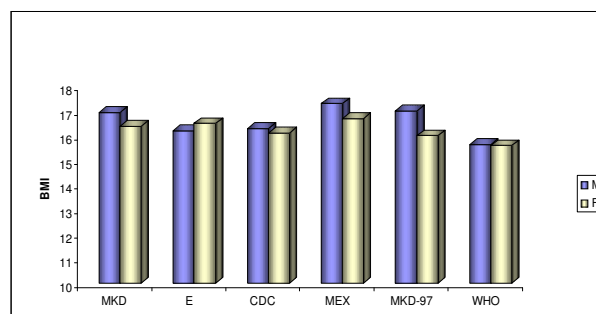


Fig. 1. The values of the 50th percentile of the BMI for 7 years-old-children from different areas and population.

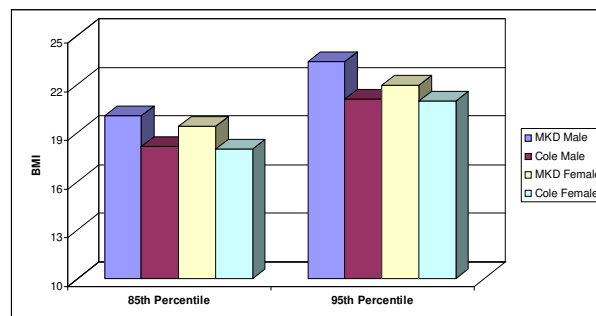


Fig. 2. The cut-off points for BMI of 85th for overweight and 95th for obesity by sex for 7 years old MKD children and Cole's cut off points from international survey

obtained from our examination are slightly higher than the international sample published by Cole et al (16).

We should mention that additional varieties of combinations of more indicators were suggested during a total evaluation of the nutritional status. For that purpose we calculated the nutritional parameters of the upper-arm, such as UFA and AFI which express the peripheral ass component. UMA or muscle mass of the upper-arm, should

be presented not only in relation to age, but also in relation to height (9,10). In relation to the parameter UMA on the 50th percentile, our male examinees had a value of 18.68 which is lower than the referential 20.27, and in female examinees it was 19.33 and the referential 18.15 (9). When it comes to UFA or mass area of the upper-arm, our male examinees showed a value of 7.60 which is similar to the referential 7.58 (Frisanko), and female examinees showed a value of 8.78, which is slightly lower than the referential 9.20 (9).

The differences between the children in this study and children in other studies are another confirmation of the existence of population differences in the anthropometric characteristics, which depends on internal (genetic) and external exogenous factors (17). The results of our study confirm the recommendation of WHO that every country should have its own anthropometric standards which are necessary for a precise classification and detection of deviations in the growth and the nutritional status in children of all age. The use of anthropometric standards from other regions and populations, such as NCHS-standards is allowed only when a country lacks national anthropometric standards (17, 18).

Conclusion

Based on the results of this study, we can draw the following conclusions:

- 7-year-old male examinees of Macedonian nationality and urban areas have slightly higher mean values for body height, mid upper-arm circumference and BMI than female examinees. Statistically significant sex differences were registered for body weight in favor of the boys and only the skin folds were significantly higher in girls.

- We also determined sex specific percentile ranks from the 5th to the 95th percentile, i.e. cut-off points for the anthropometric indexes and nutritional parameters of the upper-am in children at the age of 7.

The results we got can be applied in every day routine practice as anthropometric criteria for assessment and evaluation of the nutritional status. They should also contribute to recognizing the most common risks for the children. They point to certain misbalances and are a criterion for the selection of individuals for further clinical research. By defining border values as cut-off points we should identify children who need nutritive intervention. Undoubtedly, this has a huge practical importance in planning certain preventive measures and activities in the field of child nutrition.

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СВИТКУВАЧКИ БРАЗДИ

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Извадок

Цел: целта на студијата е да се утврдат свиткувачките бразди на стопалата кај македонската женска популација и да се воочат некои регулативи во нивното јавување.

Материјал и метода: 190 испитаници беа вклучени во оваа студија. Отисоците од стапалата беа земени по методата на Cummins i Midlo. Утврдени се типови на шари и свиткувачките бразди. Свиткувачките бразди се различно насочени во однос на должната оска на стапалото (лонгитудинална, трансверзална и коса) и се класифицирани како ф1 и ф2.

Резултат: На левото стапало од ф1 браздите доминираат хоризонталните кои се застапени кај 25.0% од испитаниците, а од ф2 косите бразди се застапени кај 30.5%. На десното стапало ф1 хоризонталните бразди се присутни кај 26.5%, а од ф2 косите бразди се присутни во 36.5% од женската популација. Постапеноста на браздите на стапалото кај една индивидуа не е симетрична. Бројноста на свиткувачките бразди е поизразена на десното стапало.

Заклучок: Секоја свиткувачка бразда на стапалото е уникатна. Така што и различниот распоред на браздите е индивидуален и уникатен. Индивидуалноста на свиткувачките бразди треба целосно да се разбере и да се објасни со отисоците земени од стапалата, нивната класификација и проучување, за потоа да се користат при понатамошни споредувања при различни популациони иследувања и различни медицински нарушувања.

Клучни зборови: отисоци на стапалото, свиткувачки бразди, жени

FLEXION CREASES

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Abstract

The aim of the study is to establish flexion creases on the feet in Macedonian females and attempt to detect regularities in their appearance.

Materials and methods: the study included 190 female examinees. Sole prints were taken using Cummins and Midlo's method and pattern types and flexion creases were determined. Flexion creases running in various directions in relation to the long axis of the foot (longitudinal, transverse, oblique) were observed and they are classified as F1 and F2.

Results: On females left foot among f1 creases horizontal ones predominate in 25% of examinees, from f2 sideways ones are spotted in 30.5%. On females right foot f1 horizontal creases are present in 26.5% examinees and f2 are sideways in 36.5% examinees. The arrangement of the creases on the feet of the same individual was not symmetric. The number of the creases on the right feet was higher.

Conclusion: Each individual crease is unique. Therefore any crease arrangement is unique and could only come from one source. The selectivity of flexion creases should be fully understood and explained on sole prints and than applied in assessing solemarks comparisons. The results of this study might serve in investigations of different populations and of different medical disorders.

Key words: sole prints, flexion creases, females.

Introduction

The Man is a child of nature. In every stage of his development his attitude towards it changed. Hands and feet were constant runners of their function and at the same time they changed and shaped so they could

serve best for locomotion and handling of the weapons with which the man adjusted the nature to his own needs. If we take a look at the man, from a biological point of view, as a complex growing system which is constantly growing, developing and his goal is survival and

continuance-of his species, then part of that system are the hands and the feet, which play a very important role, and on their surface that comes in touch with other surfaces, there is a whole system consisting of pattern elements and furrows. They form different shapes which we call skin patterns. Their function is to increase the resistance, to decrease slipping of feet and toes on different surfaces and hands and fingers while holding different objects (1).

On the skin of the foot we distinguish epidermal skin furrows (sulci cutanei) and flexion furrows (sulci flexorii). The main flexion furrows develop during embryological period and remain the same during the whole life. Small flexion furrows occur in postembryological period and they can change. Flexion furrows don't change the order of the direction of the papilar lines (2).

The skin of the plantar surface of the feet and toes is characterized by epidermal ridges (cristae superficiales) with great amount of nerve endings are also called tactile ridges. Papilar ridges are divided by shallow ridges (sulci cutanei, sulci superficiales). They are characterized by the presence of sweat glands and absence of fiber and sebaceous glands. Sweat glands open up at the epidermal ridges.

Dermatoglyphics consider only epidermal ridges and their order, while flexion furrows and other secondary saddles are not being included in that term (3).

The abovementioned flexion furrows are being used to discover individual affinities and structure of the feet and to determine their connection with genetics (4).

In literature, the description of the flexion furrows is usually excluded. This paper indicates the observations of flexion furrows in Macedonian females and tries to determine regularities in their occurrence.

Material and methods

Sample of examinees

The study included a sample of 200 female examinees, aged 16-20.

The sample consisted of students from Medical faculty randomly chosen. A survey was used to determine that the examinees were of Macedonian nationality and from different regions of the country.

Sole prints were taken at the Institute of anatomy, at the Medical faculty in Skopje.

Statistically, the sample was divided referring the sex and left or right foot.

Methods

1. Footprints taken by Cummins and Midlo's methods
 2. Statistical processing
- Footprints were taken by Cummins and Midlo's methods (5).

We draw two horizontal lines on the foot, one under the thenar elevation, we mark it as x, and the second one on the border with the heel, we mark it with y. We determine the existence of primary furrows present above the lines x and y. We recorded a route for the flexion furrows (longitudinal, transversal and sideways) also we detected if there was any symmetry between the two feet Fig.1 and 2.

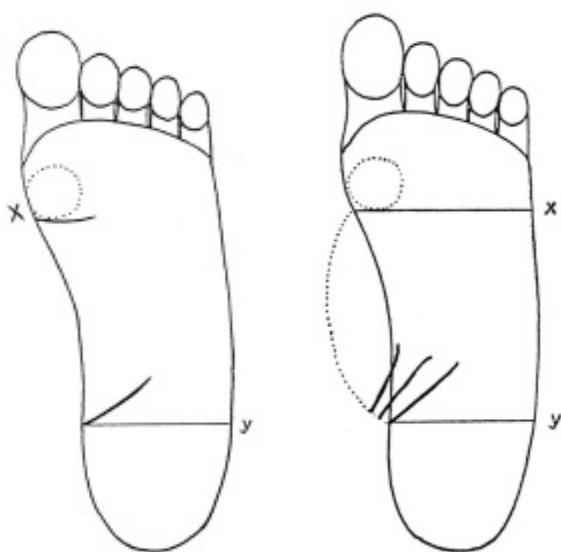


Fig.1&2

Results

The distribution of the flexion creases on the left foot in females is presented on table 1. There aren't any registered flexion furrows, from f1 in (64.5%) and f2 in (57.0%) in the mentioned percentages, in relation to the total number of examinees.

Among f1 flexion creases horizontal ones dominate and are recorded in 51 (25.5%) examinees, 4 (2.0%) are sideways, there are 7 (3.5%) double horizontal, 6 (3.0%) triple horizontal, double sideways two 2 (1.0%) and one is transversal 1 (0.5%).

From f2 flexion creases the most are those with sideways 61 (30.5%), 7 (3.5%) are double sideways, 4 (2.0%) are horizontal ones, 2 (1.0%) are double and 2 triple horizontals, in 7 (3.5%) examinees double sideways is being registered and in 9 (4.5%) triple sideways.

The distribution of the flexion creases on the right foot in females is shown in table 2. No flexion creases have been registered from f1 in (64.5%) and from f2 in (47.5%) in the mentioned percentages in relation to the total number of examinees.

Tab. 1. Flexion furrows- females/left foot

| Parameter | One (f 1) | | Two (f 2) | |
|-------------------|-----------|------|-----------|------|
| | Number | % | Number | % |
| 0 | 129 | 64.5 | 114 | 57.0 |
| Triple horizontal | 6 | 3.0 | 2 | 1.0 |
| Horizontal | 512 | 5.5 | 4 | 2.0 |
| Double horizontal | 7 | 3.5 | 2 | 1.0 |
| Kvadriph. | / | / | 1 | 0.5 |
| Sideways | 4 | 2.0 | 61 | 30.5 |
| Double sideways | 2 | 1.0 | 7 | 3.5 |
| Triple sideways | / | / | 9 | 4.5 |
| Transferzal | 1 | 0.5 | / | / |
| Total | 200 | 100 | 200 | 100 |

Among f1 flexion creases horizontal ones dominate and are recorded in 53 (26.5%) examinees, 2 (1.0%) are sideways, there are 10 (5.0%) double horizontal, 5 (2.5%) triple horizontal, double sideways one 1 (0.5%).

From f2 flexion creases the most present are those with sideways 73 (36.5%), 17 (8.5%) are double sideways, 2 (1.0%) are horizontal, 1 (0.5%) double horizontal and 2 (1.0%) triple horizontal, and in 7 (3.5%) examinees we found double sideways flexion furrows and in 8 (4.0%) triple sideways.

Discussion

Our investigations of the flexion creases have shown the following:

1. Flexion creases are present only at the arch of the foot
2. Flexion creases are not detected in the region of the heel
3. There is no symmetry among the creases on both feet
4. The most present are single horizontal f1 and sideways f2

Results are similar with those from the investigations led by Nakiela (1972) (6) who examined footprints on 1160 examinees. The mentioned author also found a longitudinal furrow 1 which we didn't find in our footprints. In the publication of Vilamovskaja (1956) (7) general conclusions are shown related with the distributions of the flexion furrows of the feet and they are complementary with our findings.

Flexion creases are usually omitted in the dermatoglyphic research. In this study we mentioned our observations of the flexion creases in females of Macedonian nationality. We tried to detect some regularity in their appearance because they present marked individual variations, in relation to their route, frequency of appearance and mutual arrangement (6).

Tab. 2. Flexiom furrows-females/left

| Parameter | One (f 1) | | Two (f 2) | |
|-------------------|-----------|------|-----------|------|
| | Number | % | Number | % |
| 0 | 129 | 64.5 | 114 | 57.0 |
| Triple horizontal | 6 | 3.0 | 2 | 1.0 |
| Horizontal | 51 | 25.5 | 4 | 2.0 |
| Double horizontal | 7 | 3.5 | 2 | 1.0 |
| Kvadriph. | / | / | 1 | 0.5 |
| Sideways | 4 | 2.0 | 61 | 30.5 |
| Double sideways | 2 | 1.0 | 7 | 3.5 |
| Triple sideways | / | / | 9 | 4.5 |
| Transferzal | 1 | 0.5 | / | / |
| Total | 200 | 100 | 200 | 100 |

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УЛОГАТА НА НЕКОИ АНТРОПОМЕТРИСКИ ПАРАМЕТРИ НА ФЕТУСОТ ВО ПРОЦЕНКА НА GESTАЦИСКАТА СТАРОСТ

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Извадок

Целта на овој труд е да се прикаже значењето на некои антропометриски параметри на фетусот во проценка на феталната старост.

Беа опфатени мерења на 180 фетуси ex utero и според гестациската возраст беа поделени во 3 старосни групи (прва група 17-19г.н; втора група 20-22г.н и трета група 23-25гн). Антропометриските мерења беа извршени според методологијата на Интернационалната Биолошка Програма (ИБП), на претходно маркирани антропометриски точки на мерење со стандардна антропометриска опрема.

Измерени беа следниве антропометриски параметри: бипариетален дијаметар (БПД), обем на глава (ОФЦ), должина на фемур, обем на абдомен, должина, висина и ширина на главата на фетусот, телесна должина, телесна тежина, и доведени во корелација со гестациската старост.

Резултатите покажаа висока корелација на скоро сите измерени антропометриски параметри со гестациската старост. Беа изведени индекси на раст- особено индексот на глава кај фетусот кој се покажа како најзначаен.

Корелацијата на поедините антропометриски параметри во однос на гестациската старост се смета дека има подобра контрола во испитувањето на правилниот раст и развој на фетусот, и може да помогне во откривањето на раните фетални абнормалности во интраутериниот раст на фетусот.

Клучни зборови: гестациска старост, фетус, антропометриски параметри.

THE ROLE OF SOME ANTHROPOMETRICAL PARAMETERS OF THE FETUS IN ESTIMATION OF GESTATIONAL AGE

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Abstract

The aim of this study is to show the meaning of some anthropometrical parameters of the fetus in assesment of the fetal age.

The total number of fetuses (n=180) according to gestational age were divided in three groups (first group 17-19 g,a; second group 20-22 g.a and a third group 23-25g.a). Anthropological measurements were done using methodology of the International Biological Programme (IBP) with standard technique of measurement and equipment.

Fetal anthropometrical parameters were analyzed: biparietal diameter, head circumference, femur length, abdominal circumference, head length, head spread, head height, body weight, body length and all in correlation with gestational age.

Results showed high level of correlation with anthropometrical parameters with gestational age. Cephalic index of the fetus head was useful in fetal growth..

Fetal biometry of some anthropometrical parameters based of gestational age (GA) are more accurate and they must have role in early detection of fetal abnormalities in intrauterine growth of the fetus.

Keywords: gestational age, fetus,, anthropometrical parameters.

Introduction

The anthropometric measurements of certain fetal parameters have proved to be a useful method in determining the gestational age of the fetus.

The examinations of the fetal growth include anthropometric measurements which are classically based on the descriptions of the fetal growth. Gestational age (length of fetal life) is determined with different parameters in modern obstetrics; parameters which as routine and technical methods are used in determining the same as prenatal assessment (1). Values obtained from appropriate anthropometric measurements compared to standard

values obtained for an individual gestational age represent an indirect method for determining gestation. Information in literature shows that by measuring bi-parietal diameter as one of the most important parameters in the second trimester of the intrauterine growth of the fetus, we can diagnose intrauterine delay of the development of the fetus in 50-60% of the cases (2). Bi-parietal diameter and femur length equally correlate with gestational age, but measurements of the bi-parietal diameter have proven twice as sensitive in the assessment of fetal age, whereas in the measurements of femur length we can notice some (3).

The correlation between anthropometric parameters and gestational age provides us with standard values of the corresponding parameters for each gestational week, by statistical data processing. The anthropometric measurements of the fetal parameters are a fast, easy and noninvasive applicative method which is used in obstetrics.

Aim: The aim of this paper is to show the significance of some anthropometric parameters of the fetus in the assessment of fetal age.

Material and methods

The material consists of 180 fetuses obtained ex-utero divided into 3 age groups (n=60): first group (17-19 g.a.); second group (20-22 g.a) and third group (23-25 g.a). Fetuses without any visible anatomic macroscopic malformations served as criterion.

The following anthropometric parameters were measured: head circumference (HC), bi-parietal diameter (BPD), femur length (FL), abdomen circumference (AC), length, height and width of the fetus head, body length and body weight.

Anthropometric measurements were done following the International Biological Program (IBP) with standard equipment and measurement technique.

Central tendency and variability, SD, X, MED, MIN, and MAX were used from the descriptive statistics. The correlation between certain anthropometric parameters was determined with regressive analysis and correlating coefficients.

Results

Results show that measurements of the anthropometric parameters which correlated with gestational age as one of the basic indicators in determining fetal growth and development are of great practical importance because they provide information about whether the fetus is developing normally for its gestational week or there are deviations which lead to abnormal development. Based on the obtained results, we can see that the following anthropometric parameters showed the highest level of positive correlation with gestational age in all of the examined groups: head circumference (r=0.52); bi-parietal diameter (r=0.85); upper-leg length (r=0.80); abdomen circumference (r=0.82); head length (r=0.88); head width and weight (r=0.84 and r=0.84), body weight (r=0.89) and body length (r=0.89).

The correlation between certain anthropometric parameters and gestational age is shown in table 1.

The values of descriptive statistics in the given tables for the measured anthropometric parameters of the total number of fetuses show that all of the above-mentioned values are dependent on gestational age and crown-rump length. In the first group the mean values of the head circumference were (16.64 ± 2.11), in the second group (18.41 ± 2.19), and in the third group (21.70 ± 1.40). The bi-parietal diameter in the first group was (3.98 ± 0.71), in the second (5.05 ± 0.76) and in the third group (6.02 ± 0.58). The values of the other measured parameters of the total number of fetuses in each group are shown in table 2 (a, b, c) where we can notice an increase of all measured

Table 1. Correlation of some anthropometric parameters with gestational age and crown-rump length (r)

| | gestational age | crown-rump length |
|-------------------------|-----------------|-------------------|
| Body weight | 0.89 | 0.95 |
| Body height | 0.90 | 0.99 |
| Head circumference | 0.52 | 0.53 |
| Head length | 0.88 | 0.92 |
| Head spread | 0.84 | 0.89 |
| Abdominal circumference | 0.82 | 0.89 |
| Biparietal diameter | 0.85 | 0.89 |
| Head height | 0.84 | 0.90 |

Table 2.a. Values of some anthropometrical parameters

| n = 60 (17-19 g.w) | Body weight(gr) | Body height(cm) | Head circumf.(cm) | BPD(cm) | Abdom circumf (cm) | Femur length (cm) | Head length (cm) | Head spread(cm) |
|-----------------------|--------------------|--------------------|----------------------|---------|-----------------------|----------------------|---------------------|--------------------|
| X | 221.6 | 21.42 | 14.64 | 3.98 | 10.91 | 3.33 | 5.08 | 3.32 |
| SD | 96.16 | 2.91 | 2.11 | 0.71 | 2.06 | 0.65 | 0.78 | 0.63 |
| MED | 190 | 20.6 | 14.6 | 3.85 | 4.24 | 3.4 | 5 | 3.2 |
| MIN | 100 | 16.2 | 10.5 | 2.6 | 7.1 | 2 | 3.3 | 2 |
| MAX | 520 | 28 | 20 | 6.9 | 16.5 | 5.3 | 7 | 4.8 |

Table 2.b. Values of some anthropometrical parameters

| n = 60 (20-22 g.w) | Body weight(gr) | Body height(cm) | Head circumf.(cm) | BPD(cm) | Abdom circumf (cm) | Femur length (cm) | Head length (cm) | Head spread(cm) |
|-----------------------|--------------------|--------------------|----------------------|---------|-----------------------|----------------------|---------------------|--------------------|
| X | 416.67 | 26.63 | 18.41 | 5.05 | 14.17 | 4.00 | 6.32 | 4.19 |
| SD | 104.88 | 2.68 | 2.19 | 0.76 | 2.07 | 0.65 | 0.88 | 0.52 |
| MED | 410 | 26.8 | 18.5 | 5.1 | 14.25 | 3.9 | 6.2 | 4.3 |
| MIN | 235 | 20.7 | 12.8 | 3 | 10.5 | 2.6 | 4.2 | 2.8 |
| MAX | 650 | 33.5 | 23.3 | 7.8 | 19.6 | 6 | 8 | 5.2 |

Table 2. c. Values of some anthropometrical parameters

| n = 60 (23-25 g.w) | Body weight(gr) | Body height(cm) | Head circumf.(cm) | BPD(cm) | Abdom circumf (cm) | Femur length (cm) | Head length (cm) | Head spread(cm) |
|-----------------------|--------------------|--------------------|----------------------|---------|-----------------------|----------------------|---------------------|--------------------|
| X | 653 | 30.91 | 21.70 | 6.02 | 16.90 | 4.47 | 7.67 | 5.10 |
| SD | 130.25 | 2.07 | 1.40 | 0.58 | 2.67 | 0.71 | 0.56 | 0.61 |
| MED | 622.5 | 30.75 | 22 | 6.15 | 17 | 4.45 | 5 | 5 |
| MIN | 440 | 26.7 | 18 | 5 | 2 | 3.2 | 4.2 | 4.2 |
| MAX | 990 | 35.2 | 24.1 | 8 | 20.6 | 6 | 6.8 | 6.8 |

anthropometric parameters proportionally to gestational age.

The values of the anthropometric parameters are given in three tables according to gestational age, 2a (17-19 g.a), 2b (20-22 g.a) and 2c (23-25 g.a).

Indexes of fetal growth by gestational age and determined based on previously measured anthropometric parameters showed changes during the growth. As most significant in all of the examined groups, was the cephalic index – the index used for assessment of the shape/form of the head of the fetus which mean values were (65.30± 6.64) in male fetuses of the first group, (66.40± 10.18) in the second group, and (66.30± 4.67) in the third group. In female fetuses from the first group the mean values were (65.38± 7.97), in the second group (67.87± 10.61) and in the third group (66.25± 3.90). This index showed that the examined fetuses had mostly round heads (brachycephalic and hiperbrachycephalic).

The values of the cephalic index are shown in table 3.

Discussion

Longitudinal dimensions are some of the most reliable indicators of intrauterine growth of the fetus which show whether the growth is adequate to the given gestational week. All deviations in the linear dimensions lead to further observation in order to establish the type, degree and etiology of the altered growth (4). Results from numerous anthropometric studies confirm that body weight and body length are some of the most important markers for determining the normal development of the fetus and they highly correlate with gestational age, which was also shown in our study. By recommendation of WHO (5) other, more reliable parameters are included in the classification, such as head circumference, bi-parietal diameter, upper-leg length, limbs circumference. Measurements of femur length, as well as upper-leg circumference are potential parameters for the assessment of fetal weight with even distribution of muscle mass and fat tissue during fetal growth and development (6,7). According to T. Evans, measurement of the bi-parietal

Table 3. Values of cephalic index in male and female fetuses

| | (17-19 g.a) | (20-22 g.a) | (23-24 g.a) |
|---------------|-------------|-------------|-------------|
| male | | | |
| X | 65.30 | 66.40 | 66.30 |
| SD | ± 6.64 | ± 10.18 | ± 4.67 |
| female | | | |
| X | 65.38 | 67.87 | 66.25 |
| SD | ± 7.97 | ± 10.61 | ± 3.90 |

diameter proved dependent on the shape of the fetal head, whereas measurement of head circumference is independent from its shape (8). Monitoring the dynamics of the growth of certain dimensions of the fetal head in the intrauterine period shows that the parameters of the head increase proportionally to gestational age. The advantages in diagnosing fetal abnormalities are biggest in the second trimester. In his paper Amir Omair at all. worked out a curve which shows the correlation between gestational age and the other parameters such as biparietal diameter, head circumference, abdomen circumference and femur length (9,10). The recommendations of WHO opened up new phases in the ideas for using other fetal parameters which highly correlate with gestation and crown-rump length and which increase the precision of determining the normal development of the fetus (11).

Conclusion

Measuring fetuses can be an additional method which will supply information about the fetal growth and the changes that can occur during the growth and development of the fetus. Crown-rump length and gestational age, as reliable fetal parameters which are routinely measured during the entire intrauterine growth of the fetus, are thought to play part in the assessment of the fetal growth and development as well as in setting a diagnosis for early fetal abnormalities in the intrauterine growth.

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ПОКРИВАЊЕ НА ДЕФЕКТИ НА ПРЕДЕН АБДОМИНАЛЕН ЗИД- ПРИКАЗ НА СЛУЧАИ

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Извадок

Дефекти на цела дебелина на предниот абдоминален зид најчесто се последица на претходна интраабдоминална операција со постоперативна компликација на оперативната рана. Како последица на изложеноста на абдоминалната содржина на надворешна средина следи понатамошно влошување на состојбата на пациентите, со губиток на течности и протеини, колонизација со интрахоспитални бактерии на раната, продолжување на хоспитализација и потреба од стална нега.

Целта на овој труд е да ја прикаже реконструкцијата на големи дефекти на предниот абдоминален зид кај четири наши пациенти со користење на локални резенки.

Во трудот се прикажани 4 случаи оперирани на Клиниката за пластична и реконструктивна хирургија, со големи дефекти на цела дебелина на преден абдоминален зид како последица на претходна операција во друга установа. Поради мултидирекционална васкуларизација на структурите на предниот абдоминален зид применивме локални ротациони или транспозициони рандом резенки во зависност од големината на дефектот.

Кај сите случаи постигнавме задоволителен резултат, со смирување на локална инфекција, заштити на интраабдоминални органи, скратување на потреба од понатамошни преврски и нега на раните, и активирање на пациентите за водење на нормален живот.

Начинот на хируршко покривање зависи од големината и локализацијата на дефектот на предниот абдоминален зид. Времето од настанок на дефектот до негова реконструкција исто така има влијание на хируршката техника и резултатот. Правилно планирање на резенките ни овозможува реконструкција и покривање и на дефекти кои зафаќаат две третини од предниот абдоминален зид.

Клучни зборови: преден абдоминален зид, големи дефекти, резенки, реконструкција.

COVERAGE OF ANTERIOR ABDOMINAL WALL DEFECTS: CASE REPORTS

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Abstract

As complications of all operations of intra-abdominal organs and repairs of abdominal-wall hernias, defects in the anterior abdominal wall might appear. They affect either the skin and subcutaneous tissue or the full thickness of the abdominal wall with muscles and peritoneum, thus exposing to external influence the intra-abdominal organs, most often the bowels.

We present 4 (2 women and 2 men) patients with different size of full-thickness defects in the anterior abdominal wall. The employed surgical procedures were transposition flaps in two patients and rotational random (ratio 2/1 length vs width of the base, without identified blood supply) flaps in two patients.

The results obtained were satisfying in both functional and esthetic aspects. Except for avoiding seldom dressings and some limitations while walking, the patients had a significantly better quality of life. All patients left the Clinic in mobile condition, with no need of help by another person.

The size and location of the anterior abdominal wall defect determine the method of surgical reconstruction. Application of random flaps is justified since it is the least aggressive method, which might be used even in patients with the most serious defects in the early phases to prevent appearance of cicatrix changes and tissue retraction at the defects' margins.

Key words: anterior abdominal wall, large defects, flaps, reconstruction

Introduction

As complications of all operations of intra-abdominal organs and repairs of abdominal-wall hernias, defects in the anterior abdominal wall might appear. They affect either the skin and subcutaneous tissue or the full thickness of the abdominal wall with muscles and peritoneum, thus exposing to external influence the intra-abdominal organs, most often the bowels (1). In cases like these the function of the abdominal prelum is lost and it is impossible to reconstruct it (2). The purpose of covering these defects is physical protection of the intra-abdominal organs with skin flap and concomitant management and further protection of wound infections and restoration of the other protective functions of the skin graft (loss of liquids and proteins, thermoregulation, etc.).

Material and Methods

We present 4 (2 women and 2 men) patients who underwent operation at the Clinic of Plastic and Reconstructive Surgery, with different size of full-thickness defects in the anterior abdominal wall. The following parameters were examined: size and location of the defect, previous treatments and comorbidity, age of the patients, vascularization of the surrounding skin. The employed surgical procedures were transposition flaps in two patients and rotational random (ratio 2/1 length vs width of the base, without identified blood supply) flaps in two patients. All patients had previous local wound infection that was treated by antibiogram pre- and post-operatively. In two patients synthetic material (Goretex mesh) was present in the defects, which supported the infection and caused physical impediment to the surgical dressing. These were intra-operatively removed. Applying mild debridement we removed fibrin plaques on the intestinal serosa that supported the infection. We previously mobilized the planned flaps and covered the defects. Separate sutures with Prolene and Silk 1-0 and 2-0 were used. Sutures were removed 14 days postoperatively. Follow-up assessment was done during 6 months.

Case reports

Case no. 1

We present an 82-year-old man previously operated for caecum neoplasm having postoperative complications and peritonitis and necrotizing fasciitis of the anterior abdominal wall. He was admitted to our Clinic four months after his first operation. He was immobile, with complete defect in the central part of the anterior abdominal wall with dimensions 30x20 (Figure 1). Right ileostomy was performed, which was difficult to be maintained due to the defect. As a result of the retraction of the surrounding healthy skin, there was fibrosis around the defect with initial epidermisation of the margins toward exposed intestinal curves. We covered the defect with rotational flap from the left thoracolumbar region, length of 40 cm, width of 25 cm (Figure 2). Postoperative necrosis appeared on the third segment of the flap to the peak,

which was extracted and the defect was covered with local rotational flap from the right iliopubic region (Figures 3 and 4). The patient spent 32 days in hospital. On discharge he was with a completely covered defect, better ileostoma maintenance and with no need of further dressing. Control assessment showed weakness of the anterior abdominal wall with herniation, which was regulated by carrying a truss/belt. There was no need of follow-up after 6 months.



Fig. 1.



Fig.2.

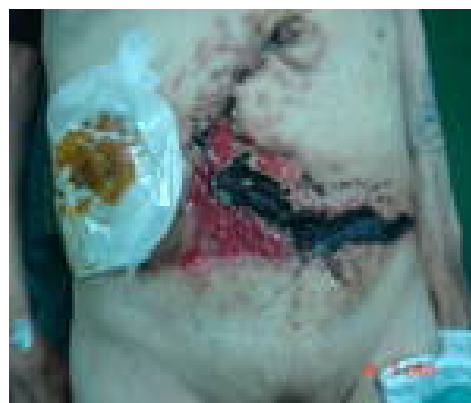


Fig. 3.



Fig. 4.

Case no. 2

A 56-year-old man was previously operated for epigastric hernia. Synthetic mesh was used for strengthening the abdominal wall. Postoperative skin and subcutaneous necrosis appeared with exposure of the synthetic material and defect 10x8 cm, with persistent local infection (Figure 5). He was admitted to our Clinic 9 months following the first operation. Synthetic material was intraoperatively removed; wound debridement was made and the defect was covered with local rotational flap (Figure 6). The patient was hospitalized for 8 days. The wound healed per primam; sutures were removed after 14 days. Dressings were not necessary 16 days after the operation.



Fig. 5.



Fig. 6.

Case no. 3

A 49-year-old woman was previously operated on for rectal neoplasm. She was referred to our Clinic from the Clinic of Digestive Surgery 16 days after the operation with a full-thickness abdominal wall defect in the right iliac region with dimensions 14x8 cm (Figure 7). Since the defect was a result of the resection of neoplastic infiltration, we did not use synthetic material. We covered the defect with local transposition flap (Figure 8). The wound healed per primam and the patient was hospitalized for 10 days. Postoperative follow-up in duration of 6 months revealed no signs of herniation and no need of dressings.



Fig. 7.



Fig. 8.

Case no. 4

A 72-year-old woman had several ventral hernia operations. The last surgical intervention was two years prior to admission to our Clinic. Postoperative necrosis of a part of the abdominal wall appeared with exposure of the used synthetic material and intestinal curves under it, with permanent local infection and secretion. Everyday dressings were applied during a two-year period. She was admitted at our Clinic with a full-thickness abdominal wall defect with dimensions of 8x7 cm, with exposed synthetic mesh, that exhibited granulation tissue growth and was intimately adhered to the intestinal curves (Figure 9). In order to avoid infection we removed the mesh first, that resulted in partial deserosing of the small intestines, which was managed with individual sutures. The defect was covered with transposition flap (Figure 10). Five days after operation secretion of intestinal content of the wound appeared resulting in creation of intestinal fistula as a complication. It was conservatively treated and the secretion stopped 11 days later. The patient was discharged after 17 days of hospitalization. Ten days after dismissal she was again admitted to the Clinic because of repeated secretion from the intestinal fistula. She was hospitalized for 14 days and there was no secretion during the last 4 days. The control examination one month later revealed normal wound healing, no fistulization and no need of dressings. Six-month follow-up presented with no complications.



Fig. 9.



Fig. 10.

Results

Having in mind that defects in all cases were covered with the so-called random flaps, the results obtained were satisfying in both functional and esthetic aspects. Except for avoiding seldom dressings and some limitations while walking, the patients had a significantly better quality of life. All patients left the Clinic in mobile condition, with no need of help by another person.

Observed complications were: necrosis of a part of the flap (1), intestinal fistula (1).

Discussion

The need of covering the anterior abdominal wall defects is indisputable. Indication for covering the defects is certainly associated with the cause of their appearance and therefore, it is essential to choose the right time in order to achieve better or optimal results. Waiting is an obstacle since creation of fibrous and cicatrix tissue around the margins of the defect aggravates tissue mobilization during flap lifting as well as compromises the circulation along the margins of the lifted flap (3, 4). Intimate relation of intestinal curves around the margins of the defect where epidermal ingrowth began after a longer period of time is also an increasing risk factor. Presence of synthetic material in conditions of chronic infection only supports the infection and they have to be removed as soon as possible.

Conclusion

The size and location of the anterior abdominal wall defect determine the method of surgical reconstruction. Anatomical relations and vascularization of the anterior abdominal wall allow each surgeon, depending on his/her experience and needs of the patient, to apply different surgical procedures and techniques. Application of random flaps is justified since it is the least aggressive method, which might be used even in patients with the most serious defects in the early phases to prevent appearance of cicatrix changes and tissue retraction at the defects' margins.

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КОМПЛЕТЕН ПОДМУСКУЛЕН СЛОЈ КАКО КРАЈНО РЕШЕНИЕ ЗА КОМПЛИКАЦИИ ПРИ АУГМЕНТАЦИЈА НА ДОЈКИ

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Извадок

Вовед: За прв пат 1960 год. се имплантирани силиконски импланти и истите сеуште се користат со некои модификации на материјалот. Кога имплантот се пласира низ хируршка инцизија на границата меѓу пигментираниот дел на ареолата и нормалната кожа на дојката, наречен периареоларен пристап, имаме од естетски поглед најмала лузна и лузна што најмалку се приметува. Имплантот може да биде пласиран: директно под жлездата, субфасцијално или под пекторалниот мускул. Подмускулниот пристап е развиен као одговор на компликациите кои се јавуваат при имплантација под самата жлезда. Посебно како чести компликации се контрактурите на капсулата и видливост и палпабилност на работ на имплантот на долниот пол на дојката. Цел: Нашата цел е да претставиме еден модифициран пристап, за кој што мислиме дека е решение за аугментирани дојки со компликации. Посебно кај оние пациенти кај кои имаме развиени контрактури на капсулата и пациенти кај кои се направени тумеректоми на дојките. Материјал и методи: Ке прикажеме неколку пациенти како прикази на случаи, на 25-45 год. старост. Кај овие пациенти се развиле компликации како резултат на претходни аугментации или се пласираат импланти за прв пат заради губиток на ткиво на дојките поради претходни операции. Оперативен пристап: Дебот се прави со класичен пристап за аугментација под пекторалниот мускул, варијацијата од овој пристап е дека не се прави откачување на инсерциите на мускулот латерално и медијално, туку имаме само широка инцизија на самиот мускул низ која го пласираме имплантот. Целта е да се добие добра обвивка од ткиво врз целиот имплант, поготово на долниот пол на дојката. Покрај долгата листа на потесијални компликации кои можат да произлезат при оперативна аугментација на дојки, сепак оваа процедура е една од најсигурните и процедура со најдобар исход. Ниската инциденца на компликации, сигурноста на хируршката процедура, предвидливиот исход, доведуваат до фактот да се повеќе пациенти се решаваат да се подвргнат на естетска корекција на дојки со импланти. Хируршкиот третман овозможува баланс меѓу волуменот и обликот на дојките и севкупно подобрување на обликот на телото.

Клучни зборови: имплант, контрактура, подмускулен слој, аугментација на дојки

TOTAL SUBMUSCULAR PLANE AS FINAL SOLUTION FOR THE COMPLICATIONS IN BREAST AUGMENTATIONS (CASE REPORTS)

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Abstract

Introduction: Silicone implants were used in 1960 for the first time and they are still used with some modifications in the material. Implants placed by an incision within the pigmented areola tissue, referred to as a periareolar incision, often result in the least conspicuous scar. Implants may be placed directly beneath the mammary gland, sub fascially or in a plane below the pectoralis major muscle. Sub muscular placement of implants was developed in response to problems associated with subglandular placement, specifically, capsular contracture and visibility of the edge of the implant. Aim: The aim of this paper is to present one approach that we assume is efficient in solving problems that arise in previously augmented breasts when complications appear, such as capsular contractures. It might also be a solution for previously operated breasts with tumerectomy. We are aware of the fact that this approach might be criticized, however, we wanted to present our results. Material and methods: We are going to present several case reports of patients aged between 25-45 years, who developed complications after the first augmentation of the breasts. Most of them had capsule contractures or, as a result of previous surgeries, developed bottoming of the implants or the

augmentation was performed because of the loss of breast tissue as a result of skin-sparing mastectomy of the breasts. Operative approach: The pocket was made under the muscle as in the classic technique for augmentation under the pectoralis muscle. The modification of this technique is that we did not detach the muscle from its insertion laterally and medially but we have just made wide incision on the muscle. The aim is to gain good tissue thickness involving the part of the muscle in the lower pole of the breast. Outcome: Despite the extensive list of potential complications, breast augmentation remains one of the safest and most predictable procedures performed. The low incidence of complications and the predictability of surgical outcome have prompted an increasing number of individuals, who currently are dissatisfied with their breasts, to undergo the procedure. The surgery provides a balance between the size and shape of the individual's breast and overall body size and shape.

Key words: implant, contracture, sub muscular layer, breast augmentation

Introduction

Aesthetic augmentation of the breast is performed to improve individuals self image and to change the volume and shape of the breast. There were various techniques through the history, but the safest and durable method was proven to be with silicone implants or implants with some other modified silicon material (1).

Silicone implants were used in 1960 for the first time and they are still used with some modifications in the material. The silicone and all other materials based on silicon are proven to be with minimal solubility and excellent viscosity. On the other hand, saline filled implants are safer for patients in the view of material that is compatible with the fluids in the body, but more than 20% of the patients develop deflation of the implants and are usually replaced with silicon filled one (2). The incision through which the implant is placed depends on the anatomy, the patient's wishes and the surgeon's experience. The axillary approach avoids scarring in the breast, but it provides limited exposure of the surgical site and requires endoscopic instruments. Incision through inframammary fold provides the best exposure of the surgical site but the scarring is very visible.

Implants placed by an incision within the pigmented areola tissue, referred to as a periareolar incision, often result in the least conspicuous scar (3). However, dissection of the pocket required for implant placement is more difficult with a periareolar incision. Dissection must proceed through a portion of the breast tissue or in the subcutaneous plane. Problems with subcutaneous dissection include nodularity and inflammation. Incisions placed through the breast tissue or in the subcutaneous plane are associated with micro calcification and cyst formation. Medial placement of the periareolar implant incision within the areola avoids the fourth intercostal nerve (4), which supplies sensation to the nipple and areola.

Implants may be placed directly beneath the mammary gland, sub fascially or in a plane below the pectoralis major muscle. Advantages attributed to

placement below the gland include ease of dissection, predictable sizing and contouring, and satisfactory results provided capsular contracture does not occur. Placement of larger implants in a subglandular position than in a submuscular position is also feasible (5). Submuscular placement of implants was developed in response to problems associated with subglandular placement (6), specifically, capsular contracture and visibility of the edge of the implant.

Additional benefits attributed to submuscular placement include reduced sensory changes in the nipple, decreased rates of capsular contracture, and ease of interpretation of mammographic studies. The submuscular plane is avascular and incidence of hematoma may be reduced by placement in the submuscular plane (7). Disadvantages include potential limitations on the size of the implant, increased postoperative pain, and possibility of lateral displacement of the implant. In addition, obtaining significant cleavage is more difficult with submuscular placement. If significant cleavage is desired, it is recommended to detach the inferior portion of the pectoralis musculature from its sternal attachments. This results in increased postoperative discomfort. Complications are like in other augmentations: haematoma, infection, sensory changes, scars, and asymmetry contour irregularity etc (8).

Hematoma: The frequency of hematomas is less than 2% (8). Typical symptoms of hematoma are unilateral pain, swelling, and occasionally fever. Hematomas may develop slowly without symptoms or rapidly with symptoms. Small hematomas may resolve without intervention, but large hematomas require drainage. Often, delaying drainage until liquefaction of the clot has occurred is preferable. However, if hematoma is painful or large, it must be drained immediately.

Infection: Infection usually becomes apparent 7-10 days postoperatively but may manifest at any point. Distinctive presenting symptoms of infection include swelling, discomfort, pain, drainage, and cellulitis overlying the breast. In general, we have to drain and irrigate the wound. Removal of the implant may not be necessary, particularly

if a periareolar incision was used with initial surgery. Prescription of antibiotics with wide spectrum is necessary. **Sensory changes:** Changes in nipple-areolar sensation are common postoperatively in patients who have undergone breast augmentation. Most patients exhibit a temporary dysesthesia, which tends to resolve in a period of months. However, a small percentage of individuals may present with long-term sensory changes in one or both nipples following breast augmentation.

Scars: are uncommon following breast augmentation. The lowest incidence of hypertrophic scarring appears in periareolar incisions.

Asymmetry: of the implant position may result from shifting of the implant, increased contraction of the capsule unilaterally, or ptosis of the implant.

The most common cause of contour irregularity is a tight capsular contracture that may develop around the implant. A wide range of incidence of capsular contracture, in 0-74% of patients, has been observed following breast implantation. The incidence of capsular contracture appears to be approximately 30% of individuals who have undergone the procedure (9). Classification of the contracture is highly subjective.

In 1980, Little and Baker developed a classification for the capsular contracture found in patients following breast augmentation, which has remained the standard for evaluating this complication in patients (9). The grades of capsular contracture are divided into 4 types:

Grade I: Capsular contracture of the augmented breast feels as soft as an unoperated breast.

Grade II: Capsular contracture is minimal. The breast is less soft than an unoperated breast. The implant can be palpated but is not visible.

Grade III: Capsular contracture is moderate. The breast is firmer. The implant can be palpated easily and may be distorted or visible.

Grade IV: Capsular contracture is severe. The breast is hard, tender, and painful with significant distortion present. The capsule thickness is not directly proportional to palpable firmness, although some relationship may exist.

Aim

The aim of this paper is to present one approach that we assume is efficient in solving problems that arise in previously augmented breasts when complications appear, such as capsular contractures. It might also be a solution for previously operated breasts with tumerectomy. We are aware of the fact that this approach might be criticized, however, we wanted to present our results

Material and methods

We are going to present several case reports of patients aged between 25-45 years, who developed complications after the first augmentation of the breasts. Most of them had capsule contractures or, as a result of previous surgeries, developed bottoming of the implants or the augmentation was performed because of the loss of breast tissue as a result of skin-sparing mastectomy of the breasts.

Operative approach:

The approach was made on the same incision as previous (periareolar), the implant was removed and we performed capsulotomy of the pocket over the muscle and capsulectomy of the part on the mammary gland (10). The new incision was made on the pectoralis muscle above the insertion of the muscle, thus the part of the muscle stayed intact in the lower pole. The pocket was made under the muscle as in the classic technique for augmentation under the pectoralis muscle. The modification of this technique is that we did not detach the muscle from its insertion laterally and medially but we have just made wide incision on the muscle. The aim is to gain good tissue thickness involving the part of the muscle in the lower pole of the breast (11). In the end we made classic suture of the gland and sub-cutis; in cases where there was excess of skin we performed peri-areolar mastopexy (cases where new implants with less cc. are implanted). During the follow-up assessment of two years we observed no problems with contractures or problems in the view of contracting the breasts when patient contracts the pectoralis muscles (12). In the post operative, period of two months, fitness or hard physical activity was strictly forbidden to the patients.

Pro Arguments:

1. The implant is fully covered by the muscle or fascia, which helps to camouflage the edges of the implant, as well as ripples in the implant, having complete sub-muscular placement has the least risk of visible rippling (13).
2. The fascia serves as support to the lower pole, whereas with partial sub-muscular placement the skin tissue supports the weight of the implant. Complete sub-muscular layer serves as sort of an "internal bra".
3. Reduces the risk of capsular contracture;
4. Better mammogram reading in diagnostics;
5. Reduced risk of bottoming out;

Con Arguments:

1. More post operative discomfort;
2. Breasts tend to sit a bit high at first, until the muscle relaxes;



before



after

Fig. 1. Case 1



before



after

Fig. 2. Case 2



before



after

Fig. 3. Case 3



before



after

Fig. 4. Case 4



before



after

Fig. 5. Case 5

3. Implant distortion in some cases when the muscle is tightly flexed;
4. If the breasts are widely spaced, it can be difficult to create cleavage especially with texture implants (14).

Outcome and prognosis

Despite the extensive list of potential complications, breast augmentation remains one of the safest and most predictable procedures performed. The low incidence of complications and the predictability of surgical outcome have prompted an increasing number of individuals, who currently are dissatisfied with their breasts, to undergo the procedure. The surgery provides a balance between the size and shape of the individual's breast and overall body size and shape.

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ГАНГЛИОН ВО ПРЕДЕЛ НА КОЛЕНИОТ ЗГЛОБ - ПРИКАЗ НА СЛУЧАЈЦолева-Толевска Роза¹, Попоска А¹, Самарџиски М¹, Георгиева Д¹, Стефановска Е²¹Универзитетска клиника за ортопедски болести, Скопје.²Универзитетски институт за радиологија, Скопје
Медицински факултет Скопје, Р. Македонија**Извадок**

Презентираме случај на 40 годишен пациент кој пред 2 години забележал оток локализиран од медијалната страна на левото колено во предел на pes anserinus. Клинички присутен беше мекоткивен тумор со големина на орев (5x3 cm), без палпаторна болна осетливост и без знаци за инфламација. Кај пациентот беа направени: лабораториски иследувања, туморски маркери, рентгенграфија на колено, ехосонографија на колено и магнетна резонанса. Индицирано беше оперативно лекување и екстирпација на мекоткивниот тумор во целост. Патохистолошки добиен е наод за ганглион во предел на коленото. Ганглионот има периартикуларна локализација и тоа со интраартикуларна, екстраартикуларна, периостална до интраосална локализација. Во нашиот случај имавме екстраартикуларен ганглион. Заклучок: Цистичните лезии околу коленото се релативно чести. Познавањето на истите, нивното појавување и локализација, како и познавањето на дијагностичкиот протокол, овозможува добар третман и прогноза.

Клучни зборови: ганглион, цистични лезии**GANGLION CYST OF THE KNEE – CASE REPORT**Dzoleva-Tolevska Roza¹, Poposka A¹, Samardziski M¹, Georgieva D¹, Stefanovska E²¹University clinic for orthopedic surgery,²University institute for radiology,
Medical Faculty, Skopje, R. Macedonia.**Abstract**

We present a 40 year old patient who had a swelling localized on the medial side of the left knee around pes anserinus. Clinically it was a soft tissue tumor, with 5x3 cm size, without pain on palpation, and without any signs of inflammation. We have done several investigations such as: laboratory investigations, haemostasis, tumor markers, RTG, Ultrasonography of the knee and MRI. After we diagnosed the ganglion around the knee, we indicated operation and the ganglion were extirpated. Pathohistological examination confirmed our diagnosis. Ganglia have a predilection for periarticular location arising from variable intraarticular, extraarticular, intraosseous end periosteal locations.

In our case we had an extraarticular ganglion.

Conclusion: Cystic lesions around the knee joint are common. Knowledge of characteristic appearance and location of cystic masses around the knee, as well as knowledge of protocol for diagnosis always gives good treatment and prognosis.

Key words: ganglion, cystic lesions**Introduction**

Cysts can occur in many shapes and forms around the knee. A cyst is defined as closed cavity, or sac, that is lined with epithelium. It can contain liquid or semisolid material and can occur in soft tissue or in bone.

Cysts around the knee have multiple etiologies.

Cysts include inflamed or irritated bursa, meniscal cysts, ganglia, Baker cyst and extra neural cysts.

Case report

We present a 40 year old patient who had a swelling localized on the medial side of the left knee around pes anserinus. This swelling persisted two years, with same size from the beginning till now. The patient had pain at maximal flexion of the knee and at physical activity.

Clinically it was a soft tissue tumor, with 5x3 cm size, without pain on palpation, and without any signs of inflammation.

We have done several investigations such as:

- laboratory investigations – with normal parameters
- haemostasis – with normal parameters
- tumor markers – with normal parameters
- RTG – the knee was with normal morphology and structure of the bone
- Ultrasonography of the knee – of the medial side of the knee there was a cystic formation fulfilled with liquid. (Fig.1)

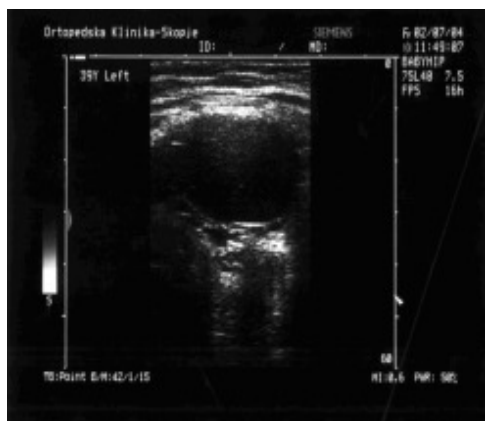


Fig. 1. Ultrasonography of the cyst

- MRI – on MR imaging there was a lobulated cystic formation (5x2 cm), with fluid collections. Ganglion was localized periarticular between lig.collaterale mediale and m.semimembranosus on the medial side and m.sartorius and m.gracilis on the lateral side. (Fig.2 et 3)

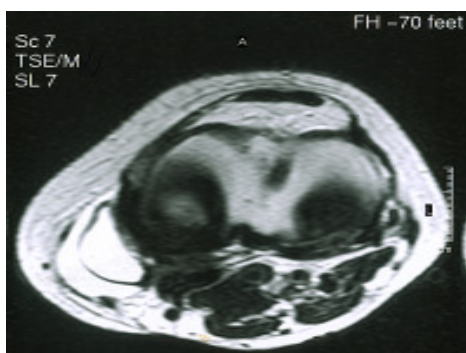


Fig. 2. MRI of the cyst



Fig. 3. MRI of the cyst

After we diagnosed the ganglion around the knee, we indicated operation and the ganglion were extirpated.

Pathohistological examination confirmed our diagnosis. On the histological slide (preparation), there were fissures fulfilled with mucinous fluid, the wall was with connective tissue, and there were some parts with mixoid degeneration of the connective tissue.

Discussion

Ganglion is benign cystic mass with dense fibrous capsule from outside and mucinous fluid inside. The pathogenesis of ganglia remains controversial. Most authors believe that ganglion cysts are result of mucous degeneration in a collagen structure. Ganglia are most commonly located in areas under continuous stress, such as a joint capsule or tendon. With repeated activity in these areas, the periarticular connective tissue is thought to undergo mucous degeneration with the formation of amorphous gelatinous material.

Another etiological theory therefore includes primary cellular hyperplasia with associated mucin secretion and secondary cystic degeneration of connective tissue.

The frequent periarticular location of ganglia fostered the theory that they originate from synovial herniation of the joint capsule or tendon sheath due to a defect or traumatic tear.

Another theory suggests that ganglia arise from displaced synovial remnants during embryogenesis.

Ganglia have a predilection for periarticular location arising from variable intraarticular, extraarticular, intraosseous end periosteal locations.

In our case we had an extraarticular ganglion.

Differential diagnosis:

- Meniscal cyst
- Bursitis of medial collateral ligament
- Bursitis anserinus
- Synovialchondromatosis
- SynovioSa

Conclusion

Cystic lesions around the knee joint are common. Knowledge of characteristic appearance and location of cystic masses around the knee, as well as knowledge of protocol for diagnosis always gives good treatment and prognosis.

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YOLK SAC TUMOR НА ОВАРИУМОТ СО КОНКОМИТАНТЕН МАТУРЕН ЦИСТИЧЕН ТЕРАТОМ КАЈ НУЛИПАРА: ПРИКАЗ НА СЛУЧАЈ

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Извадок

Вовед: Туморите на жолчната вреќа се втора најчеста оваријална неоплазма со потекло од герминативни клетки по дисгерминомите, опфаќајќи приближно 20% од сите малигни герминативни тумори на овариумот и 5% од сите оваријални малигни неоплазми. Туморите на жолчната вреќа се високо агресивни неоплазми кои имаат тенденција за брза интра-абдоминална дисеминација и метастазирање. Покрај тоа, заради фактот дека овие тумори преодминантно се јавуваат кај жени во фертилен период, зачувувањето на фертилноста е многу значајно.

Приказ на случај: Презентиравме случај на оваријален тумор на жолчна вреќа со конкомитантен матурен цистичен тератом кај 28 годишна нулипара. Пациентката беше хоспитализирана на нашата клиника заради тапа болка во долен дел на абдомен, чувство на надуеност и диспареунија претходните 2-3 месеци. Имиџинг тестовите прикажаа хетерогена, преодминантно солидна туморска маса со потекло од десниот овариум која ја исполнува целата карлица и долниот дел на абдоменот. Лабораториските наоди покажаа зголемена седиментација и зголемени концентрации на АФП и ЦА-125. Кај пациентката беше направена десна салпинго-оофоректомија, по што беа администрирани 4 курса на цитостатска терапија по БЕП протоколот во обид да се зачува фертилноста на пациентката. По терапијата, беше постигната ремисија на болеста која се задржа за време на целиот контролен период (една година по хируршкиот третман). Конечната хистопатолошка дијагноза беше малиген тумор на жолчна вреќа на десниот овариум стадиум ИЦ со конкомитантен матурен цистичен тератом.

Заклучок: Минимално инвазивната хирургија, следена со конвенционална БЕП хемотерапија е легитимна опција за третман на оваријални герминативни тумори, доколку е потребно зачувување на фертилноста на пациентката.

Клучни зборови: оваријален тумор на жолчна вреќа, зачувување на фертилност

YOLK SAC TUMOR OF THE OVARY WITH A CONCOMITANT MATURE CYSTIC TERATOMA IN A NULLIPAROUS PATIENT: A CASE REPORT

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Abstract

Introduction

Yolk sac tumors are the second most common malignant ovarian germ cell tumors after dysgerminoma, and comprise approximately 20% of malignant ovarian germ cell tumor representing about 5% of all ovarian malignancies. Yolk sack tumors are highly aggressive malignancies that show early intra-abdominal dissemination and metastasis. In addition, because these tumors occur principally in girls and women of childbearing age, the preservation of fertility is important.

Case report

We present a case of an ovarian yolk sac tumor with a concomitant mature cystic teratoma in a nulliparous twenty-eight year old patient. The patient was admitted at our Clinic because of dull lower abdominal pain, abdominal bloating and dyspareunia during the previous 2-3 months. The imaging revealed a heterogenous, predominantly solid mass that arised from the right ovary and occupied the entire pelvis and lower abdomen. The laboratory findings showed elevated ESR, as well as AFP and CA125 levels. The patient underwent a righ salpingo-oophorectomy followed by four courses of BEP once every three weeks in an attempt to preserve fertility. Remission was achieved and maintained during the entire follow up period (up to one year after surgery). The final histopathologic diagnosis was a malignant yolk sac tumor of the right ovary stage IC with a concomitant mature cystic teratoma.

Conclusion

Minimal surgery in ovarian germ cell and surgical staging, followed by conventional BEP chemotherapy is a viable treatment option when preservation of fertility is required.

Keywords: ovarian yolk sac tumor, fertility-sparing treatment

Introduction

Yolk sac tumors are the second most common malignant ovarian germ cell tumors after dysgerminoma, and comprise approximately 20% of malignant ovarian germ cell tumor representing about 5% of all ovarian malignancies [1, 2]. Yolk sack tumors are highly aggressive malignancies that show early intra-abdominal dissemination and metastasis. In addition, because these tumors occur principally in girls and women of childbearing age, the preservation of fertility is important. Before the introduction of effective combination chemotherapy, the prognosis of yolk sac tumors was extremely dismal; approximately 80–90% of patients were dead of the disease within 2 years of diagnosis [3, 4]. In the last few decades, treatment outcomes of the patients with ovarian yolk sac tumors have improved, in parallel with the improvements in the treatment of testicular germ cell tumors and malignant ovarian germ cell tumors. However, the prognosis for YST remains unsatisfactory among subtypes of malignant ovarian germ cell tumors.

We present a case of an ovarian YST with a concomitant mature cystic teratoma in a nulliparous twenty-eight year old patient.

Case report

A twenty eight year old nulliparous patient was first admitted at the Department of Gynecologic Oncology at our Clinic in January 2010. The patient complained of dull lower abdominal pain, abdominal bloating and dyspareunia in the past 2-3 months. The patient is nulliparous, non-smoker with a rather uneventful medical history. She was fairly well built and nourished, and her vital parameters were stable on admission. The vaginal examination revealed an irregular, firm, mobile and tender mass that arises from the pelvis and occupied the entire lower abdomen. The ultrasound examination detected a normally sized uterus displaced posteriorly from a solid tumor mass arising from the right ovary. The mass was predominantly solid with numerous hypochoic zones and a small cystic part near the upper pole. The left ovary had normal ultrasonographic morphology. There was a small amount of free fluid detected in the vicinity of the mass. Next, MRI was performed which showed a heterogeneous mass measured around 18cm in diameter occupying the pelvis and lower abdomen. It was deemed free from contact with the surrounding anatomical structures. Enlarged

lymph nodes were not detected. The laboratory findings showed and elevated ESR (64mm/h) and elevated levels of CA-125 (239U/ml) and α -fetoprotein (AFP) (331ng/ml). The patient underwent an explorative laparotomy on January 20th 2010.

At laparotomy, the entire pelvis was dominated by a fleshy grayish-yellow mass arising from the right ovary, with visible hemorrhagic zones. There was a small amount of ascites in the peritoneal cavity. The mass was mobile and free from the surrounding structures. Taking into consideration that the patient was nulliparous, a right salpingo-oophorectomy was performed in an attempt to preserve fertility. The postoperative period was uneventful. The final histopathologic diagnosis was a malignant yolk sac tumor of the right ovary with a concomitant mature cystic teratoma of the right ovary. The surgical stage was IC, according to the AJCC staging rules.

The patient received four courses of BEP (bleomycin, etoposide, and cis-platinum), once every three weeks. After the chemotherapy, AFP and CA-125 reduced to reference levels. The follow up ultrasonographic examinations and AFP and CA-125 levels at 6 months and 1 year after surgery revealed a clean pelvis and confirmed the remission. The patient was in good health during the entire follow up period.

Discussion

Yolk sac tumors, unlike most ovarian malignancies, have been known to be highly responsive to combined chemotherapy agents. This is the rationale behind using chemotherapy after surgical resection in the initial stages of the disease or as first line in more advanced cases. Furthermore, because these tumors occur principally in women of childbearing age, a minimally invasive approach that would preserve the patient's fertility is of utmost importance.

From the review of the available literature on the subject of treatment of malignant ovarian germ cell tumors (more notably ovarian yolk sac tumors), the outcomes of fertility-sparing surgery appear to be no worse than that of radical surgery and similar rates of menses and fertility are seen in patients with ovarian yolk sac tumor after fertility-sparing surgery followed by chemotherapy, as compared with healthy populations. Mitchell et al. reported in 69 patients with malignant ovarian germ cell tumor, including 45 patients with yolk sac tumor, that fertility-

sparing surgery was at least as effective as radical surgery. In a recent study, it was shown that forty out of forty-one women who underwent fertility-sparing surgery remain potentially fertile and pregnancy was achieved in 12 of 16 (75%) women who attempted conception [5]. A study that investigated long-term fertility in 132 patients with malignant ovarian germ cell tumor, including 22 patients with yolk sac tumor, and showed that menses and reproductive status of 76 patients who underwent fertility-sparing surgery and received adjuvant platinum-based chemotherapy were not different from the healthy control group [6]. However, preservation of fertility is difficult in cases of bilateral involvement. Kurman et al. and Ayhan et al. have reported bilateral tumor incidence rates of 8.4 and 8%, respectively [3, 7]. Kawai et al. have not reported bilateral tumor incidence rates in their series including 29 patients [2]. Therefore, because bilateral ovarian yolk sac tumors are rare, biopsy of the contralateral ovary that has seemingly normal macromorphology at the time of the initial surgery in patients with unilateral tumor should not be routine as it may also adversely affect fertility.

Conclusion

Minimal surgery in ovarian germ cell tumor is unilateral oophorectomy or salpingo-oophorectomy and surgical staging. If conservation of fertility is an issue of concern, preservation of contra-lateral ovary and uterus must be considered as well. Even in the presence of metastatic disease, due to high sensitivity of these tumors to chemotherapy, preserving fertility would be recommended.

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ХИРУРШКИ ЗОНИ НА ПОВРЕДИ НА ЕКСТЕНЗОРНИ ТЕТИВИ НА ШАКА -современи принципи на хируршкиот третман

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Извадок

Намерата на авторите на овој труд е да се прикажат современите принципи на хируршкиот третман на повредите на екстензорните тетиви на дорзумот на шаката. Добро познавање и разбирање на сложената анатомија на екстензорниот “апарат”, кој е составен од “внатрешни-мали” и “надворешни-големи” мускуло-тетивни елементи, како и својствена физиолошка функција со синхронизирано испружање на фалангите на прстите е “condicio sine qua non” за правилен хируршки третман на повредените екстензорни тетиви. Поделбата на повредените екстензорни тетиви на : акутни, стари, занемарени, отворени и затворени повреди, како и нивната класификација на осум (8) топографски зони на дорзумот на шаката е со цел за правилно разбирање и лекување на карактеристичните проблеми од нивните повреди. Во овој труд посебно внимание е посветено на повредите на екстензорните тетиви во зоните кои се од најголем хируршки интерес: првата(над дисталниот интерфалангеален зглоб), третата(над проксималниот интерфалангеален зглоб), петата зона(над метакарпофалангеалниот зглоб), како и четвртата зона кај палецот заради честота на повредите и можните испади и деформитети во случај на нивно нелекување или лошо хируршко лекување.

Клучни зборови : *шакa, екстензорни тетиви, зони на повреда, хируршки третман*

SURGICAL ZONES OF THE EXTENSOR TENDON INJURIES OF THE HAND - Principals of surgical treatment

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Abstract

This article deals with current concept of surgical treatment of the extensor tendon injuries in the hand. By understanding of complex anatomy of the extensor apparatus (consisting of intrinsic and extrinsic elements with four main insertions in the fingers) and appropriate physiology (advantage of running an almost entirely extrasynovial course as a superficial structure and, disadvantage of limited excursion in the hand) it is possible to ensure correct approximation and suturing of divided extensor tendon ends. Division of the extensor tendon injuries into VIII topographic zones is due to specific problems in different zones of the hand arising from extensor tendon injuries, also depending if there are acute, old or neglected injuries. Specific attention is given to characteristic zones of injuries as: Zone I(over distal interphalangeal joint-DIP), Zone III(over proximal interphalangeal joint-PIP), Zone V(over metacarpo-phalangeal joint-MCP) and Zone T IV(over snuffbox) in the thumb, due to frequency of injuries and possible failures and deformities as a result of maltreatment or neglected extensor tendon injuries.

Key words : *hand, extensor tendon, zone of injury, surgical treatment*

Introduction

There is a common misconception that extensor tendon injuries of the hand are repaired with ease and heal uneventfully. Although circulation to the extensor mechanism is very good, factors, conspiring against a good outcome after wounding and repair are :

- the flat, thin nature of the tendon distal to the metacarpophalangeal joint (MCP), permitting easy fraying with improper handling,
- the risk of rupture owing to the overwhelming force of the flexors on the palmar surface after repair; and
- the structural complexity of the extensor system, particularly at the level of the proximal interphalangeal joint.

Anatomy of the Extensor Apparatus- extensor system of the hand is complex and combination of extrinsic (m.

extensor digitorum et proprii) and intrinsic muscle-tendon elements (m.m. interossei, m.m. lumbricales and retinacular ligaments). The common aponeurosis of the extensor apparatus of the finger is tensed by the extensor digitorum, by interosseus and lumbrical muscles, and by the retinacular ligaments. There are four sites of insertion : (1) The sagittal bands are the most proximal insertion of the extensor tendon running into the interglenoid ligament on each side of the MCP, (2) Inconstant insertion of the extensor tendon into the base of the proximal phalanx, (3) The insertion of the middle (central) extensor (this central tendon is formed by the junction of the middle bands originating from both the intrinsic muscles and the extensor digitorum) tendon into the base of the middle phalanx is by far the most important, (4) Insertion of the terminal extensor tendon (two lateral extensor tendons

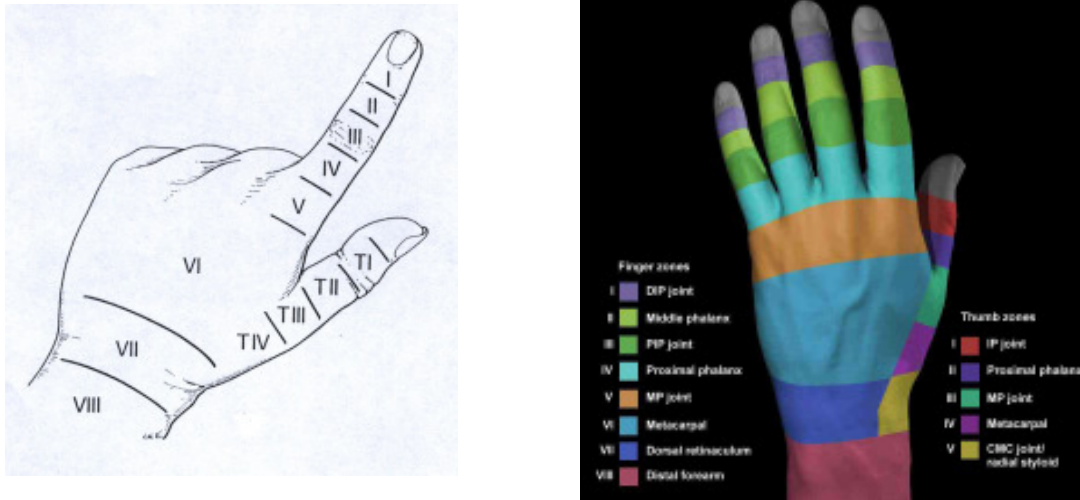


Fig. 2. Surgical Zones of the extensor tendon injuries of the hand



Fig. 3. Open surgical treatment of incised wound “ mallet finger”(schematic presentation-left), finger deformity(middle),after operation (right)

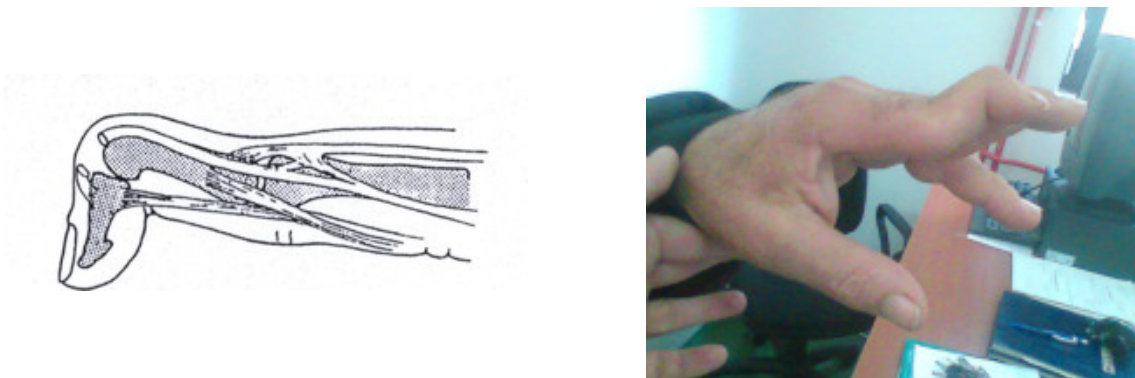


Fig. 4. “Swan-neck”, recurvatum deformity , schematic presentation(left), finger deformity(right)



Fig. 5. Operative treatment of incised wound extensor tendon division in Zone III(schematic presentation- left), before operation-(middle)), after operation(right)

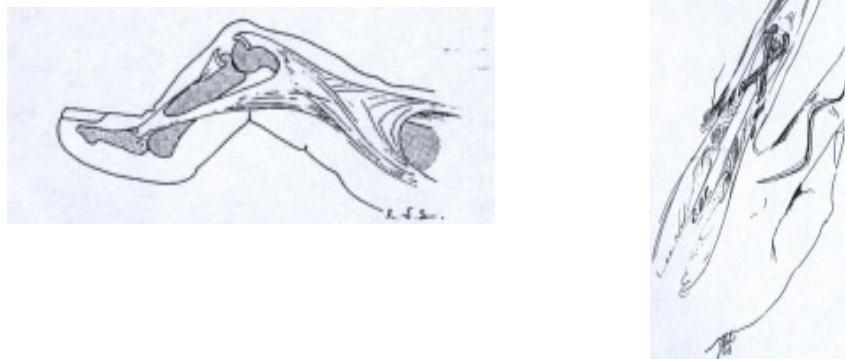


Fig. 6. "Boutonniere deformity" ,schematic presentation (left), reconstructive technique(right)

Zone III (proximal interphalangeal joint level) extensor tendon divisions

Incised wounds at the level of the proximal interphalangeal joint (PIP) may divide the central extensor tendon just proximal to its insertion on the proximal dorsal lip of the middle phalanx, and may also divide one or both lateral bands. The central extensor tendon is repaired with either interrupted fine suture or a monofilament continous pull-out suture, the lateral bands are repaired by sutures as well. The joint is transfixed in full extension with a stainless steel wire-Kirschner, for about 6 weeks. Closed rupture of the central extensor slip over the PIP is manifested by impaired active extension of the joint, usually following

a forced-flexion injury. These injuries are treated by splinting the joint in full extension for about six weeks, and up on occasion assisted by a fine transarticular Kirschner wire.

Disruption of the central extensor tendon over the PIP requires early treatment to prevent development of a "Boutonniere deformity", as a result with progressive volar displacement and shortening of the lateral bands, which are released from their dorsal position when the central slip is disrupted. The consequence is flexion position of the middle phalanx and hyperextension of the terminal phalanx. Treatment options are: splinting the PIP in full extension for about six weeks, and surgical reconstruction of the disrupted central slip.(8,9)



Fig. 7. "Boutonniere deformity" ,local findings(left), after reconstruction(right)

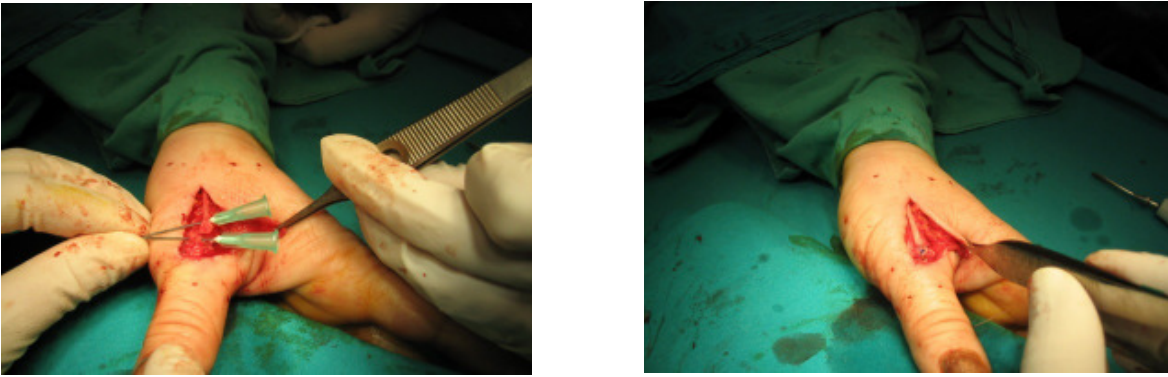


Fig. 8. Division of the extensor pollicis longus tendon (left), after reconstruction(right)

Zone V – Division at the Metacarpophalangeal Joint (MCP) level

This is common extensor tendon division due to the skin is thin over the knuckle on MCP, and tendons are vulnerable to injury. However, as it is at the level of the broad hood expansion, the extensor system is rarely severed completely, thus retraction of the proximal end is not a problem. The intimate relation of the extensor mechanism and the capsule of the MCP results in the joint frequently being open. In these cases the tendon ends and joint capsule are approximated and sutured as one layer with a single running monofilament suture, and postoperative splinting the joint in extension for about four weeks.(9,10)

Zone TIV (extensor pollicis longus division over first metacarpal)

Following division of the extensor pollicis longus over first metacarpal it is uniquely prone to proximal retraction through the third dorsal compartment to a position just proximal to the extensor retinaculum. Retrieval is generally possible by long instrument or with the aid of a plastic catheter placing through a transverse wrist incision. After approximation the tendon ends are sutured by modified Kessler technique with fine monofilaments and the thumb is splinting in full extension for about four weeks.

Zone VI, VII and VIII (Back of the Hand, Wrist, and Forearm)

Division of the extensor tendons at these levels presents no problem of diagnosis, with careful examination for injury to the superficial branch of the radial nerve. Early repair is strongly indicated, due to rapid retraction and contracture of the proximal ends, making direct repair after more than a few days difficult or impossible. Repair is by direct approximation of tendon ends by modified Kessler fine monofilament sutures , followed by protective splinting in the position of relaxed extension for about four to five weeks. (11,12)

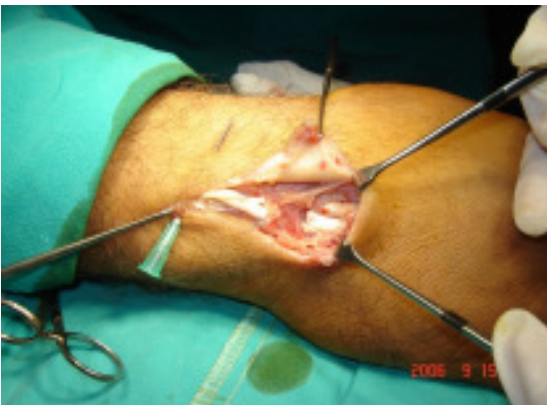


Fig. 9. Division in Zone VI/VII (left), After operation (right)

Postoperative Care

The principles of postoperative care following repair of extensor tendons are:

- sufficient immobilization for the development of adequate tensile strength to resist the power grip of the flexor tendons;
- restoration of glide in these relatively weak, fast-moving structures ; and
- prevention of deformities at the joint levels.

Zone I and some Zone II injuries require immobilization only at the DIP for a period of 6-8 weeks. Zone II,III ,IV,V,VI, VII and distal zone VIII injuries require 4 weeks of immobilization in the position shown. Patients are then instructed to squeeze a sponge in warm water gently for 5-

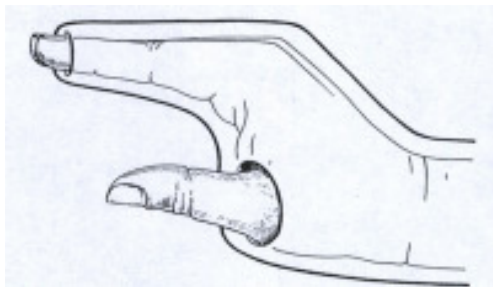


Fig. 10. Postoperative passive splinting with plaster cast,,schematic presentation(left),on patient (right)

10 minutes three to four times a day and to avoid power gripping for an additional 2 weeks.(12,13)

Discussion

The repair of severed extensor tendons in the hand with consistent success remains one of the great surgical challenges. Fixed adhesions preventing gliding remains the major problem of tendon repairs. It is apparent that the prognosis of tendon repairs is determined primarily by what tissue lie in contact with the repair of tendons. This observation has given rise to classification of the hand in to numerous “zones”. Unfortunately, far more attention has been paid to the digital flexor mechanism than the extensor, for it has been customary to regard extensor tendon injury as a relatively simple surgical condition, a consensus not generally shared by experienced hand surgeons. Extensor reintegration can be equally and possibly more challenging surgically than restoration of flexor function. The extensor system with its dual extrinsic and intrinsic power mechanism is far more complex than is readily appreciated. The conjoined extensor tendons lie in a shallow dorsal subcutaneous bed closely applied to periosteum, joint capsule and synovia, making repair especially difficult. The investing paratenon, though normally allowing free movement of the flattened extensor tendons and aponeurosis over the dorsum of the hand and fingers, is highly reactive when damaged and it results too often in tendon fixation at the site of injury and loss of function. Unlike the flexor mechanism, useful extensor function is readily jeopardized by the alteration of even a few millimeters excursion in the conjoined central and lateral tendon length relationship.(,13,14,15,16)

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РЕКОНСТРУКЦИЈА НА ОЧНИТЕ КАПАЦИ И ПЕРИОРБИТАЛНАТА РЕГИЈА СО РЕЗАНКИ

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Извадок

Реконструкцијата на дефектите на очниот капак (о.к.) после ексцизија на тумор или траума често претставува голем предизвик за хирургот. Реконструкцијата се стреми да ги реконструира природните обележја и функција на очниот капак што воедно ќе ги врати естетските карактеристики на лицето.

Материјал и Методи. Ретроспективна студија во која беа вклучени 140 пациенти кај кои беше извршена реконструкција на очните капаци, со употреба на најразлични резанки на Клиниката за пластична и реконструктивна хирургија во Скопје, во период од 1998 до 2010. Пациентите постоперативно беа следени од 3 месеци до 2 години со цел да се евалуира преживувањето на резанката, функцијата на капациите, повторување на болеста и естетскиот изглед.

Резултати. Најчеста локализација на дефектите беше на долниот о.к., најчестата патолошка дијагноза кај нашите пациенти беше базоцелуларниот карцином (91). Најчесто употребувана резанка беше глабеларната резанка.

Заклучок. Употребата на резанките за реконструкција на о.к.и периорбита од околните ткива, во нашата серија обезбедуваат добра боја и квалитет на кожа, соодветна васкуларизација, и дозволуваат лесно затварање на давачката регија со минимални лузни.

Клучни зборови: дефекти на очните капаци, реконструкција, резанки.

RECONSTRUCTION OF EYELID AND PERIORBITAL AREA WITH FLAPS

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Abstract

Reconstruction of eyelid defects after trauma or excision of a tumor often poses a great challenge for the surgeon. It aims to reconstruct the natural shape and function of the eye lid and at the same time preserve the aesthetic characteristics of the face.

Materials and Methods. The retrospective study included 140 patients who had reconstruction of the eyelids with different kinds of flaps. These were done at the Clinic for Plastic and Reconstructive Surgery in Skopje between 1998 and 2010. The patients were followed up from 3 months to 2 years postoperatively, in order to evaluate the viability of the flap, the function of the eye lids, recurrence of the disease and the esthetic appearance.

Results. The most common location of the defects is the lower eyelid, The most common diagnosis in our patients was BCC (91 patients). The glabellar flap is the most commonly used.

Conclusion. The use of surrounding tissue flaps in the reconstruction of the eye lids and the periorbital area provide good color and skin quality; adequate vascularisation, and allow easy closure of the tissues with minimal scarring.

Key words: eyelid defects, reconstruction, flaps

Introduction

Reconstruction of eyelid defects after trauma or excision of a tumor often poses a great challenge for the surgeon. It aims to reconstruct the natural shape and function of the eye lid and at the same time preserve the aesthetic characteristics of the face [1].

Local flaps with intact vascular stem are of great help in reconstruction of at least one of the both lamellas. Flaps from the surrounding tissues provide excellent match

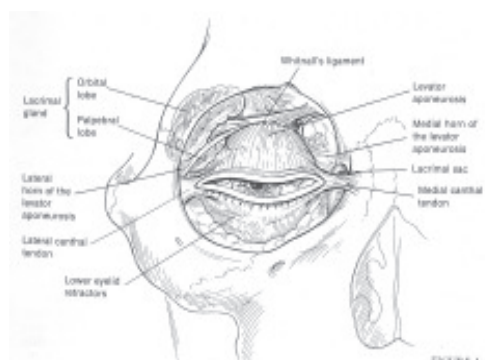
of the color of the skin , adequate blood supply and easy closure of the donor region with minimal scarring.

This study gives report about the functional and anatomical results of the use of flaps in reconstruction of defects of the eyelids and periorbital area in 140 patients.

The aim of the reconstruction is to preserve the function of the eyelids with acceptable cosmetic results and adequate protection of the eye itself.

Form a surgical point this region is very unique regarding reconstruction. The complexity, the free margins

and the anatomical characteristics can be easily disturbed. Solid knowledge of the anatomy and the physiology of the eyelid is an imperative for a successful surgical outcome [2].



Anatomy and physiology

The eyeball, the external eye muscles, the lacrimal gland, blood vessels and nerves are inserted in the orbital fat tissue and are protected by the bones of the orbit. The eye lid protects the eye surface from foreign bodies, light and UV radiation. It also distributes a film of tears over the eye surface by blinking therefore protecting to cornea from drying. Good position and function of the eyelids is a prerequisite for good eyesight [3].

Both upper and lower eyelids are formed in a same way. The anterior lamella consists of skin and muscle and the posterior lamella consists of tarsal plate and conjunctiva. The posterior lamella provides smooth posterior surface and the stability is provided by the tarsus. The tarsus is attached medially to the periosteum and temporally to the periorbital ligaments. The opening of the eyelids is done by the levator palpebrae muscle whose aponeurosis extends in the upper eyelid in a shape of a fan; while the closing of the eyelids is done by the orbicularis oculi muscle which forms a ring round the eye and is innervated by the facial nerve [4,5].

Materials and methods

The retrospective study included 140 patients who had reconstruction of the eyelids with different kinds of flaps. These were done at the Clinic for Plastic and Reconstructive Surgery in Skopje between 1998 and 2010.

The reasons for eyelid defects were: excision of tumors (in 135 patients) and trauma (5 patients). In 72 patients the reconstruction was done on the eyelids and in 68 periorbitally. The defects of the eyelids and periorbital area were ranging from medium to large and also non-marginal and marginal defects of eyelids with full or partial thickness.

In the cases of eyelid trauma the edges of the wound were refreshed before the reconstruction.

Firstly the defect of the eyelid or periorbital area is thoroughly explored. The size; location; configuration; depth and the age of the patient all play part in the decision making which technique to be applied.

In patients with transconjunctival flaps the second phase of the reconstruction was done between 3-4 weeks post initial surgery. In patients with Mustarde method the second phase was done 2 weeks post initial surgery and 4-6 weeks in patients who underwent Cutler Beard method. The patients were followed up postoperatively to estimate the viability of the flap as well as the functional and cosmetic results.

The patients were between 15 and 80 years of age. All the patients were submitted to thorough investigations preoperatively and the function of the eye and periorbital region was tested.

In patients with eyelid tumors, an excision of minimum of 4mm within the healthy tissue was done. All the tumors were sent for histopathology to confirm the diagnosis. In all the cases the margins were clear and the excisions were done appropriately. Most of the operations were performed under local anesthetic but 30% of the cases required general anesthesia. These were cases with advanced tumors.

The preservation and protection of the eye is of paramount importance and has to be maintained during every step of the process.

The patients were followed up from 3 months to 2 years postoperatively, in order to evaluate the viability of the flap, the function of the eye lids, recurrence of the disease and the esthetic appearance.

Results

The age range of the patients was 15-80 years. The most common diagnosis in our patients was BCC (91 patients). Indications for reconstruction are presented in Table 2.

There were no major intraoperative or postoperative complications. The follow up if the patients were done during the period of 3 months to 2 years. In all the cases satisfactory results were achieved, meaning good function of the eye lids and nearly normal appearance.

Five percent of the patients had postoperative complications and they are listed in Table 4.

Table 1 lists all the methods used on our patients. The glabellar flap was the most common method used on our patients. Only 5 patients had recurrence of the disease and they were subsequently operated and treated.



Fig. 1. Large BCC of the lower eyelid



Fig. 2. Defect post radical excision of BCC



Fig. 3. Lifted flap – Mustard Method



Fig. 4. Earlobe cartilage as replacement for tarsus



Fig. 5. Cheek flap Mustard Method



Fig. 6. Complete reconstruction of all anatomical layers of the eyelid



Fig. 7.Two weeks post op.



Fig. 8.Two weeks post op.

Table 1. Types of Flaps

| Type of Flaps | Number of Cases |
|-------------------------------|-----------------|
| Glabelar | 42 |
| Mustarde | 24 |
| Frontal | 17 |
| MacGregor | 16 |
| Fricke | 15 |
| Tensel | 11 |
| M. Orbicularis & Chond. Graft | 3 |
| Tripier | 9 |
| V-Y | 2 |
| Cutler Beard | 1 |

Table 2. Indications for Operation

| Indications for Operation | Number of Cases |
|------------------------------|-----------------|
| BCC | 91 |
| SCC | 32 |
| Melanoma | 5 |
| Sebacious Glands Carcinoma | 3 |
| Keratoachantoma | 2 |
| Haemangioma | 1 |
| Nevus | 1 |
| Trauma | 5 |
| Total Number of Cases | 140 |

Table 3. Localization

| Localization | Number of Cases |
|----------------|-----------------|
| Upper Eyelid | 7 |
| Lower Eyelid | 39 |
| Both Eyelids | 3 |
| Lateral Cantus | 8 |
| Medial Cantus | 15 |
| Periorbital | 68 |

Table 4. Postoperative Complication Discussion

| Post Operative Complications | Number of Cases |
|------------------------------|-----------------|
| Lagofthalmos | 1 |
| Ectropion | 1 |
| Trichiasis | 2 |
| Epiphora | 3 |

The use of surrounding tissue flaps in the reconstruction of the eye lids and the periorbital area provide good color and skin quality; adequate vascularisation, and allow easy closure of the tissues with minimal scarring. The flaps are used in all kinds of eyelid defects. Thorough understanding of the principles of the palpebral and periorbital reconstruction is mandatory [6]. The flaps provide excellent aesthetic and functional results with minimal complications.

The frontal flap is the most commonly used. It can be positioned medially or laterally and it also can provide enough width and length. Primary closure of the forehead is most common. It can be used in reconstruction of both the eyelid and the periorbit. The flap has good color but thicker and sometimes cannot be rotated at the base.

The glabellar flap is used for reconstruction of defects of the medial canthus skin.

Mustarde flap is most commonly used for reconstruction of the lower eyelid, lateral canthus and the 2/3 of the lateral eyelid [7].

Fricke's supraorbital flap is used for repair of defects of the lower eye lid [8].

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ПРОГНОСТИЧКИ ФАКТОРИ ЗА ПОЈАВА НА МЕТАСТАЗИ КАЈ МАЛИГНИ МЕЛАНОМ НА ЕКСТРЕМИТЕТИ

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Извадок

Цел на овој труд е да се утврди поврзаноста на прогностичките фактори (поединечно или во комбинација) со појавата на метастази во регионалните лимфни жлезди.

Испитувани се 60 пациенти со малигни меланом на горни и долни екстремитети поделени во две групи: испитувана и контролна група од по 30 пациенти.

Анализирани беа: дебелина на примарниот тумор по Breslow, инвазија на туморот по Clark, лимфоцитна инфилтрација, присуство на улцерации, присуство на сателити, како и нивната поврзаност со појава на метастази во регионалните лимфни жлезди.

Анализата на податоците покажа дека постои зависнот помеѓу појавата на метастази и вертикалната дебелина на меланомот по Breslow и анатомското ниво на инвазија во кожата по Clark.

Комбинацијата на вертикалната дебелина на туморот по Breslow, присуство на сателитски промени околу примарниот тумор, анатомска инвазија на туморот по Clark, заедно со присуство на улцерација и лимфоцитна инфилтрација на туморот, како помалку важни фактори, при мултифакторијална анализа може со голема веројатност да го претскаже статусот на регионалните лимфни жлезди кај повеќето случаи.

Клучни зборови: малигни меланом, метастази, лимфни жлезди

PROGNOSTIC FACTORS FOR ONSET OF METASTASES IN MALIGNANT MELANOMA OF THE EXTREMITIES

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Abstract

The aim of this paper was to define the correlation between prognostic factors (separately or in combination) and onset of metastases in the regional lymph nodes.

A total of 60 patients with malignant melanoma on upper and lower extremities were analyzed. Patients were divided into two groups: examined and control group, each consisting of 30 patients.

The following parameters were analyzed: primary Breslow tumor thickness, Clark levels of invasion, lymphocytic infiltration, presence of ulcerations, presence of satellite lesions and their relation with onset of metastases in the regional lymph nodes.

The analysis showed a positive correlation between onset of metastases and Breslow vertical melanoma thickness, and between onset of metastases and anatomical level of Clark skin invasion.

Using multifactorial analysis of the combination of Breslow vertical tumor thickness, presence of satellite lesions around the primary tumor, Clark anatomical tumor invasion, and the less important factors - presence of ulceration and lymphocytic tumor infiltration, might predict with great probability the status of the regional lymph nodes in majority of the cases, but not in all.

Key words: malignant melanoma, metastases, lymph nodes

Introduction

Melanomas are generally presented as solitary lesions. In more than 50% they arise from normal skin without presence of any previous lesions. They may appear anywhere on the skin, but very often they can spread to other parts of the body where cannot be seen by self-examination. Most often they appear at the age between 40-70 years; the mean age at melanoma diagnosis is 53 years, but there is a significant tendency of their development at younger age (1). They are rarely found in children, although cases of patients younger than 15 years have been described.

Surgical excision is the method of choice in melanoma treatment (2, 3). Recommendations for the width of excision from the borders of the tumor are undergoing changes (4, 5, 6).

Identification and influence of different factors in melanoma progression remain unclear in treatment of this disease (7). Several studies recommend a model for assessment of metastases and survival based on clinical and histological factors. Prognostic factors include: primary tumor thickness or Breslow thickness, tumor invasion or Clark level of depth, tumor infiltrating lymphocytes, presence of ulceration, presence of satellite

lesions and the number of lymph nodes with malignancy. An important predictor for recurrence as well as a prognostic factor for survival is presence or absence of metastases in the regional lymph nodes (8). However, the most relevant surgical-pathologic system for survival assessment or disease recurrence before and after the curative surgical intervention is classification of melanoma staging.

The aim of this paper was to define the correlation between prognostic factors (separately or in combination) and onset of metastases in the regional lymph nodes.

Material and methods

A total of 60 patients with malignant melanoma on upper and lower extremities were analyzed. The patients had undergone surgery at the Clinic of Plastic and Reconstructive Surgery, Clinical Center, Skopje in the period from April 2001 until May 2005.

All patients included in the study were informed about the planned surgical procedure and they gave a written informed consent.

Patients were divided into two groups: examined and control group, each consisting of 30 patients.

Patients in the first or examined group met the following inclusion criteria: primary malignant skin melanoma on the extremities, without clinically present signs for metastases in the regional lymph nodes or distant metastasis. Exclusion criteria were presence of any type of metastasis.

Patients in the second or control group met the following inclusion criteria: primary malignant skin/cutaneous melanoma on the extremities, with clinically present metastases in the regional lymph nodes, without

signs for distant metastases. Exclusion criteria were presence of distant metastasis.

The following parameters were analyzed: primary Breslow tumor thickness, Clark levels of invasion, lymphocytic infiltration, presence of ulcerations, presence of satellite lesions and their relation with onset of metastases in the regional lymph nodes.

All patients underwent routine preoperative examinations (laboratory blood analyses, chest x-ray, abdominal ultrasound). In clinically differential diagnostic dilemma for an early stage of melanoma consultative examinations (dermoscan and dermatoscope) of the changes were done along with lymphoscintigraphy of the affected extremity and regional lymph nodes.

Intraoperatively a radical excision of malignant melanoma with a margin in healthy tissue was done depending on the clinical finding (1-3 cm of healthy tissue). The skin defect was managed with three surgical techniques depending on the situation (direct suture, local surgical flap and free skin transplant). The wound was closed with direct suture and passive drainage.

The results were statistically analyzed. Statistical significance of the differences between the series was tested with chi-square test.

Results

The percentage differences between control and examined groups with reference to vertical Breslow melanoma thickness were statistically insignificant, for $p > 0.05$, except for the vertical Breslow melanoma thickness up to 2 (6.7% vs 36.7%), for $p = 0.0066$ (Table 1).

Table 1. Distribution of patients in the examined groups according to Breslow vertical melanoma thickness

| mm | control group | | examined group | |
|-------|---------------|------|----------------|------|
| | No | % | No | % |
| < 2 | 2 | 6,7 | 11 | 36,7 |
| 2-3 | 7 | 23,3 | 6 | 20,0 |
| 3 - 4 | 7 | 23,3 | 7 | 23,3 |
| >4 | 14 | 46,7 | 6 | 20,0 |

Presence of ulcerations was registered in both examined groups. The percentage difference between the control (63.3%) and the examined (53.3%) group was statistically insignificant, for $p = 0.4353$, and was due to our random samples (Table 2)

Table 2. Distribution of patients in the examined groups according to presence of ulcerations

| ulcerations | control group | | examined group | |
|-------------|---------------|------|----------------|------|
| | No | % | No | % |
| positive | 19 | 36,7 | 16 | 53,3 |
| negative | 11 | 63,3 | 14 | 46,7 |

There was no difference between the examined groups according to the anatomical level of tumor skin invasion by Clark (Table 3).

Table 3. Distribution of patients in the examined groups according to the anatomical level of Clark tumor skin invasion

| Clark | control group | | examined group | |
|-------|---------------|------|----------------|------|
| | No | % | No | % |
| 3 | 14 | 46,6 | 8 | 26,7 |
| 4 | 11 | 36,7 | 13 | 43 |
| 5 | 5 | 16,7 | 9 | 26,7 |

The difference of the lymphocytic infiltration in the examined groups was statistically insignificant and was due to our random samples, $p > 0.05$ (Table 4).

Table 4. Distribution of patients in the examined groups according to the lymphocytic infiltration

| infiltration | control group | | examined group | |
|--------------|---------------|------|----------------|------|
| | No | % | No | % |
| No | 16 | 53,4 | 9 | 30,0 |
| Midle | 10 | 33,3 | 16 | 53,3 |
| Severe | 4 | 13,3 | 5 | 16,7 |

Larger percentage (36.7%) of satellite lesions in the control group as compared to the examined group (13.3%) was statistically significant, for $p < 0.0360$ (Table 5).

Fig. 2.

Table 5. Distribution of patients in the examined groups according to presence of satellite lesions

| type | control group | | examined group | |
|----------|---------------|------|----------------|------|
| | No | % | No | % |
| positive | 11 | 36,7 | 4 | 13,3 |
| negative | 19 | 63,3 | 26 | 86,7 |

The analysis done with the chi-square test showed a positive correlation between onset of metastases and Breslow vertical melanoma thickness ($\chi^2=4.43$ $df=1$ $p=0.03$) (Table 6).

Table 6. Presence of metastases in correlation with Breslow vertical melanoma thickness

| thickness | negative | positive |
|-----------|----------|----------|
| ≤ 2 | 13 | 4 |
| >2 | 5 | 8 |

The analysis done with the chi-square test showed no positive correlation between onset of metastases and presence of ulcerations ($\chi^2=0.2$ $df=1$ $p=0.0654$) (Table 7).

Table 7. Presence of metastases in correlation with presence of ulcerations

| ulcerations | negative | positive |
|-------------|----------|----------|
| negative | 9 | 5 |
| positive | 9 | 7 |

The analysis done with the chi-square test showed no positive correlation between onset of metastases and presence of lymphocytic infiltration ($\chi^2=1.3$ $df=1$ $p=0.26$) (Table 8).

Table 8. Presence of metastases in correlation with presence of lymphocytic infiltration

| lymphocytic infiltration | negative | positive |
|--------------------------|----------|----------|
| negative | 4 | 5 |
| positive | 14 | 7 |

The analysis done with the chi-square test showed a positive correlation between onset of metastases and anatomical level of Clark skin invasion ($\chi^2=7.251$ df=2 $p=0.0266$) (Table 9).

Table 9. Presence of metastases in correlation with the anatomical level of Clark skin invasion

| Clark | negative | positive |
|-------|----------|----------|
| 3 | 12 | 2 |
| 4 | 4 | 7 |
| 5 | 2 | 3 |

Discussion

Identification of the risk factors for development and progression of malignant melanoma has been and remains a major challenge in management of this disease. Many international studies have been conducted in order to detect and adequately interpret the influence of different factors on the progression of malignant melanoma (9, 10, 11). Previous studies have promoted a prognostic model of tumor metastases and survival based on clinical and histological findings, not taking into account the status of the lymph nodes (12, 13). In 1989 Clark created a method that found mutual correlation and dependence between histology of the primary tumor and survival in the first stage of the disease, disregarding the status of the lymph nodes. Contrary to his observation, over the last decade the status of the regional lymph nodes in melanoma has become a crucial factor for the prognosis of the disease outcome and overall survival. Since 2002, with the latest changes in the disease staging, besides changes of the histological parameters (thickness of the primary tumor in mm, presence of ulcerations), major role in determination of the disease staging has been given to the presence or absence of metastases in the regional lymph nodes, where the number of the affected nodes is valued instead of the size of the affected node as in the previous classification. Without a finding related to the status of the regional lymph nodes, it is not possible to determine subgroups of clinical stage III according to the latest classification (14). In 1992 Morton introduced into the routine procedure determination of sentinel lymph node, which helped in avoiding the opposite attitudes concerning diagnostic and therapeutic procedures. The value and validity of the procedure to assess spreading of the disease as well as its prognosis has been confirmed by several internationally organized multicenter trials (15, 16). Intraoperative determination of the first drainage node using a vital dye and radioactive carrier/tracer is a solid alternative to elective dissection of regional lymph nodes in patients with clinically negative finding of metastasis (17).

Today the widely spread and generally accepted is the classification of the melanoma staging according to the recommendations of the American Joint Committee of Cancer and Union International Contra le Cancer, which has being revised and updated in line with the latest

knowledge since 1988. Thus, the newest revised edition is that from 2010. This classification is being supplemented with classifications according to the Breslow vertical melanoma thickness and according to the anatomical level of Clark skin invasion.

Microstaging of malignant melanoma is determined by Breslow according to the vertical melanoma thickness in millimeters: up to 1 mm or less, from 1.0 to 2.0 mm, from 2.0 to 4.0 mm and from 4.0 mm and larger.

According to the anatomical level of skin invasion, Clark differentiates:

- Stage I: confined to the epidermis (melanoma *in situ*)
- Stage II: partial invasion of the papillary layer/dermis
- Stage III: filling of the papillary layer, with no extension into the reticular layer
- Stage IV: invasion of the reticular dermis, without involvement of the subcutaneous tissue
- Stage V: invasion of the subcutaneous tissue.

The analysis of the skin change thickness by Breslow in our study showed a significant difference between the two groups only for the subgroup with thickness up to 2 mm, for $p=0.0066$ (2 cases or 6.7% in the control group against 11 cases or 36.7% in the examined group). Although not statistically significant, the difference worth mentioning is the thickness >4 mm found in 14 (46.7%) subjects from the control group versus 6 (20%) subjects from the examined group. This parameter has shown to be a statistically significant prognostic factor for onset of metastases when it was analyzed with the chi-square test, for $p=0.03$. Our finding coincided with Breslow's results and the latest findings of Balch (18, 19) where the thickness change in millimeters was emphasized as a distinct indicator for the staging and prognosis of malignant melanoma. There was no subgroup of patients in our investigation with tumor thickness of 1 mm, which has been assigned in a separate group in the large world investigations and in the latest classification. Therefore, although our study was randomized one, patients with advanced stage of the disease were comprised.

Presence of ulceration as a separate factor was registered in both groups, slightly more often in the control group (63.3%) than in the examined group (53.3%), but this difference was not statistically significant and was due to our random samples, $p=0.4354$. Our finding was not in agreement with the results in the other studies comprising a larger number of subjects, where ulceration had a statistically significant value for the prognosis and disease staging. Our finding might be due to the small number of patients and to the fact that there were no patients in the early stage of the disease in relation to the overall analysis of our material (20).

The analysis of presence of satellite lesions revealed a larger percentage (36.7%) of satellites in the control group than in the examined one (13.3%), which was statistically significant for $p<0.0360$ and confirmed that presence of satellite lesions is one of the important prognostic factors.

Conclusion

Using multifactorial analysis of the combination of Breslow vertical tumor thickness, presence of satellite lesions around the primary tumor, Clark anatomical tumor invasion, and the less important factors - presence of ulceration and lymphocytic tumor infiltration, might predict with great probability the status of the regional lymph nodes in majority of the cases, but not in all. Thus, removal of sentinel gland and its histological analysis remain a gold standard for determination of the status of regional lymph nodes in malignant melanoma of the extremities.

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УПОТРЕБА НА УЛТРАСОНОГРАФСКИ ПАРАМЕТРИ ВО РАЗЛИКУВАЊЕТО НА КОНГЕНИТАЛНАТА ОПСТРУКТИВНА И НЕОПСТРУКТИВНА ХИДРОНЕФРОЗА КАЈ ДЕЦАТА

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Извадок

Вовед: Постои дилема во однос на дијагностичката процедура со која што се прави разлика помеѓу конгениталните опструктивни и неопструктивни хидронефрози, бидејќи стандардниот диуретски радиоренограм, во висок процент дава еквивокални резултати.

Цел: Целта на овој труд е да се определи вредноста на ултрасонографските параметри во проценката на конгениталната опструктивна и неопструктивна хидронефроза.

Материјали и метод: Во оваа студија предмет на анализа се ултразвучни мерења во процесот на обработка на децата со хидронефроза. Во клиничкиот материјал предмет на опсервација беа 30 оперирани деца (група 1) со опструкција на пилоуретерален сегмент, како и 32 деца (група 2) со неопструктивна хидронефроза, кои беа лекувани конзервативно. Во група 3 се бележеа резултати од ултразвучни мерења на 586 здрави деца, што претставуваа референтни вредности.

Резултати: Во протоколот за работа се нотираа резултати од следниве ултразвучни мерења: површина на паренхимот и на собирниот систем на хидронефротичниот бубрег, со пресметување на нивниот количник; дебелината на паренхимот на хидронефротичниот бубрег; должината на контралатералниот бубрег.

Заклучок: Акцелерација на растот на контралатералниот, здрав бубрег, има висока предиктивна вредност (80.8%) во одредување на опструкција на хидронефротичниот бубрег; количникот на површините на паренхимот и на собирниот систем, ако е помал од 1.6, дава сензитивност поголема од 95% за постоење на опструкција; дебелината на паренхимот на хидронефротичниот бубрег под 5 мм. укажува на афункционалност на бубрегот.

Овие резултати покажуваат дека ултразвучните мерења се квалитетна дијагностичка алатка, што е комплементарна на диуретскиот радиоренограм, за дистинкција на опструктивниот од неопструктивниот хидронефротичен бубрег.

Клучни зборови: хидронефроза, дијагноза, ултразвук, дете

ULTRASONOGRAPHIC PARAMETERS IN THE DIFFERENTIATION OF CONGENITAL OBSTRUCTIVE AND NON-OBSTRUCTIVE HYDRONEPHROSIS IN CHILDREN

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Abstract

There is a dilemma concerning the diagnostic procedure, with which the distinction between obstructive and non-obstructive hydronephroses is made, because standard diuresis renography has equivocal results in high percentage.

Aim: The aim of this study is to determine the value of the ultrasonographic parameters in the evaluation of congenital obstructive and non-obstructive hydronephroses in children.

Material and method: In the clinical material we subjected to analysis the ultrasound measurements obtained from 30 operated children with ureteropelvic obstruction (group 1) and 32 children with non-obstructive hydronephrosis (group 2) treated conservatively. In the third group, we registered the results of ultrasound measurements of 586 healthy children, and they served as reference values.

Results: In the work protocol, we have recorded the results of the following ultrasound measurements: surfaces of parenchyma and collecting systems of hydronephrotic kidney, with calculation of their quotient; parenchymal thickness of hydronephrotic kidney as well as length of the contralateral kidney.

Conclusions: The acceleration of growth of the contralateral, healthy, kidney has a high predictive value (80.8%) in determining the obstruction of the hydronephrotic kidney. When the quotient of the parenchyma surfaces and collecting systems' areas is lower than 1.6, it shows that obstruction sensitivity is higher than 95%. Parenchymal thickness of the hydronephrotic kidney lower than 5 mm. suggests presence of afunctional kidney. The ultrasound measurements are a quality tool, which is complementary to the diuresis renography in the distinction between obstructive and non-obstructive congenital hydronephroses.

Key words: hydronephrosis, diagnosis, ultrasound, child

Introduction

The ureteropelvic junction (UPJ) stenosis is the most common cause of upper urinary tract obstruction in the pediatric age group (1). The frequency of UPJ stenosis is 1 per 1500 live births. Antenatal ultrasound can detect a fetal uropathy in 1% of the pregnancies, 50% of which manifest as hydronephroses (2). Every fifth antenatally diagnosed uropathy needs to be treated surgically. UPJ stenosis is the most common cause of prenatal dilatation of the urinary tract, clinically presenting postnatally as an obstruction (3). The antenatal diagnosis is undoubtedly a diagnostic benefit, but its incorporation in the daily clinical practice demands a careful and critical approach (2).

The dilatation of the upper urinary tract might be a result of obstruction, vesicoureteral reflux, diuretic phenomenon or it can be a consequence of the spontaneous or operative resolution of a developmental anomaly (4).

Since dilatation of the renal pelvis and calices can exist without an obstruction, the term hydronephrosis should be used as a descriptive, anatomic entity, defined as enlargement-dilatation of the renal collecting system (3). Although there is a clear connection between a hydronephrosis and an obstruction, it is indeed obvious that the two terms are not synonyms (6).

The widely accepted Koff's definitions of the obstruction causing hydronephrosis, state that: "If not corrected, the restriction of the elimination of urine from the kidney will cause a progressive renal deterioration." (7). The unilateral renal obstruction can also be defined as: "Deterioration of the renal function of one of the kidneys, accompanied with growth acceleration of the contralateral kidney." (8). The term obstructive uropathy refers to the damage of the renal parenchyma caused by an obstruction present on any level of the urinary tract (9). Contemporary concepts point out that the obstructive uropathy produces an obstructive nephropathy via a hemodynamic, cascade reaction which causes ischemic injury (10, 11).

The surgical (opened or laparoscopic) reconstruction with the Hynes-Anderson method has a 95% success rate, but nevertheless the operative treatment per se accounts for its own morbidity (11, 12). The former consideration poses the obligation to differentiate obstructive and non-obstructive congenital hydronephroses.

The diuretic radioisotope renography (DRRG) has an important role in the diagnosis of the obstructive uropathies. The DRRG is a physiological study, which evaluates the ability of the kidney to respond to the change in volume induced by a diuretic (13). The analysis of data provided by the DRRG reveals the existence of an obstruction: according to the radiorenogram curve model (RRG) or according to T/2 (the time needed to eliminate 50% of the tracer from the zone of interest). The relative function of the kidneys (the percentage of the glomerular filtration rate, GFR) is also determined. According to the T/2 judging the curves, Kass et al. (14) suggest that obstruction exists if T/2 is longer than 20 minutes;

obstruction is excluded if T/2 is shorter than 15 minutes, and the result between 15 and 20 minutes is considered equivocal. The curve models (according to O'Reilly) are depicted in Figure 1. There are many factors that can influence the performance of the test and the interpretation of the results. The controllable factors contributing to an unsuccessful interpretation of the test are the following: operator dependence; hydration status; full bladder; diuretic dosage; timing of the diuretic administration; method of T/2 determination; regions of interest; patient positioning and type of isotope (15). Uncontrollable factors that modify the results include: renal function (if strongly diminished); failure to respond to diuretic drug and an enormous dilatation of the renal collecting system.

The normally developed kidney can be visualized from the 18th to the 20th gestational week. During this period, which corresponds to routine antenatal check-ups, dilatation of the urinary tract can be detected (as an indirect sign of an existing renal lesion) or oligohydramnion (as a direct suggestion of impaired renal function). Postnatal ultrasonography is mandatory in all newborns with prenatally detected hydronephrosis. The examination should be performed on the second day of postnatal life, thus avoiding the period of physiologic dehydration which can lead to false negative results. The ultrasonography is non-ionizing, noninvasive, cheap, easy to repeat investigation, and if necessary it can be performed easily on different locations since due the equipment is mobile. Although ultrasound exams cannot evaluate renal function, many other valuable information can be obtained concerning: morphology, size and position of the kidneys; echogenicity (hypo-/hyperechogenicity when compared to the liver and spleen) (16); parenchymal thickness (compared to the contralateral kidney); presence of calculi in the renal collecting system. The length and the width of the kidney can be measured in different planes and surfaces of the areas of interest can be calculated using software (8, 17, 18, 19). The dilatation of the urinary tract can be detected as well (20). In order to compare the results The Association of Fetal Urology proposed a system by which hydronephroses are graded in five degrees (0-4) (21).

The aim of this study was to determine the value of the ultrasonographic parameters (lengths of the hydronephrotic, obstructed and contralateral-healthy kidney as well as the surfaces of the parenchyma and the collecting system of the kidneys) in the evaluation of congenital obstructive and non-obstructive hydronephroses in children.

Materials and method

This study was performed at the University Clinic of Pediatric Surgery and the Institute of Radiology at the Medical Faculty in Skopje.

The clinical material consisted of children aged from 0 days to 14 years of age. The single including criterion in this study was presence of an isolated, unilateral, congenital hydronephrosis. The control group comprised healthy children.

We clinically analyzed 62 children with unilateral, congenital hydronephrosis, without any accompanying anomaly. The children were brought for consultation because of the following complaints: serious urinary tract infection; colicky pain; gastrointestinal discomfort (pain, malaise, nausea, vomiting); hematuria (spontaneous or following a minor injury); palpable tumefaction. Some of the patients were evaluated due to prenatally detected hydronephrosis on a routine ultrasound check-up.

In all children, vesicoureteral reflux was excluded by miction cystography. DRRG was used to delineate between obstructive and non-obstructive hydronephrosis. Details of urinary tract morphology and function were further revealed by intravenous urography.

The analyzed children were divided in 3 groups:

Group 1: Consisted of 30 patients with UPJ stenosis with a consecutive hydronephrosis, treated operatively.

Group 2: Consisted of 32 children with hydronephrosis without a verified obstruction, which were clinically observed.

Group 3: Control group, consisted of 586 healthy children in whom we measured the biggest length of t kidney.

Inclusion criteria for operative treatment (group 1) were the following: persisting complaints regardless routine, conservative treatment; severe degree hydronephrosis detected by ultrasonography and oth radiological investigations; obstructive type of curve the diuretic radiorenogram with T/2 longer than 20 minutes

The children not fulfilling the aforelisted criteria were periodically followed up (group 2).

In the first group (operatively treated children) 23 were male and 7 female. In the second group (conservatively treated children), 20 were male and female. The series included 43 (69.3%) male children and 19 (30.7%) female children. This series corresponds that found in literature data (4).

In group 1, the mean age of the treated patient was 83 months, while in group 2 the mean age was 78.5 months. The mean age of children included in the series was 80.9 months. In 18 children of group 1,

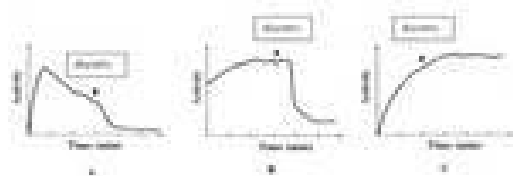


Fig. 1. Types of diuretic radiorenogram curves according to O'Reilly. A-Normal curve B-Hydronephrosis without an obstruction C-Obstructive curve

hydronephrosis was left-sided and in 12 right-sided. Eighteen hydronephroses were left-sided in group 2, while 14 were right-sided in this group. In the whole series, 36 (58.06%) children had left-sided hydronephrosis and 26 (41.94%) right-sided. This also coincided with the results in the literature, where the representation of left versus right hydronephrosis is 3:2.

The ultrasonographic examination was performed using a 3.5 or 5 MHz sector or convex probe, and special preparation of the patient was not needed. The lodges of the kidneys were examined by cross-sectional, longitudinal and transversal measurements, the most important being the biggest longitudinal length and the real transverse section antero-posteriorly that were looked for and measured. The approach was subcostal or intercostal with the spleen and liver used as a window. Posterior approach was also employed with the patient lying prone. As a standard the kidneys were measured in the two planes and the markers were set to the most distal points of the cortex. The thickness of the parenchyma in the central region of the kidney was also measured. If necessary, the circumference and the surface of the kidney



Fig. 2. Ultrasonographic surface measurement of the renal parenchyma and the collecting system

A full bladder exploration in transverse and sagittal plane consisted of: determination of volume and rest urine, and eventually prevesically dilated ureters were detected. If signs of urinary tract obstruction were present, the dimensions of the canal system were measured and the degree of hydronephrosis was determined. The dimensions of the renal pelvis and ureter were also specified. In order to compare the results, we used the system proposed by The Association of Fetal Urology from 1993 (21, 22), according to which the hydronephroses are graded in five degrees (from 0 to 4) (Figure 3):

- 0- No hydronephrosis
- 1- Only renal pelvis visualized
- 2- Visualization of the renal pelvis and few calyces
- 3- All calyces visualized
- 4- Same as 3, but with accompanying reduction of the parenchyma if compared to the healthy side

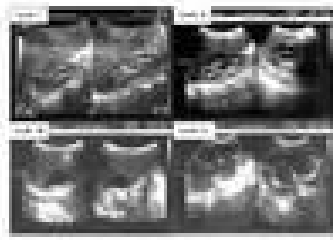


Fig. 3. Ultrasonographic classification of hydronephroses



Fig. 4. Plott chart for age dependant kidney dimensions (mm); (mean value \pm 2 standard deviations)

In the control group we recorded the measures in healthy children, without urological or any other malformations. Ultrasound measurements of the biggest lengths of the left and right kidney were performed on 586 children, 272 male and 314 female, divided in 17 age-groups. In this manner we plotted a reference chart for the age-dependant normal values of renal dimensions (in millimeters) (Figure 4).

The results obtained were statistically analyzed.

Results

The results are shown in Table 1.

There is a statistical difference between the length of healthy kidneys in groups 1 and 2. Furthermore, when compared to the reference values (group 3, children with none whatsoever urologic disease), the lengths of the contralateral kidneys in group 1 (obstructive hydronephroses) statistically differ significantly. On the other hand, the lengths of the contralateral kidneys in group 2 (non-obstructive hydronephroses) show no significant statistical difference. The diagnostic test of the acceleration of the kidney contralateral to the obstructed one, expressed by the bigger length measured by ultrasound has a 80.8% positive predictive value, 84.4% specificity, 71% sensitivity and 77.4% accuracy.

The thickness of the renal parenchyma in children with obstructive (group 1) and non-obstructive (group 2) hydronephrosis were analyzed using the Mann-Whitney U test. The results from testing the differences between two independent samples are shown in Table 2. There is no statistically significant difference between the parenchymal thickness of the diseased and the healthy kidney in both groups. It is clear from the analysis of the results that kidneys with parenchyma measuring less than 5mm have separate function gained through the GFR, which is less than 10% in all of the cases. There is an obvious right proportional correlation between the parenchymal thickness and the renal function ($r=0.54$), determined by the Spearman's test.

In groups 1 and 2, the surface of the affected kidneys and their collecting systems was measured separately in mm². Afterwards their quotient was determined with a numerical value. The quotient represents the surface of the affected kidney divided by the surface of the collecting system. The obtained results are shown in Table 3.

The results point out to a statistically significant difference in the surfaces of the collecting systems in groups 1 and 2.

Table 1. Kidney length in all three groups, processed with the t-test for independent samples (t)

| Parameter | Group | t | p |
|---------------------------|-------|------|-------|
| Length of healthy kidney | 1 | 2.27 | 0.02 |
| Length of diseased kidney | 1 | | |
| Length of healthy kidney | 2 | 2.4 | 0.016 |
| Length of diseased kidney | 2 | | |
| Length of healthy kidney | 1 | | |
| Length of healthy kidney | 2 | | |
| Length of diseased kidney | 1 | 2.76 | 0.007 |
| Length of diseased kidney | 2 | | |
| Length of healthy kidney | 1 | | |
| Length of healthy kidney | 3 | | |
| Length of healthy kidney | 2 | | |
| Length of healthy kidney | 3 | | |

Table 2. Parenchymal thickness in groups 1 i 2, processed with the Mann –Whitney U test

| Parameter | Group | p |
|----------------------------|-------|------|
| Healthy kidney parenchyma | 1 | 0.57 |
| Healthy kidney parenchyma | 2 | |
| Diseased kidney parenchyma | 1 | 0.34 |
| Diseased kidney parenchyma | 2 | |

Table 3. The surface areas of the renal parenchyma and the collecting system, the quotient of the surfaces of the hydronephrotic kidneys in both groups processed with Mann-Whitney U test

| Parameter | Group | p |
|--------------------------------|-------|---------|
| Kidney parenchyma surface area | 1 | 0.001 |
| Collecting system surface area | 2 | |
| Kidney parenchyma surface area | 1 | 0.95 |
| Kidney parenchyma surface area | 2 | |
| Quotient of the surfaces | 1 | 0.00016 |
| Quotient of the surfaces | 2 | |

Cost et al. (23, 24) in 1996 introduced the criterion that the quotient of the surface value of 1.6 or less is significant for obstructive hydronephroses. Chart 1 depicts the distribution of the surfaces quotient in hydronephrotic kidneys of both groups in regards to the critical value of 1.6.

The diagnostic test determining the quotient of the surfaces of the parenchyma and the collecting system, for which a critical line is drawn from <1.6, measured with ultrasound, has a sensitivity of 96.6%, specificity of 78% and 83.9% of accuracy.



Chart 1. Quotient of the surfaces of the renal parenchyma and the collecting system in groups 1 and 2

Discussion

Until the 1980s of the last century if hydronephrosis was confirmed in a child with an abdominal mass, a urinary infection, hematuria or a renal colic, the existence of an UPJ obstruction was considered a certainty rendering the child a candidate for further operative treatment. With the massive use of antenatal ultrasound diagnostics, an enormous number (up to 1%) of fetuses with a dilatation of the urinary tract emerged, at least half of them representing isolated hydronephroses. This information drastically differed from the predetermined incidence of UPJ stenosis (1:1500 children).

Although the fetal kidney is the precursor of the postnatal kidney, their anatomy and physiology differ in physiological terms as well as in the response of the kidney when submitted to obstruction (17). The offered possible explanation for the spontaneous resolution of the hydronephrosis is:

1. The bigger compliance of the fetal ureter as the result of its tortuous configuration as well as the difference in elastin/collagen deposition in the ureter are two conditions that can lead to transitory hydronephrosis but resolve pre- and postnatally.
2. Persistent ureteral folds and the delayed establishment of normal peristalsis can be causative to transitory obstruction and hydronephrosis (17).

However, the spontaneously resolved obstructions produce hydronephrosis as an anatomic entity to a certain degree.

It is clear that a portion of the ante- and postnatally diagnosed hydronephroses have an obstructive component. Obstruction attributes to a number of functional, biochemical, histological and anatomic changes in the kidney, which at the end of the line lead to a reduction in the renal function to the level of complete loss of renal function.

As an anatomic entity the hydronephrosis presents a benign condition, but the obstruction leads to obstructive uropathy, which seriously endangers kidney function. Therefore, the need to distinguish between these two conditions arises.

The dilemma of whether a kidney is obstructed or not would be resolved easily if a suitable diagnostic tool, procedure or test existed. Unfortunately, such a gold standard is unavailable even with modern medicine. The use of the so- called “well-tempered” DRRG is considered to be most credible (15). Even with this method, 10-20% of the results are equivocal.

Employing ultrasound measurements we tried to point out reliable result in the distinguishing of obstructed versus non-obstructed hydronephrotic kidneys.

In the 1920s of the 20th century Hinman postulated a theory of counterbalance, that the contralateral healthy kidney only partially overtakes the function of the obstructed one. Chevalier et al. (26) experimentally proved the theory in 1999. Koff et al. (8) considered that a distinction between obstructed and hydronephrotic kidney is possible judging the acceleration of contralateral kidney growth.

Using the ultrasound measures conducted on healthy children we plotted a chart for the age dependant development of the kidney, measuring the biggest longitudinal length.

Our results show that the specificity of this measurement is 84.4% and its sensitivity 71%. Many authors (8, 27) consider this diagnostic test especially important; on the other hand, others (22) think that evaluation is difficult due to the wide range of normal length values for healthy kidneys. Commenting this positions Koff et al. (28, 29) suggest that a single value in one point of time should not be judged. Instead, the acceleration as a function of time should be observed, meaning that the growth of the kidney should be compared to the normal growth curves of referent kidneys, thus obtaining accuracy greater than 95%.

No conclusive results were obtained in our measurements of the parenchymal thickness, except for the fact that a parenchyma of less than 5mm is indicative of complete loss of renal function (GFR <10%).

The measurements of the surfaces of both the parenchyma and the collecting system might serve in calculating the quotient of these two values. If the quotient was less than 1.6, we considered the kidney to be obstructed. Our results show sensitivity of 96.6%, specificity of 78% and accuracy of 83.9%.

Conclusion

Employing ultrasonography the dimensions of the hydronephrotic as well as the dimensions of the healthy contralateral kidney can be obtained. The accelerated, compensatory growth of the healthy kidney while the other one is obstructed has a positive predictive value of 80.8%, specificity of 84.4% and accuracy of 77.4%; obtained by a single measurement, a result which will be improved with serial measurements which will be compared to the developing kidneys values in the reference chart.

The surface quotient of the parenchyma and the collecting system of the hydronephrotic kidney has a critical value of 1.6, thus the kidneys with values less than 1.6 are obstructed (with 96.6% sensitivity).

The ultrasound measurements are a quality tool, which is complementary to the diuresis renography in the distinction between obstructive and non-obstructive congenital hydronephroses.

The responsibility of the surgeon stems from the fact that hydronephrotic kidneys do not require operation, while if not timely operated on obstructed kidneys partially lose their function. This means that unnecessary surgery should be avoided and when indicated surgery should be timely realized.

We hope that this study gives a moderate contribution to the solution of this significant clinical dilemma.

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ТРЕТМАН НА ФРАКТУРИ НА ТИБИЈА КАЈ ДЕЦА СО ФЛЕКСИБИЛНИ ЕНДЕР-ОВИ КЛИНОВИ

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Методиј, Скопје, Република Македонија

Извадок

Цел: Целта на овој труд е да го прикажеме нашето искуство и резултатите од третманот на нестабилните фрактури на тибигјата со употреба на флексибилни интрамедуларни клинови кај децата третирани на нашата Клиника во периодот од 2000 до 2006 година.

Вовед: Фрактурите на дијафизата на тибигјата се чести во детската возраст. Нивниот третман е најчесто конзервативен, но кај одредени типови на фрактури постои потреба од оперативна стабилизација.

Материјал и методи: Ретроспективната студија опфаќа 64 деца на возраст од 4 до 14 години со фрактура на дијафизата на тибигјата, третирани со примарна остеосинтеза со Ендер-ови клинови. Проценката на функционалниот исход се врши според функционалната скала на Карлстром-Олеруд, 16 недели по хируршката интервенција.

Резултати: Педесет и три пациенти (78%) покажуваат одличен резултат, 11 (16%) добар, додека за 4 пациенти (6%) функционалниот резултат е прифатлив.

Заклучок: Употребата на флексибилни интрамедуларни Ендер-ови клинови во третманот на фрактури на тибигјата кај децата овозможува рано оптоварување, обезбедува добри функционални резултати и е придружена со ниска стапка на постоперативни компликации. Остеосинтезата со флексибилни Ендер-ови клинови претставува метод на избор во третманот на нерепонибилни и неретинибилни фрактури на тибигја кај децата.

Клучни зборови: фрактура на дијафиза на тибигја, интрамедуларен клин, функционален исход

MANAGEMENT OF TIBIAL FRACTURES IN CHILDREN WITH FLEXIBLE INTRAMEDULLARY ENDER NAILING

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Abstract

Aim: The aim of this study was to present our experience and results from the flexible intramedullary nailing of unstable tibial fractures in children treated at our Clinic in the period between 2000 and 2006.

Introduction: The fractures of the tibial shaft are common in the pediatric age group. Their treatment is primarily conservative, but certain types of fractures require operative stabilization.

Material and methods: Sixty-four children, aged from 4 to 14 years were treated with primary Ender nailing for a tibial shaft fracture. The functional outcome was assessed by the Karlstrom-Olerud scoring system at 16 weeks after the surgical intervention.

Results: Fifty-three (78%) patients had excellent result, 11 (16%) good and 4 (6%) patients had acceptable functional outcome.

Conclusion: Flexible intramedullary nailing with Ender nails for tibial fractures in children enables early weight bearing, provides good functional results and is accompanied with a low rate of postoperative complications. It is a method of choice for irreducible and unstable tibial fractures in children.

Key words: tibial shaft fracture, intramedullary nail, functional outcome

Introduction

Fractures of tibial shaft in children are common injuries, following fractures of the femur and the forearm (1). Their treatment is primarily conservative (1), offering a good functional result. In certain cases, such as unstable fractures without adequate reduction, open fractures and

polytraumatized patients, operative treatment is needed (2).

Surgical treatment of tibial shaft fractures in children differs from treatment in adults. Rigid intramedullary fixation is not used due to risk of epiphyseal growth plate injury. The available surgical methods are:

pin in plaster, external fixation and flexible intramedullary fixation.

Flexible intramedullary fixation for long bone fracture treatment in children was introduced in the early 1980's (3).

Flexible intramedullary nails provide internal fixation which maintains reduction and does not allow shortening. It allows for movements at the fracture site, which stimulates callus formation (4, 5). The flexible intramedullary nails are successfully used in the treatment of tibial, femoral, humeral and forearm fractures in children (6, 7).

The aim of this study was to present our experience and results from the flexible intramedullary nailing of unstable tibial fractures in children for the period between 2000 and 2006.

Materials and methods

The medical records of patients aged 4 to 14, with tibial shaft fractures who had been managed with flexible intramedullary nailing with Ender nails at the University Clinic of Pediatric Surgery between 2000 and 2006 were reviewed. Data about the age, mechanism of injury, fracture type, timing of operative intervention and postoperative period was gathered.

In the period between 2000 and 2006, sixty-eight children (42 male / 26 female) were treated. The mean age was 10.6 years. The fractures were classified according to the AO classification (**Table 1**) and according to the Gustilo-Anderson open fracture classification (**Table 2**). Indications for Ender nailing were: unstable closed tibial shaft fractures (irreducible and unretainable), open tibial shaft fractures and tibial shaft fractures in polytrauma patients.

Table 1. AO Classification of the tibial shaft fractures treated with flexible intramedullary nailing

| | No | % |
|-------|----|-------|
| A1 | / | / |
| A2 | 4 | 6.25 |
| A3 | / | / |
| B1 | 12 | 18.75 |
| B2 | 8 | 12.50 |
| B3 | 6 | 9.37 |
| C1 | 17 | 26.56 |
| C2 | 13 | 20.31 |
| C3 | 4 | 6.25 |
| Total | 64 | 100 |

Table 2. Open fractures classified according to the Gustilo-Anderson classification

| | I | II | III | | | Total |
|----|-------|-------|-----|---|---|-------|
| | | | A | B | C | |
| Nº | 12 | 5 | / | / | / | 17 |
| % | 70.59 | 29.41 | / | / | / | 100 |

Surgical technique: All patients were treated under general anesthesia. They were positioned supine on a radiolucent table. The injured leg was disinfected and draped without being fixed. The entry spot was determined under fluoroscopic control, taking care to avoid the growth plate (**Figure 1**). Through small incisions, the periosteum of both sides of tibia was exposed. Under fluoroscopic guidance, drill-holes were made in the anteromedial and anterolateral cortices of the proximal part of the tibia, approximately 1cm distal to the proximal tibial physis and 2cm posterior to the tibial tubercle apophysis (**Figure 2**). The flexible nails were prebent so that the apex of their curvature would be at the fracture site and the tip was bent in a 45 degree angle. Under fluoroscopic guidance, the medial and lateral prebent flexible nails were successively advanced from the tibial metaphysis into the diaphysis (**Figure 3**), across the fracture site, and into the distal fragment, to a point approximately 1 cm proximal to the distal tibial physis. The reduction was achieved trough nail maneuvering (**Figure 4**).

Postoperative period: The average hospital stay of patients with tibial shaft fracture, treated with intramedullary Ender nailing was 8 days. Partial weight bearing was started the 12th postoperative day. Weight bearing was started the 5th week after surgery. X ray control was done the 2nd, 8th and 14th week after surgery. Physical therapy was initiated after hospital discharge. The functional outcome was assessed 16 weeks after the initial treatment, when all patients were assigned a score according to the Karlstrom-Olerud scoring system at 16 weeks after the surgical intervention.

Results

Sixty-eight children were treated for tibial shaft fracture by intramedullary Ender nailing at the University Clinic of Pediatric Surgery-Skopje from 2000 to 2006. Four were excluded from the study due to lack of postoperative follow-up or incomplete patient records. Forty-two were males. The mean age was 10.6 years.

From the patient records we obtained data about the mechanism of injury. Thirty-four patients were injured during a game. Ten injuries were due to bicycle falls. Traffic accidents accounted for 16 fractures and were accompanied by other injuries. Six were gunshot fractures. There were 17 open fractures.

The functional outcome was assessed according to the Karlstrom-Olerud scoring system (**Table 3**). Fifty-three (78%) patients had an excellent result, 11 (16%) good and 4 (6%) patients had acceptable functional outcome (**Table 4**).

Two patients (3%) had above 10° angular deformities in coronal and sagittal plane, which did not

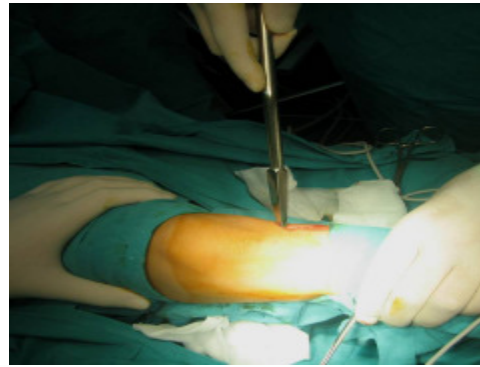


Fig. 1. Determining the entry spot

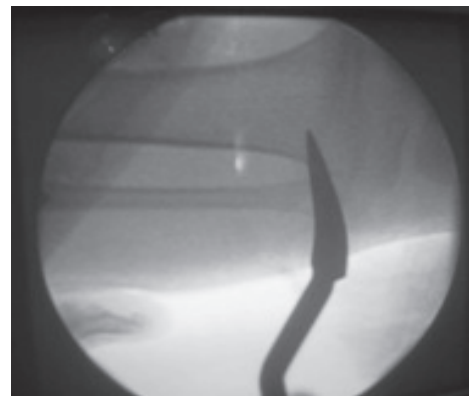


Fig. 2. Making the drill holes

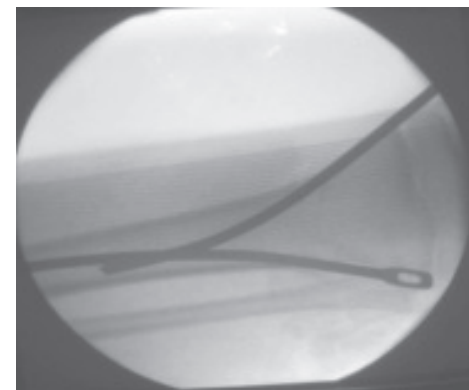


Fig. 3. Advancing the nails from the metaphysis to the diaphysis

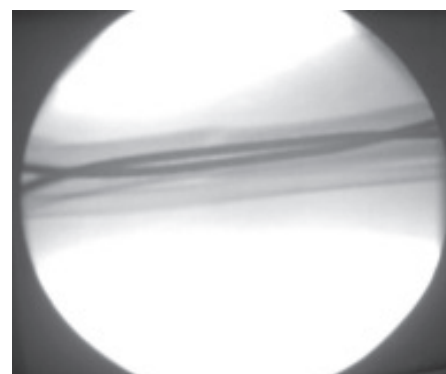


Fig. 4. Reduction achieved by nail maneuvering

Table 3. The Karlstrom-Olerud scoring system

| MEASURES | 3 points | 2 points | 1 point |
|--|----------|-------------|----------------|
| Pain | no | little | severe |
| Difficulty in walking | no | moderate | severe limping |
| Difficulty in climbing stairs | no | supported | unable |
| Difficulty in previous activity (playing) | no | limited | unable |
| Limitations/school absence | no | moderate | unable |
| Skin status | normal | discolored | ulcer/fistula |
| Deformity | no | little | remarkable |
| Muscle atrophy (cm) | < 1 cm | 1 cm- 2 cm | 2 cm |
| Shorter lower extremity (cm) | < 1 cm | 1 cm - 2 cm | >2 cm |
| Loss of motion in the knee (°) | <10° | 10° -20° | >20° |
| Loss of motion in the ankle (°) | <10° | 10° -20° | >20° |
| Loss of motion in the subtalar joint (°) | <10° | 10° -20° | >20° |

Table 4. Functional outcomes according to the Karlstrom-Olerud scoring system

| | | N° | Percent |
|--------------|-------|----|---------|
| Excellent | 36 | 53 | 78 |
| Good | 35-33 | 11 | 16 |
| Satisfactory | 32-30 | 4 | 6 |
| Moderate | 29-27 | / | / |
| Poor | 26-24 | / | / |

require additional intervention. Five patients from the open fracture group had infection. Delayed union occurred in one patient with C1 (AO) fracture. There were no cases of nonunion. Four patients (6%) had shortening of more than 1cm.

Discussion

Closed reduction and plaster cast immobilization can and should be used for management of tibial shaft fractures in children, in cases where acceptable reduction of the fragments can be achieved and sustained. Operative treatment of fractures in children is being more frequently used, not only for intraarticular fractures and

epiphyseolysis, but also for long bone fractures, in order to retain optimal reduction and allow early mobilization and weight bearing. Both methods have their spokesmen to argue pro and contra surgical treatment of tibial shaft fractures in children.

Flexible intramedullary nailing, predominantly used for femoral fractures in children, is being more often used in tibial fractures management. It has several advantages over the other methods of surgical treatment: it allows stability with the 3 point fixation in the medullary canal and prevents angulation and malrotation; the elasticity of nails allows micromovements, essential for

callus formation. The operative procedure is performed through two small incisions, distant from the fracture site and the nails can be used in a retrograde manner for distal shaft fracture. Reaming is not performed and the endosteal blood flow remains intact.

There are only a few papers about intramedullary nailing of tibial shaft fractures in children. In a retrospective study of 31 tibia fracture in children, Kubiak et al. (8) compared results of external fixation and elastic intramedullary nailing. They showed a significant difference in union time (18 weeks for external fixation and 7 weeks for intramedullary nailing), incidence of complications (7 in the external fixation group versus 1 in the intramedullary nailing group), timing of implant removal and functional outcome. Time to full weight bearing was significantly shorter in the intramedullary nailing group (7 weeks) compared to external fixation group (10 weeks). However, they did not take into consideration the differences between the two groups in the fracture type and the number of open fractures in each group. Comminution, initial shortening and contamination of open fractures may have contributed to the worse outcome in the external fixation group, considering that external fixation is most frequently used in the Gustilo Anderson type II and III fractures. External fixation on the other hand provides quick and stable fixation without additional soft tissue damage. It allows easy access to the wound and does not require knee or ankle immobilization. The disadvantage of this method of treatment is the high incidence of pin tract infection, which may affect the long term outcome.

Vallamshetla et al. (9) made a retrospective analysis of 56 tibial shaft fractures managed with flexible intramedullary nailing with titanium nails. They reported 10 weeks mean union time, both clinically and radiologically confirmed. They had one delayed union, 2 angulations and 2 shortenings. Infection developed in 3 patients (2 open fractures).

Quidwai et al. (10) performed a retrospective study of 84 tibial shaft fractures treated with intramedullary Kirschner wire fixation. Mean union time was 9.5 weeks.

Literature did not provide us with any prospective studies concerning flexible intramedullary nailing of tibial shaft fractures in children. There was no comparison between conservative treatment outcomes and intramedullary treatment outcomes, due to the difference in fracture types in the two groups.

Our study comprised 68 tibial shaft fractures treated with Ender nailing. The treatment results are satisfactory and comparable to other studies. This method has been established as a routine procedure at our Clinic. The number of unsatisfactory results is small, none of those patients had a significant functional or esthetic deficit nor required additional surgical intervention.

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ЕВАЛУАЦИЈА НА ФУНКЦИОНАЛНИ И РАДИОЛОШКИ РЕЗУЛТАТИ ПО КОНЗЕРВАТИВЕН ТРЕТМАН НА СКРШЕНИЦИ НА ДИСТАЛНИОТ КРАЈ НА РАДИУСОТ

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Извадок

Скршениците на дисталниот крај на радиусот претставуваат едни од најчестите повреди во скелетната траума. И покрај многубројните студии поврзани со оваа повреда, третманот се уште е котроверзен. Целта на третманот е постигнување на функционално ниво на рачниот зглоб како пред повредата.

Изборот на третман е детерминиран од неколку фактори: типот на скршеницата и нејзината стабилност како и возраста и активноста на пациентот.

Во оваа студија беше користен клинички материал од Универзитетската клиника за трауматологија, Медицинскиот факултет-Скопје. Во студијата беа опфатени 40 пациенти со скршеници на дисталниот крај на радиусот, со средна возраст од 58.6 години (24-82 години). Период на следење беше дванаесет месеци.

Кај сите пациенти беше спроведен соодветен дијагностички протокол кој опфаќаше физикален преглед, радиолошка евалуација на повредениот рачен зглоб. Беа одредувани и радиолошки мерки: радијална инклинација, радијална должина и палмарен тилт.

Скршениците беа класифицирани според ОТА класификацијата.

Третманот беше конзервативен: затворена репозиција со гипсена имобилизација.

Евалуација на радиолошките резултати се правеше според Lidstorm radiological wrist score, а евалуација на функционалните резултати според Gartland and Werley wrist score.

По дванаесет месеци резултатите од функционалните испитувања покажаа: кај ОТА А групата: 34,8% одлични, 34,8% добри, 17,3% задоволителни, 13% лоши. Кај ОТА В групата: 16,6% одлични, 33,3% добри, 33,3% задоволителни, 16,6% лоши. Кај ОТА С групата: 20% добри, 20% задоволителни, 60% лоши резултати.

Исходот по конзервативен третман зависи од типот на скршеницата и правилната процена на стабилноста. За скршениците од ОТА А групата (посебно недислоцираните) конзервативниот третман во најголем процент дава одлични и добри функционални резултати.

Функционалните и радиолошките резултати покажаа дека конзервативниот третман не е адекватно решение на скршениците од ОТА В, а особено од ОТА С. Корелацијата помеѓу функционалните и радиолошките крајни резултати е статистички несигнификантна ($p=0,530$).

Клучни зборови: скршеници на дистален крај на радиус, функционални резултати, радиолошки резултати, конзервативен третман, Gartland and Werley wrist score, Lidstorm radiological wrist score

EVALUATION OF FUNCTIONAL AND RADIOLOGIC OUTCOME AFTER CONSERVATIVE TREATMENT OF DISTAL RADIUS FRACTURES

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Abstract

Distal radius fractures remain one of the most frequent injuries in skeletal trauma. Despite the number of studies regarding this type of injury, no consensus has been reached on treatment. The ultimate goal of treatment is to restore the wrist to its prior level of functioning. Choice of treatment is determined by: fracture type and stability and the age and activity level of the patient.

In this study 40 patients treated for distal radius fractures at the University clinic of traumatology-Skopje were evaluated. The mean age was 58,6 years (range from 24-82 years). Follow up period was 12 months.

All patients were evaluated by standard diagnostic protocol: physical exam, radiologic evaluation and specific radiologic measurements (radial length, radial inclination and palmar tilt).

OTA classification system was used to describe the fracture pattern.

All patients were treated conservatively, with closed reduction and cast immobilization.

Radiologic results were evaluated according Lidstrom radiological wrist score, the functional results were evaluated according Gartland and Werley wrist score.

After 12 months, the result functional evaluation for OTA A group was 34,8% excellent,34,8% good,17,3% fair,13% bad. For OTA B group: 16,6% excellent,33,3% good,33,3% fair,16,6% bad. For OTA C group: 20% good,20% fair,60% bad.

According to our study the outcome correlates with the type of fracture and the accurate determination of fracture stability. For OTA A group the conservative treatment is appropriate for most of the cases. Also, functional and radiological evaluation showed that conservative treatment is not adequate for fractures classified OTA B, especially OTA C. Correlation between functional and radiological evaluation end results is statistically insignificant ($p=0.530$).

Key words: distal radius fractures, functional outcome, radiologic outcome, non-operative treatment, Gartland and Werley wrist score, Lidstrom radiological wrist score.

Introduction

Distal radius fractures remain one of the most frequent injuries in skeletal trauma. The greatest frequency occurs in two age groups: those 6 to 10 years of age and those between 60 and 69 years old. These fractures occur more commonly in women than in men and increase in frequency with advancing age.^(4,13)

With the population aging, the incidence of these injuries is expected to increase in the years to come.⁽¹⁶⁾

Although Colles first described the distal radius fracture in 1814, considerable controversy remains regarding the classification, appropriate treatment, and anticipated outcome of these injuries. The principle that Colles stated, that the wrist joint should gain “perfect freedom in all of its motions and be completely exempt from pain” is still in use.⁽¹³⁾

Despite the number of studies regarding this type of injury, no consensus has been reached on treatment.^(1,6,8,13)

The ultimate goal of treatment is to restore the wrist joint congruency by a method that won't compromise its function in order to restore the wrist to its prior level of functioning.^(2,10,13)

The management of these fractures can be non-operative (closed reduction and cast immobilization) or operative(different modalities of operative fixation)^(8,10,13)

Choice of treatment is determined by: fracture type and stability and the age and activity level of the patient.^(4,12, 13,14)

Classification systems serve as a basis for treatment and provide a means of evaluating the outcome of different treatment procedures. There are a lot of classification systems which are in use. One of the most used classification system is the AO/OTA classification. This classification system emphasizes the increasing severity of the bony injury^(3,7)

The functional anatomy of the wrist and the anatomic radiologic parameters contribute to better understanding of the treatment and the outcome of these fractures.^(2,14,15)

Purpose

The purpose of this study was to analyze and to evaluate the functional and radiological outcome after non-operative treatment (closed reduction and cast immobilization) of distal radius fractures and to point out the advantages and disadvantages of this treatment modality.

The focus was made on the functional outcome related to radiologic findings in period of 12 months.

Complications related to closed reduction and cast immobilization technique was excluded from this study although they can change the end functional outcome.

Materials and methods

In this study were evaluated 40 patients treated for distal radius fractures at the University clinic of traumatology-Skopje. The mean age was 58,6 years (range from 24-82 years). Follow up period was twelve months. The most common mechanism of injury was fall on outstretched hand (low energy trauma) 73%. (**Table 1**)

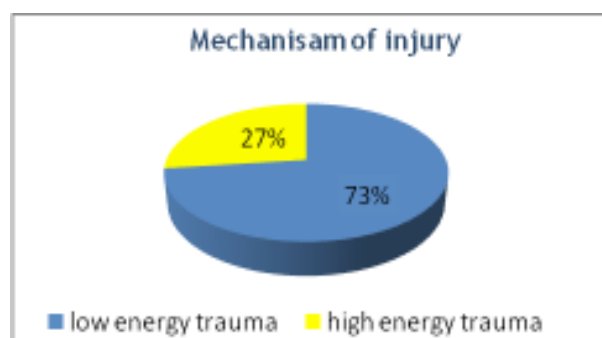
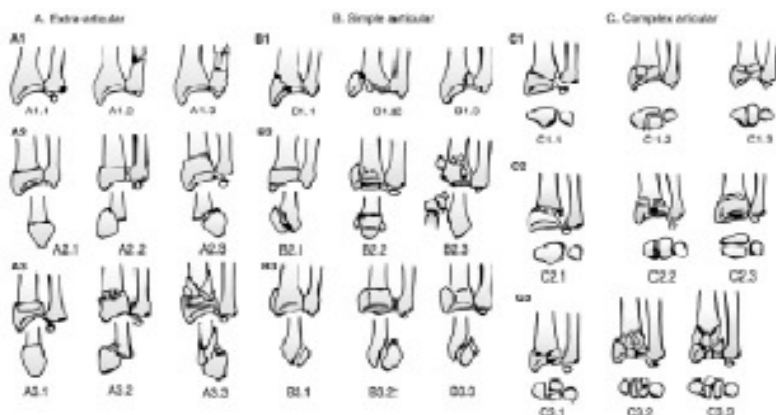


Table 1. Mechanism of injury

Table 2. AO/OTA classification of distal radius fractures

| OTAA | OTAB | OTAC |
|----------------|--------------------------|---------------------------|
| Extraarticular | Partially intraarticular | Completely intraarticular |



OTA classification system was used to describe the fracture pattern⁽³⁾. (**Table 2**) Total of 40 patients, 23 were classified as OTA A, 12 as OTA B and 7 as OTA C.

All patients were treated with closed reduction technique which consists of: an application of local anesthesia (hematoma block), manual traction, closed reduction and cast immobilization for an average time of 4-6 weeks (mean 5 weeks).

All patients were evaluated by standard diagnostic protocol: physical exam, radiologic evaluation (A-P and lateral view) and specific radiologic measurements (radial length, radial inclination and palmar tilt).

Radial length refers to the distance between the tip of the radial styloid process and the distal articular surface of the ulnar head. The average radial length is 12 mm (range from 10-13mm).

Radial inclination is the angle measured off the perpendicular to the radial shaft and a line that merges the radial process and the ulnar side of the distal radius and it averages 23° (range from 21-25°).

Palmar tilt is determined on the lateral radiograph and is measured as the angle that slopes through the distal articular surface of the radius and a line perpendicular to the radius shaft. It averages 11° (2°-20°).

Radiologic results were evaluated according Lidstrom radiological wrist score.⁽¹¹⁾ Lidstrom Radiological Wrist Score is a system for evaluation of radiologic measurements after healed distal radius fracture. According to severity of dorsal comminution and radial length shortage it stages into 4 types of deformity. No

significant deformity is determined if dorsal angulation is < 90° and radial shortage less than 3mm. Light deformity – dorsal angulation is from 91°-100° and the radial shortage is from 3-6mm, Moderate deformity- dorsal angulation is from 101°-114° and the radial shortage is from 7-11mm, Severe deformity- dorsal angulation is > 115° and the radial shortage is more than 12mm.

Radiological measurements were taken on the day of injury and after twelve months (complete radiological healing of the fracture).

The functional results were evaluated according Gartland and Werley wrist score.⁽⁵⁾ Gartland and Werley wrist score is a physician-based scoring system that summarizes the residual deformity, the subjective evaluation, the objective evaluation and the complications. According to the number of points the results are: excellent (0-2 points), good (3-8 points) fair (9-20 point) and poor (>20 points).

Functional evaluation was done after 3 and 12 months after the injury.

Results

After 3 and 12 months, the results from the functional evaluation for OTA A group was 26,1% and 34,8% excellent, 34,8% good, 17,3% fair, 17,3% and 13% bad. For OTA B group: 16,6% excellent, 33,3% good, 25,5 and 33,3% fair, 16,6% bad. For OTA C group: 20% good, 20% fair, 60% poor. (**Table 3**)

The results showed that optimal outcome is seen in OTA A type after 12 months. This is the mean time for complete consolidation of the fracture and proper

Table 3. Results Gartland and Werley wrist score

| Period(months) | OTA A 23 patients | | | | OTA B 12 patients | | | | OTA C 5 patients | | | |
|----------------|-------------------|------|----|------|-------------------|------|----|------|------------------|----|----|----|
| | 3 | % | 12 | % | 3 | % | 12 | % | 3 | % | 12 | % |
| Excellent | 6 | 26,1 | 8 | 34,8 | 2 | 16,6 | 2 | 16,6 | / | / | / | / |
| Good | 8 | 34,8 | 8 | 34,8 | 4 | 33,3 | 4 | 33,3 | 1 | 20 | 1 | 20 |
| Fair | 5 | 21,8 | 4 | 17,3 | 3 | 25,5 | 4 | 33,3 | 1 | 20 | 1 | 20 |
| Bad | 4 | 17,3 | 3 | 13 | 3 | 25,6 | 2 | 16,6 | 3 | 60 | 3 | 60 |

rehabilitation therapy. That’s why the functional evaluation after 12 months has higher scores then the functional evaluation made 3 months after injury.

Almost 70% (69,6%) of the patients with OTAA type of fracture have excellent and good functional results that practically means that they were fit to restore prior function with no or very few limitations. In opposite, patients with OTA C type of fractures have a fair and poor results that implies permanent disability and limited restoration of prior activities.

Results from Lidstrom Radiological Wrist Score evaluated after 12 months of injury showed: In OTA A group- 10 patients with no significant deformity, 8 patients with light deformity, 5 with moderate deformity and none with severe deformity. In OTA B group 1 patient with no significant deformity, 4 patients had light deformity, 5 had moderate deformity and 2 had severe deformity. In OTA C group there were no patients without significant deformity, 1 of each for light and moderate deformity and 3 patients with severe deformity. (Fig.1)

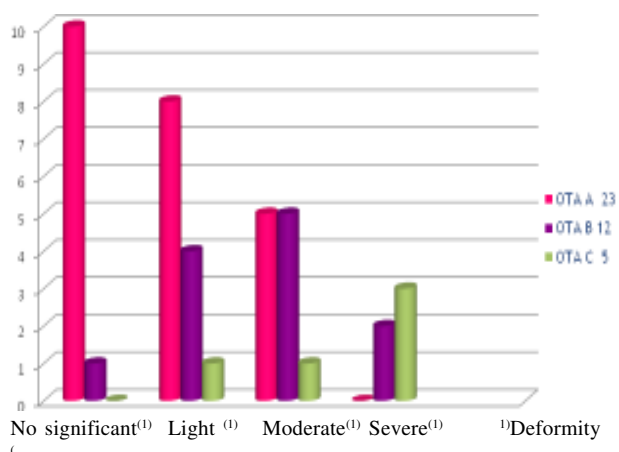


Fig.1. Lidstrom Radiological Wrist Score

Results from Lidstrom Radiological Wrist Score showed that most of the patients with distal radius fractures classified as OTA A had no significant or light deformity. Despite this in OTA C group most of the patients had severe deformity.

Although there was an obvious association between the radiologic finding and the functional outcome

there was no statistically significant correlation between the radiologic finding and functional outcome after 12 months (p=0,530).

Discussion

The non-operative treatment with closed reduction and cast immobilisation still remains the most frequent choice in treatment of distal radius fractures. It is also the least expensive and simplest mode of treatment of these fractures. (1,4)

In the orthopedic trauma the fractures of the distal radius are underestimated in the everyday surgical practice. Despite this, the appropriate treatment of these fractures is still ambiguous. The key point for non-operative treatment is to determine when can be achieved optimal functional outcome. In practice, that is to restore to prior activities with minimal residual deformity and restriction in wrist motion. (2,12,13,15)

Never the less, the proper technique of fracture reduction and proper cast immobilization is very important for the final outcome. It implies that it is no longer the main goal to achieve satisfactory position of the bone fragments which leads to fair and bad functional outcome. (1, 2, 15)

The difficulty in treating patients with cast immobilization lies in the ability to accurately predict the fracture’s position at final union. It is difficult to assess the fracture stability especially in the geriatric population. Factors that contribute to fracture stability are: the anatomic type, the degree of metaphyseal comminution, the quality of the bone, the energy of the injury, and the degree of initial displacement.

The redisplacement after initial fracture reduction leads to collapse of the bone fragments and unsatisfactory radiologic and functional outcome. (12,16)

The anatomic type, the fracture stability, the assessment of the patient’s needs and functional requirements and predicted outcome from the treatment should be taken in order to determine the type of treatment of the distal radius fractures. (4,9,13)

The operative management allows stable fixation with an earlier rehabilitation and recovery of motion and function. (6,8,9,10)

The operative treatment with different manners of fracture fixation still remains one of the possibilities for adequate treatment which allows good functional outcome with small percentage of complications. ^(6,8,9,10)

Conclusion

According to our study the outcome from non-operative treatment of distal radius fractures with closed reduction and cast immobilization correlates with the type of fracture and the accurate determination of fracture stability. For OTA A fracture type (especially non-displaced fractures) the non-operative treatment gives excellent and good functional outcome in most of the cases. In opposite, our study showed that the non-operative treatment is not a treatment of choice for fractures type OTAB especially OTAC. Different operative treatment options enable better functional outcome for these fractures.

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АГОЛНА КОРЕКЦИЈА СО КОРИСТЕЊЕ КОНЗЕРВАТИВЕН ТРЕТМАН НА ФРАКТУРИ НА ТОРАКО-ЛУМБАЛНИОТ СЕГМЕНТ НА РБЕТОТ

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Извадок

Фрактурите на торако-лумбалниот дел на рбетниот столб денес представуваат 12-20% од сите трауматски повреди на мускулно-скелетниот систем. Лоренц Белер, со методот кој тој лично го развива и во 1972 го објавува под наслов “Conservative treatment of fractures of the thoracic and lumbar spine”, стабилните фрактури на тораколумбалниот рбет без невролошки дефицит ги третира со некрвава репозиција и имобилизација.

На Клиниката за Трауматологија во периодот 2006-2008 год. конзервативно се третирани 32 пациенти со скршеници на тораколумбалниот сегмент Тх12-Л3, од кои 19 мажи и 13 жени. Третирани се пациенти кај кои е поставена индикација за конзервативен третман (некрвава репозиција и Белер гипс).

Веднаш по приемот се направени стандардни рендгенграфии во АП и профил, а кај одреден дел и КТ на тораколумбалниот дел од рбетниот столб. Кај сите пациенти на профилната рендгенграфија е мерен аголот на компресивно скршениот прешлен, на почетните рендгенграфии и на контролните рендгенграфии по репозицијата и имобилизацијата. Според добиените резултати од овој метод, најдобра корекција со репозиција и поставување на Белер гипс се постигнува кај прешлените Тх12 и Л1 за 15 степени додека кај Л2 и Л3 се постигнува корекција за 11, односно 12 степени.

Правилно поставена индикација за конзервативен третман на овој тип на скршеници како и коректно направената репозиција и поставување на Белер гипсот, даваат добри резултати на корекција на аголот на скршените прешлени на тораколумбалниот сегмент на рбетникот.

Клучни зборови: Белер гипс, фрактури на тораколумбален рбет, имобилизација.

ANGULATION CORRECTION USING CONSERVATIVE TREATMENT OF COMPRESSION FRACTURES OF THE THORACO-LUMBAL SPINE

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Abstract

Fractures of the thoraco-lumbar spine represent 12-20% of all traumatic injuries to the muscular-skeletal system. As with other spine trauma, thoracolumbar injuries occur most frequently in male patients between 15 and 29 years of age. Today there are different opinions regarding the optimal management, foremost patients with no neurologic deficit. The stable fractures of the thoraco-lumbar spine without neurologic deficit, the Type A thoracolumbar spine fractures classification according to AO is treated in this paper with a non-bloody reposition and immobilization by using the Böhler cast.

In the University Clinic for Traumatology in the period from the year 2006-2008 we treated conservatively 32 patients with fractures on the thoraco-lumbar segments from Th 12 to L3 of the spine, of whom 19 were male patients and 13 were female patients. The patients were treated upon diagnosing and indication for the use of the conservative method (non-bloody reposition and using the Böhler cast).

After admission of the injured patients, standard radiographs were made (AP and Lateral), and in certain number of patients a CT of the thoraco-lumbar spine was made. In all patients on the profile RTG shot the angle of the compressively fractured vertebrae was measured – on the initial RTG shots and on the control RTG shots after the reposition and the immobilization. According to the results that we acquired using this method, the best correction with reposition and by applying the Boehler cast is achieved at level of Th 12 and L1 with correction by 15 degrees, while at the level of L2 and L3 the correction was achieved by 11 and 12 degrees, respectively.

The on-time and justified indication for the conservative treatment of this type of fractures as well as the correctly achieved reposition and correct application of the Boehler cast, can give good and satisfying results of correction of the angle of the fractured vertebrae of the thoraco-lumbar segment of the spine.

Key words: Boehler cast, thoraces-lumbar fractures, reposition, immobilization

Introduction

Reports of trauma to the thoracolumbar spine with associated neurologic injury were described as early as 3000 BC. The most frequent fractures of the thoraco-lumbar spine are those of the level of L1 and L2, which are frequently accompanied with injuries to the level Th11 and Th12 (1). These fractures can be stable or unstable. The mechanism of injury is either an indirect excessive trauma (by fall on the coccyx or heels, or a traffic accident), or the mechanism of injury can be a direct trauma (direct action of the force on the thoraco-lumbar spine). The injuries to the thoraco-lumbar spine represent 12-20% of all traumatic injuries to the muscular-skeletal system, 15-20% of them are accompanied with a neurologic lesion and thus require urgent operational treatment(2). Subaxial and thoracolumbar fractures are classified according to Magrel et al., a classification which the AO group have adopted (3). (Figure 1).

The “Three Column Spine Concept” according to Denis in fractures of the thoracolumbar spine

In the year 1984 Denis publishes his article “Spinal instability as defined by the three-column spine concept in acute spinal trauma”, in which he elaborates his concept for the spinal column divided between three columns. The first column, made out of the first two-thirds of the vertebrae, ligamentum longitudinale anterior and the respective part of anulus fibrosus, nucleus pulposus and the vertebral body (4). The middle column, made out

of ligamentum longitudinale posterior, the back third of the vertebral body and the respective segments of anulus fibrosus and nucleus pulposus. The third column, made out of lig. supra- et interspinosum, ligg. flava and the capsular ligaments. This column contains the bony elements of the processus spinosus, laminae and the pedicles with their respective articular appendages. The judgment for the stability of the spinal column is important. From this judgment of stability the decision will be made whether the injury will be conservatively or operatively treated. Denis defines the instability as a disruption of at least two of the three columns.

Indications for the conservative treatment

In his 1972 article “Conservative treatment of fractures of the thoracic and lumbar spine”, Lorenz Boehler elaborates the conservative treatment of thoracolumbar spine. The conservative treatment is made out of a non-bloody reposition and immobilization. The indications are as follows: fractures of the thoraco-lumbar spine in the horizontal (or oblique) plane in which the fracture line does not extend to the back wall of the vertebrae, the vertebral body has undergone a nail-like shape, and when there is a certain angulation of the spinal column that can be repositioned, corrected in a hyperlordotic position and then the Boehler cast is applied. The best indication for the appliance of the Boehler cast are injuries between Th12 and L4 (5). A position of maximal lordosis is used. The supporting points

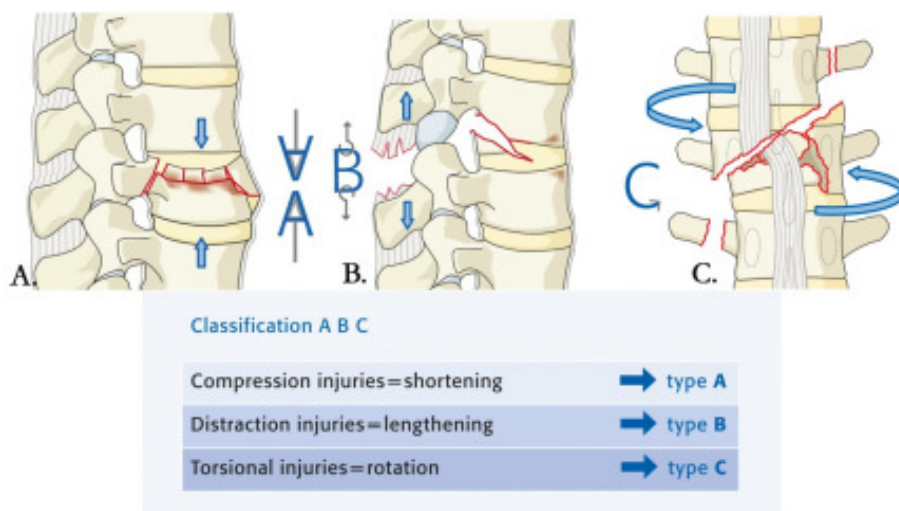


Fig. 1. AO Muller Classification of thoracolumbar fractures

on the body are the symphysis pubica, manubrium sterni and the point of maximal lordosis of the lumbar spine of the spinal processes.

Patients and methods

In the University Clinic for Traumatology in the period from 2006-2008 we treated conservatively 32 patients with compressive fractures on the thoraco-lumbar spine (segments Th12 to L3), of which 19 were male patients and 13 were female patients between the ages of 35-73 years. All patients fulfilled the indication for the conservative treatment (non-bloody reposition and the application of the Boehler cast). After admission standard radiographs were taken (AP and lateral), certain number of patients also had a CT taken of the thoracolumbar spine. In all patient with lateral X-ray's we measured the angle of the compressively fractured vertebrae, on the initial

radiographs and on the control radiographs following reposition and immobilization.

Results

From the results we obtained, we could come to the conclusion that the best correction with the reposition and the application of the Boehler cast was obtained at vertebrae levels Th12 and L1 for 15 degrees, while at the level of L2 and L3 we achieved a correction of 11 and 12 degrees, respectively. If we compare the acquired results we achieved with the reposition (from 10 to 12 degrees) with the normal angle of non-injured vertebrae (from 0 to 8 degrees), we come to the conclusion that we have a tolerant angle of alignment ranging from 2 to 4 degrees. The angle measurements in the fractured vertebrae and the angle after the correction and the application of the Boehler cast gave the following results (Table 1):

Table 1. Pre- and post repositioned angle comparison of fractured vertebrae in 32 patients

| Vertebrae | Patients |
|-------------------|-------------------------------------|
| Th 12 | |
| · Initial angle | 25 22 28 25 24 18 30 25 28 |
| · Corrected angle | 10 10 12 08 08 08 14 10 12 |
| L1 | |
| · Initial angle | 26 28 22 30 22 26 18 31 24 22 18 28 |
| · Corrected angle | 12 10 08 10 08 12 08 12 10 08 08 12 |
| L2 | |
| · Initial angle | 24 22 26 18 24 28 |
| · Corrected angle | 10 12 12 10 12 12 |
| L3 | |
| · Initial angle | 20 25 24 20 18 |
| · Corrected angle | 10 12 12 10 08 |

Table 2. Statistical analysis between the initial and corrected angles

| Parameter | mean | Std.Dev. | p-level |
|-----------------------|------|----------|---------------|
| Initial angle Th 12 | 25.0 | 3.6 | 0.000001 Sig. |
| Corrected angle Th 12 | 10.2 | 2.1 | |
| Initial angle L1 | 24.6 | 4.3 | 0.000001 Sig. |
| Corrected angle L 1 | 9.8 | 1.8 | |
| Initial angle L2 | 23.7 | 3.4 | 0.00015 Sig. |
| Corrected angle L 2 | 11.3 | 1.1 | |
| Initial angle L3 | 21.4 | 2.9 | 0.00006 Sig. |
| Corrected angle L 3 | 10.4 | 1.7 | |

p (t test for dependent samples)

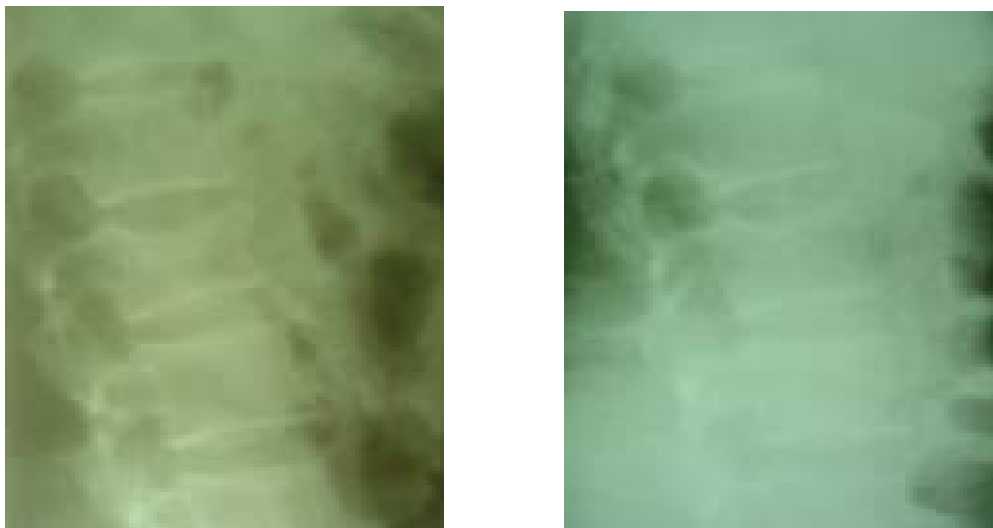


Fig. 2&3. X-ray of 48 year old male patient with a compressive fracture of L3 (according to AO Classification - Type A) as a consequence of a car accident (high-energy trauma) before and after the application of the Boehler cast.

In our series of patients we obtained the following results: Th12 – the average angle in fractures of the thoraco-lumbar spine was 25 degrees; after reposition and application of the Boehler cast the angle measured 10 degrees; L1 - the average angle in fractures of the thoraco-lumbar spine was 24 degrees; after reposition and application of the Boehler cast the angle measured 19 degrees; L2 - the average angle in fractures of the thoraco-lumbar spine was 23 degrees; after reposition and application of the Boehler cast the angle measured 12 degrees; L3 - the average angle in fractures of the thoraco-lumbar spine was 21 degrees; after reposition and application of the Boehler cast the angle measured 11 degrees

The statistic analysis confirmed high statistically significant difference between the initial and corrected angles on all of the analyzed levels: Th 12, L1, L2 and L 3 (Table 2).

Discussion

The positive sides to this method are: conservative treatment, satisfying results, relatively cheap method (short hospitalization time), the patient is not bed-bound. The negative sides to this method are: the uncomfortable handling of the reposition and placing of the Boehler cast, the uncomfortable and hard maintenance of the patient's hygiene, the cast wearing of minimum 3 months. Our experience is founded on the instant correction of the angle with reposition and immobilization. World experiences show that after 6-12 months there is a vertebral collapse. To stop this vertebral collapse some authors (Roy-Camile) recommend a longer time-period for

the application of the cast, up to 6 months. A team of orthopedic surgeons comes to similar results. In this article, 150 patients are treated by the same surgical team with the Boehler cast in a follow-up period of one year. (6) According to them, this technique is safe, minimally – invasive and an inexpensive treatment.

Conclusion

The measurements and results from our study have shown that the on time and justified indication for the conservative treatment of this type of fractures as well as the correctly applied reposition and application of the Boehler cast give satisfactory results for the correction of the angle of the fractured vertebrae of the thoraco-lumbar segment (vertebrae Th12-L3) of the spinal column. The correction of the angle (7) and the long enough time-period of the application of the Boehler cast are major requirements for the good end results in the conservative treatment of this type of fractures.

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СИМПТОМАТСКА ЕПИЛЕПСИЈА КАЈ ПОСТАРИ ЛИЦАЧепреганова-Чанговска Татјана¹, Лазарова С¹, Таравари А¹, Стојчев С²¹Универзитетска Клиника за неврологија-Скопје, Македонија²ГОВ "8-ми Септември"-Скопје, Македонија**Извадок**

Цел: Целта на ова студија е да се оценат клиничките и анатомото-морфолошките карактеристики кај постари пациенти со симптоматска епилепсија.

Методи: Ретроспективно ревидирани се клинички записи на 200 пациенти (105 машки и 95 женски) кои во текот на студијата беа на возраст од 65 години и постари.

Резултати: Епилепсиите беа класифицирани на генерализирани кај 33 пациенти (16,5%), парцијални кај 125 (62,5%), комплексно парцијални напади кај 36 пациенти (18%) и тонично-клоничен статус епилептикус кај 6 пациенти (3%). Симптоматската парцијална епилепсија ја имаше во сите возрасти (од 65 до 81 годишна возраст), пациентите имаа фамилијарна анамнеза за епилепсија, а половина од нив имаа позитивна анамнеза за цереброваскуларно заболување. Со МНР егзаминацијата кај овие пациенти беа детектирани мозочни тумори, пост-травматски секвели, пост васкуларни секвели и невродегенеративни заболувања.

Заклучок: Неуроимиџинг методите се важни во дијагнозата на симптоматските епилепсии кај постарите пациенти. Цереброваскуларните заболувања се најчестата причина за напади кај постарите лица и комплексно парцијалните напади се тип на најчести напади кај оваа возрасна група на пациенти. Точната локализација на фокусот на нападот може да биде соодветна на оние пациенти кај кои би можело да се изврши хируршка интервенција и најдобра прогноза може да се очекува при куративните хируршки процедури.

Клучни зборови: симптоматска епилепсија, парцијални, комплексно парцијални напади, неуроимиџинг

SYMPTOMATIC EPILEPSY IN THE ELDERLYCepreganova-Cangovska Tatjana¹, Lazarova S¹, Taravari A¹, Stojcev S²¹University Clinic of Neurology-Skopje, Macedonia²GOB "8-mi Septemvri"-Skopje, Macedonia**Abstract**

Purpose: The aim of this study was to evaluate the clinical, and anatomo-morphological characteristics of elderly patients with symptomatic epilepsy.

Methods: We retrospectively reviewed the clinical records of 200 patients (105 males and 95 females) aged 65 years or older at the time of study.

Results: Epilepsies were classified as generalized in 33 patients (16.5%), partial in 125 (62.5%), complex partial seizures (CPS) in 36 (18%) and tonic-clonic status epilepticus (SE) in 6 (3%). Symptomatic partial epilepsy (SPE) began at all ages (65 to 81 years), patients had no family history of epilepsy and half of them had a past history of cerebrovascular disease. MNR detection of the symptomatic epilepsy was brain tumors, posttraumatic sequels, post vascular sequels and neurodegenerative diseases.

Conclusions: The neuroimaging methods are the option for diagnostic in elderly patients with symptomatic epilepsy. Cerebrovascular disease is the most common cause of seizures in the elderly, and complex partial seizures (CPS) are the most common seizure type in this age group. Precise localization of the seizure focus can be appropriate surgical candidates and a favorable prognosis is expected with curative surgical procedures.

Key words: symptomatic epilepsy, partial, complex partial seizure, neuroimaging

Introduction

Old age is the most common time to develop seizures (1). Elderly persons with epilepsy are expected to be an increasing larger group among patients with epilepsy in view of population aging and the higher onset of epilepsy in the elderly as compared to any other age group.

Epilepsy is known to begin most commonly at young ages. The elderly, defined as person’s age 65 years and older, are the most rapidly growing segment of the population. Epidemiological studies from many countries have shown that onset of epilepsy is higher in the elderly than in any other age group(2).The elderly are not a homogenous group. The elderly have been subdivided into the “young old,” those 65–74 years of age, “middle old” or “ old,” those 75–84 years of age, and the “old old,” those 85 years or older. Old people are particularly vulnerable to the sequels of seizure, including physical injury, loss of confidence and reduced independence.

The diagnosis of epilepsy is generally made only after a person has had two or more seizures. However, physicians may begin treatment with AEDs in the elderly after a single seizure because the risk of second seizure is perceived to be high (3).

In the elderly, a clear distinction must be made between the causes of seizures and causes of epilepsy. Many conditions can cause seizures in the elderly: cardiac dysfunctions, metabolic defragments, respiratory compromise, alcohol abuse etc. These must be excluded before a diagnosis of an epileptic seizure can be made. In the elderly the most common identifiable cause of epilepsy is stroke, which accounts for 30-50% of all cases (4). Brain tumor, head injury and Alzheimer’s disease are other major causes. However, in a large number of causes, the precise cause cannot be identified and the etiology is cryptogenic (3).

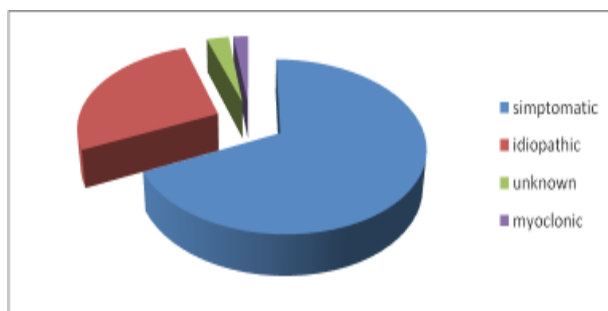


Fig. 1. Incidence of seizure types in elderly people
From reference 1

Patients and methods

We retrospectively collected 200 patients with symptomatic epilepsy, (105 M and 95 F, F/M ratio 1,1). aged 65 years and older at their last visit to our Department of Epilepsy and Intensive Care Unit, during the period from January 2006 to December 2010. The clinical records

of these patients, including EEGs and neurological images were reviewed retrospectively. Epilepsies were classified according to the criteria proposed by Commission on Classification and Terminology of the International League Against Epilepsy (5).

Any other conditions causes for epilepsy were excluded -electrolyte imbalance, febrile illness, cardiac dysfunctions, alcohol abuse, hypoglycemia or hypoglycemia, may also provoke seizures, but these conditions should be easily recognized by laboratory tests or physical examinations, and they do not need to be treated with chronic antiepileptic drugs.

Results

a) Classification of epilepsy

The epilepsies were classified as generalized in 33 patients (16,5%), partial in 125 (62,5%), complex partial seizures(CPS) in 36 (18%) and tonic-clonic status epilepticus (SE) in 6 (3%) . All patients were with symptomatic epilepsy. Symptomatic partial epilepsy (SPE) began at all ages (65 to 83 years), “young old” were 52(26%) , “middle old” were 148(74%),and nobody in “old old”. Patients had no family history of epilepsy and half of them had a past history of cerebrovascular disease.

Table 1.

| <i>class. of epilepsy</i> | <i>patients</i> | |
|---------------------------|-----------------|--------|
| generalized | 33 | 16,5 % |
| partial | 125 | 62,5 % |
| CPS | 36 | 18% |
| SE(tonic-clonic) | 6 | 3% |
| <i>subdivide groups</i> | | |
| young old (65-74) | 52 | 26% |
| middle old(75-84) | 148 | 74% |
| old old(85 and older) | x | x |

MNR detection of the symptomatic epilepsy were post vascular sequels, brain tumors, posttraumatic sequels, and neurodegenerative diseases.

Table 2.

| <i>Causes</i> | | |
|-------------------------|-----|-----|
| cerebrovascular disease | 100 | 50% |
| brain tumor | 40 | 20% |
| posttraumatic | 38 | 19% |
| neurodegenerative | 22 | 11% |

Table 3.

Types of EEG

| | |
|-------------------------|-------------------------|
| Post stroke+brain tumor | epileptiform discharges |
| Other | abnormal interictal EEG |

Most seizures in our study in elderly patients are partial onset with or without secondary generalization. Six were in tonic clonic status epilepticus (table 1).

Magnetic resonance imaging is the gold standard detecting all pathology more accurately than computerized tomography with the exception of subarachnoid haemorrhage. All patients fit MRI criteria of epilepsy. One hundred patients were with symptomatic epilepsy after stroke, brain tumor we found in 40 patients, posttraumatic epilepsy in elderly were in 38 and neurodegenerative disease in 22 patients (table 2).

Electroencephalography (EEG) is less specific and sensitive than neuroimaging, older patients with seizures have abnormal interictal EEGs, post stroke seizure and EEG of brain tumors are associated with epileptiform discharges on a surface EEG (table 3).

Six patients with tonic-clonic status epilepticus were in intensive care, they were in middle age, two of them have brain tumor, and the other four were with post vascular sequels.

Discussion

The elderly are most rapidly growing segment of the population and incidence of epilepsy is higher in the elderly than in any other age group. Among persons 65 years and older, the active epilepsy prevalence rate is approximately 1,5%, about twice the rate of younger adults (1, 6). High male/female ratio likely reflects the preponderance of men among our series.

However, as persons develop health issues at different times, further subdivisions have been proposed when referring to elderly patients with epilepsy (7). In our study elderly patients from middle old develop epileptic seizures.

Underlay in hospital-based studies, 10-30% of elderly patients presented with tonic-clonic status epilepticus (8), in this study only 3% of patients develop tonic-clonic status epilepticus with cause of post vascular sequels.

In the elderly, the most common identifiable cause of epilepsy is stroke, which accounts for 30-50% of all cases, in our cases in was 50%. Cerebrovascular disease is the single most common pathological factor underlying epilepsy in elderly patients (9, 10). The disorder is the leading cause of status epilepticus in elderly (11).

Dementias of non-vascular origin give rise to seizures that are often easy to control (12). Cerebral atrophy can be shown on imaging. Alzheimer disease and epilepsy commonly coexist. The association with Pick's and Jakob-Creutzfeldt disease is less clear (13). Patients who have severe cognitive impairment might be at greatest risk of developing seizures.

The most common tumors found to produce seizures in later life are gliomas, meningioma and metastases (10, 14). Older people with cerebral tumors are less likely than younger patients to present with seizures, but age is a risk factor for increased mortality in people who do develop seizure (15).

Trauma is common in old age. Older people are more likely than younger patients to develop post-traumatic epilepsy.

Underlying abnormalities such as infarctions, neoplasms and vascular malformations can be identified in 80% of causes with magnetic resonance imaging (16).

Only 30-40% of post stroke seizures and cerebral tumors are associated with epileptiform discharges on EEG. Therefore, the surface EEG should be interpreted with caution, although it can occasionally help to identify seizure type (17).

Conclusions

Epilepsy in old age is becoming increasingly common. Cerebrovascular disease is the most common cause of seizures in the elderly, and partial and complex partial seizures (CPS) are the most common seizure type in this age group. The neuroimaging methods are the option for diagnostic in elderly patients with symptomatic epilepsy. Precise localization of the seizure focus can be appropriate surgical candidates and a favorable prognosis is expected with curative surgical procedures. Optimum management requires rapid investigation, accurate diagnosis, effective treatment, sympathetic education and assured support. A coordinated programme among health-care workers is advised to maintain the independence and improve the quality of life of this vulnerable patient population.

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ВРЕДНОСТ НА рН НА ВАГИНА КАЈ ПАЦИЕНТКИ СО СПОНТАНО ПРЕДВРЕМЕНО ПОРОДУВАЊЕ

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Извадок

Одредување на вредноста на рН на вагина кај пациентки со спонтано предвремено породување. Асцендентната генитална инфекција е една од најчестите причини за предвремено породување. Каскадата започнува со нарушување на вагинално мие и пораст на вредноста на рН на вагина. Доколку не се детектира и третира во оваа фаза, процесот продолжува со равој на бактериска вагиноза, асцендирање на инфекција, промени на цервиксот, контракции и предвремено породување. Многу студии потврдиле зголемена вредност на рН на вагина кај пациентки со предвремено породување.

Во студијата се вклучени 62 пациентки со спонтано предвремено породување. Кај секоја од нив, пред породување при присутни знаци за предвремено породување (регуларни контракции, Bishop скор >7), беше измерена вредноста на рН на вагина со хартиени ленти со индикатор, со гранична вредност 4,5. Се направи анализа на присуство на субјективни знаци и ризик фактори според Светската Асоцијација за Перинатална Медицина (САПМ). Пациентките со предвремена руптура на околуплодови обвивки, цервикално или утерино крвавење, абрупција на постелка, докажана цервикална инсуфициенција, јатроген прематуритет и ризик фактори според САПМ од претходни бремености беа исклучени од студијата. Резултатите беа статистички обработени со X^2 и Фишер-ов егзактен тест.

Зголемена вредност на рН на вагина беше регистрирана кај 46 од вкупно 62 пациентки (74.19%), а кај останатите 16 (25.81%) беше регистрирана нормална вредност. Статистички сигнификантна асоцијација беше регистрирана помеѓу зголемена рН вредност на вагина и вагинална-цервикална инфекција, болки во слабините или во сакрална регија и повремено контрахирање на утерусот.

Зголемената вредност на рН на вагина кај поголемиот дел од пациентките со предвремено породување, ја потврдува нејзината улога во каскадата која преку асцендирање на инфекцијата води до предвремени контракции и породување.

Клучни зборови: рН на вагина, предвремено породување

VAGINAL pH VALUE IN WOMEN WITH SPONTANEOUS PRETERM DELIVERY

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Abstract

To assess the value of the vaginal pH in women with preterm labor and delivery.

Ascending infection is the most frequent cause of preterm delivery. The cascade starts with the disturbance of the vaginal milieu and rising vaginal pH. If not detected and treated, the process continues to the next stages of developing bacterial vaginosis, ascending infection, changes on the cervix, preterm labor and delivery. Many studies confirmed the increased vaginal pH among women with preterm delivery.

The study includes 62 women with preterm labor (regular contractions, Bishop score over 7) who had a spontaneous preterm delivery. Women with preterm ruptured membranes, cervical or uterine bleeding, placental abruption, proved cervical insufficiency, iatrogenic prematurity and risk factors from previous pregnancies were excluded from the study. We measured vaginal pH using indicator strips, with a cut-off value of 4.5. We also analyzed the presence of risk factors according to the World Association of Perinatal Medicine and the subjective signs in each woman. The results were statistically evaluated using chi-square and Fisher exact test.

Vaginal pH was increased in 46 (74.19%) out of 62 evaluated women. The remaining 16 women (25.81%) had a normal pH value (<4,5). Statistically significant association was registered between increased vaginal pH and vaginal-cervical infection, aching in the groin or in the sacral region and temporary repeated hardening of the uterus.

The increased pH value in the majority of women with signs of preterm delivery, confirms its role as a precursor in the cascade through ascending infection to preterm labor and delivery.

Key words: vaginal pH, preterm delivery.

Introduction

Preterm birth refers to a birth that occurs prior to 37 completed weeks of gestation (gw) (1). Preterm birth is one of the most important problems in the field of perinatal medicine. One of the most urgent tasks of modern obstetrics is to reduce the rate of very early prematures (< 32+0gw), and those with a very low birth weight (< 1500 g). These infants form the group of newborns with the highest mortality and morbidity. (2)

Ascending genital infection is one of the most frequent causes of late abortion and very early premature births. The association between infections and prematurity has been proved in many studies. As this connection is undisputed, much research has focused on finding infectious risk factors suitable for screening. If early diagnosed, infections can often be treated effectively. Most of the avoidable causes in the cases of preterm deliveries, particularly before 32 gw, are to be found in patients with ascending genital infections, urinary tract infections and sometimes with systemic infection, even parodontitis, thus suggesting to have the main emphasis on prevention of infections, not neglecting other causes (e.g. psycho-social stress) if possible. In cases of other prematurity causes the possibility of intervention and successful therapy is clearly not so good. (3)

The human vagina possesses a bio-system which under normal conditions provides a balance between physiologic lactobacilli and pathogenic bacterial flora, and thus ensures a good protection against the spreading of pathogens, including their ascension to the uterine cavity. Importance of lactobacilli for the normal vaginal milieu was first described by Döderlein in 1892. Lactobacilli produce acids, mainly lactic acid, hydrogen peroxide (H₂O₂), which releases oxygen and has a disinfecting effect. These factors, combined with bacteriocines inhibit the growth of pathogens which are always present in the vagina. They also produce biosurfactants, which cover the surface of the vaginal wall, thereby inhibiting the adhesion of pathogens and coaggregation molecules which block the spread of pathogens. Some strains are more effective against specific infections than others.(4)

Unfortunately, there are also some microorganisms, the growth of which is not or only marginally inhibited by lactobacilli (e.g. Streptococci and Candida).

Lactobacilli are the main regulating factor of the vaginal milieu. They keep the vaginal pH value at the vaginal introitus (at a depth of approximately 2-3 cm) under 4.5 (measured with indicator paper). A simple way of measuring the vaginal pH is to use a small, portable pH-meter, or indicator strips which are introduced into the area of the vaginal introitus with the finger before vaginal examination and compare the color of the indicator with the corresponding color chart. Disturbance of the vaginal milieu means threatened infection. This means reduction of Lactobacillus flora and consequently increasing of the vaginal pH value.

Measurement of the vaginal pH gives us insight into this protective Lactobacillus bio-system. Vaginal pH measurement was already used by Döderlein, in order to distinguish pathological from normal vaginal fluid. (5) High level of acidity in the vaginal milieu does not guarantee completely secure protection against ascending infections, but it is certainly very effective. Vaginal pH can increase due to intercourse, vaginal douching and the presence of blood or cervical mucus. Disturbances of the vaginal milieu can be detected by pH-measurement at regular intervals, before bacterial vaginosis develops (6).

Bacterial vaginosis is not due to a single organism. Instead it represents a complex change in the vaginal flora characterized by a reduction in concentration of the normally dominant hydrogen-peroxide producing lactobacilli and an increase in concentration of other organisms, especially anaerobes. These include Gardnerella vaginalis, Mycoplasma hominis, Prevotella species, Porphyromonas species, Bacteroides species, anaerobic Peptostreptococcus species, Fusobacterium species and Atopobium vaginae. Absence of inflammation is the basis of the term "vaginosis" rather than "vaginitis" (7, 8)

Bacterial vaginosis has proved to be associated with an increased risk of preterm delivery. It is thought that bacterial by-products, such as phospholipases, could trigger prostaglandin production and stimulate contractions, while protease by-products would weaken the collagen structure in the gestational sac and allow premature rupture of membranes.

Risk of premature rupture of the membranes before 37+0 gw is three times higher when the vaginal pH is repeatedly above 4.5, compared to pregnant women with pH < 4.5.(9) According to published data, main reason for good results is not early detection of existing infections, but early detection of their precursors, namely disturbances of the vaginal milieu. (Fig. 1)

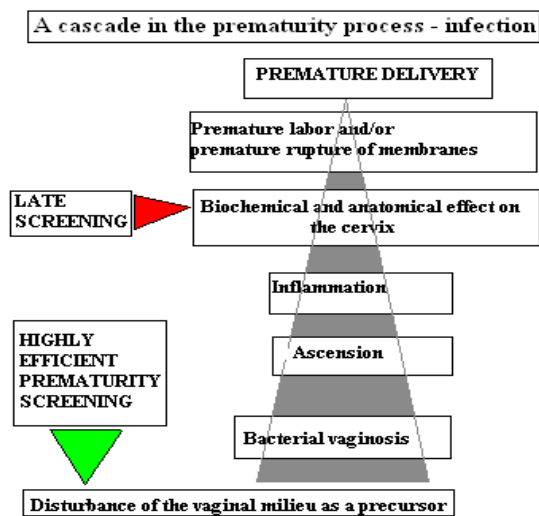


Fig. 1. A cascade in the prematurity process

Preterm deliveries account for 70% of all perinatal mortality and 50% of all long-term neurologic morbidity. Most serious sequel occur in infants born before 32 gw or weighing <1500 g. Overall, approximately 10% of all deliveries are pre-term.

Objective of our study was to assess the value of the vaginal pH among women with preterm labor and delivery.

Methods

We conducted a prospective study at the University Clinic of Obstetrics and Gynecology that included 62 women with pregnancy before 37 completed gw, with preterm labor and spontaneous preterm delivery.

Inclusion criteria: preterm labor which means critical uterine contractions (if they occur more than twice per hour, or more than 10 times during the whole day) and critical cervix state (Bishop score over 7) that progressed to preterm delivery.

Exclusion criteria: preterm ruptured membranes, cervical or uterine bleeding, placental abruption, proved cervical insufficiency, iatrogenic prematurity and risk factor from the previous pregnancies according to the World Association of Perinatal Medicine (WAPM) (Table 1).

Protocol

We measured vaginal pH in each woman, using indicator strips (1.09542.0001 pH-indicator strips pH 4.0-7.0 Special Indicator – Merck KGaA) or a CarePlan® VpH test-gloves, with a test indicator paper fixed on the tip of the index finger specially developed for this purpose. Indicator strips were introduced into the area of the introitus vaginae with the finger. We compared the indicator with the color chart and read the pH value. We used pH 4.5 as a cut off value.

We analyzed the presence of risk factors according to WAPM (Table 1) and the subjective signs as shown on Table 2 in each woman. We registered the gestational week at the delivery.

The results obtained were statistically evaluated using nonparametric statistics - X^2 test and Fisher exact test. The level of significance was set at $p < 0.05$.

Results

Among the total number of 62 women who had a preterm delivery, increased vaginal pH value (≥ 4.5) was registered in 46 (74.19%). Vaginal pH in the rest 16 women (25.81%) was in normal range.

From the analyzed risk factors according to WAPM, 7 (11.29%) of 62 women had a poor social status and 4 of them had an increased pH value; excessive professional stress and/or family demands was registered in 3 (4.84%) women and only one had an increased pH value; among 3 (4.84%) women with multiple pregnancy, no one had an increased vaginal pH, as well as the only one (1.61%) woman with pregnancy after infertility treatment; only 2 (3.23%) were smokers one of them with increased pH; parodontitis was registered in 7 (11.29%) women, 5 among them with increased pH. We didn't get data from any of the women for regular alcohol consumption, use of drugs or excessive consumption of stimulants, such as coffee.

Concerning the findings during the course of the actual pregnancy, vaginal-cervical-infection was previously registered in 44 (70.97%) women and 40 of them were with increased vaginal pH; uterine bleeding in 5 (8.06%) and 3 of them with increased pH; urinary tract infection, also asymptomatic in 8 (12.90%), five of them with increased pH; polyhydramnion in 1 (1.61%) woman with pH in normal range; previous premature labor in 16 (25.81%), 14 among them with increased pH; previous critical cervix state in 11 (17.74%), 8 of them with increased pH. There were no women with diabetes mellitus (severe form) nor serious organic disease or fever. (Table 1)

Among risk factors according to WAPM, statistically significant correlation was registered only

Table 1. Anamnestic or other signs of increased risk of late abortion or premature birth according to the WAPM

| | YES | | NO | | X ² | p |
|---|--------------------------------|----------------------|-----------------------|-------------|----------------|----------|
| | Total (% from the group) | Total pH ≥4.5 (%) | (% from the group) | pH ≥4.5 (%) | | |
| Present pregnancy | | | | | | |
| • Poor social status | 7 (11.29%) | 4 (57.14%) | 55(88.71%) | 42 (76.36%) | 1.2 | 0.27 |
| • Excessive professional stress and/or family demands | 3 (4.84%) | 1 (33.33%) | 59 (95.16%) | 45 (76.27%) | 2.75 | 0.97 |
| • Multiple pregnancy | 3 (4.84%) | 0 | 59 (95.16%) | 46 (77.97%) | | |
| • After infertility treatment | 1 (1.61%) | 0 | 61 (98.39%) | 46 (75.41%) | | |
| • Smoking | 2 (3.23%) | 1 (50%) | 60 (96.77%) | 45 (75%) | 0.66 | 0.4 |
| • Regular alcohol consumption or use of other drugs (also excessive consumption of stimulants, such as coffee) | 0 | | 62 (100%) | 46 (74.19%) | | |
| • Parodontitis | 7 (11.29%) | 5 (71.43%) | 55 (88.71%) | 41 (74.55%) | 0.20 | 0.65 |
| Findings during the course of the pregnancy | | | | | | |
| • Vaginal-cervical-infection | 44 (70.97%) | 40 (90.91%) | 18 (29.03%) | 6 (33.33%) | 22.12 | 0.000026 |
| • Uterine bleeding | 5 (8.06%) | 3 (60%) | 57(91.94%) | 43 (75.44%) | 0.57 | 0.44 |
| • Placenta praevia | 0 | - | 62 (100%) | 46(74.19%) | | |
| • Urinary tract infection also asymptomatic | 8 (12.90%) | 5 (62.50%) | 54 (87.10%) | 41(75.93%) | 0.66 | 0.41 |
| • Polyhydramnion | 1(1.61%) | 0 | 61 (98.39%) | 46(75.41%) | | |
| • Premature labor | 6 (25.81%) | 14 (87.50%) | 46 (74.19%) | 32(69.57%) | 1.98 | 0.15 |
| • Critical cervix state | 11 (17.74%) | 8 (72.73%) | 51(82.26%) | 38(74.51%) | 0.96 | 0.32 |
| • D. mellitus (severe form) | 0 | - | 62 (100%) | 46(74.19%) | | |
| • Serious organic disease or fever of the mother | 0 | - | 62 (100%) | 46(74.19%) | | |

Table 2. Subjective signs in the examined group - according to the WAPM

| | YES | | NO | | X ² | P |
|--|--------------------------------|-------------|--------------------------------|-------------|----------------|-----------|
| | Total (% from the group) | pH ≥4.5 (%) | Total (% from the group) | pH ≥4.5 (%) | | |
| Aching in the groin or in the sacral region | 43 (69.35%) | 38 (88.37%) | 19(30.65%) | 8(42.11%) | 14.73 | 0.0001239 |
| Temporary repeated hardening of the uterus | 42 (67.74%) | 38 (90.48%) | 20(32.26%) | 8(40%) | 18.3 | 0.0000218 |
| Abnormally frequent urination or a burning sensation when urinating | 17 (27.42%) | 12 (70.59%) | 45(72.58%) | 34(75.56%) | 0.16 | 0.69 |
| Considerable pains similar to menstruation | 15 (24.19%) | 13 (86.67%) | 47(75.81%) | 33(70.21%) | 1.61 | 0.20 |
| Bad smelling or highly increased discharge | 12 (19.35%) | 12 (100%) | 50(80.65%) | 34(68%) | | |
| Itching or burning in the intimate region | 12 (19.35%) | 12 (100%) | 50(80.65%) | 34(68%) | | |
| Urinary infection | 8 (12.90%) | 5 (62.50%) | 54(87.10%) | 41(75.93%) | 0.66 | 0.41 |

between increased vaginal pH and vaginal-cervical infection. (Table 1)

Most frequent subjective sign that women complained on were aching in the groin or in the sacral region (43 out of 62 – 69.35%, 38 of them with increased pH) and temporary repeated hardening of the uterus (42 out of 62 – 67.74%, 38 of them with increased pH).

Seventeen (27.42%) women complained on abnormally frequent urination or a burning sensation when urinating and 12 among them were with increased pH; 15 (24.19%) complained on considerable pains similar to menstruation (13 of them with increased pH) and 12 (19.35%) complained on bad smelling or highly increased discharge and itching

or burning in the intimate region, all with increased pH. We got anamnestic data for urinary infection from 8 (12.90%) of analyzed women, five of them with increased pH. No one of the analyzed women complained on fever and/or diarrhea- conditions often associated with an increase in uterine activities. (Table 2)

Among these subjective signs, statistical analysis showed significant correlation between increased vaginal pH and aching in the groin or in the sacral region and temporary repeated hardening of the uterus. (Table 2)

Discussion

Preterm delivery represents a major public health concern. Although in industrial countries neonatologists have achieved enormous success in keeping extremely premature infants alive, mortality increases rapidly with decreasing birth weight. Immediate and long-term sequelae of prematurity are also alarming – something which is sometimes neglected when just measuring the "successes" of modern intensive care by mortality rates. Enormously high costs of intensive care and of follow-up care should be an urgent inducement to make even more efforts to reduce the number of very small prematures, if possible.

Preterm infants cause substantial emotional and economic costs to their families and communities and have a disproportionate impact on the use of health services. Various working groups have argued consistently that a reduction in preterm births is most likely to be achieved when specific prevention programs can be provided to pregnant women. Evidence shows that long term financial burden imposed by preterm birth upon families and social services exceeds by far initial costs of treatment. For example, 40% of preterm children with a birth weight below 2500g will exhibit behavioral problems later in life, including attention deficit disorders, delinquency, social problems, and anxiety problems. (10)

The published studies confirm associations between increased pH and/or bacterial vaginosis and preterm delivery, early and late spontaneous abortions. Pregnant women with elevated vaginal pH in the first trimester, have abnormal vaginal flora, abnormal morphology of the lactobacilli and suffer from low abdominal pain, which may be a warning sign for a threat of miscarriage or preterm labor.(7)

Retrospective evaluation reveals that the earlier in pregnancy the children were born, the more frequently mothers had increased vaginal pH when admitted to hospital, especially prior to 32+0 gw, The rate remained at about 60%; when born mature only 43.5 % were affected. (5) Conclusion is that ascending infections very frequently play a role concerning very early prematurity, and that in

many of these cases threatening prematurity can be detected by measurement of increased pH values. One prospective study demonstrate the practical importance of measuring the vaginal pH, which is recommend in routine prenatal care for the prevention of prematurity. (11) Increasing pH value during the course of pregnancy leads to an increased risk of prematurity, even when the pH value stays within the normal range. (12)

The results of our study demonstrate increased pH value in the majority of women with spontaneous preterm delivery. This confirms the role of increased vaginal pH as a precursor in the cascade through ascending infection to preterm labor and delivery. Early detection and treatment of disturbance of vaginal milieu is a highly efficient prematurity screening which may significantly reduce the rate of preterm delivery. (Fig. 1) Incorporation of this screening into routine prenatal care early in the second trimester may reduce the rate of spontaneous preterm deliveries by 50%.

Our results support the hypothesis that increased vaginal pH is strongly associated with a risk of preterm delivery due to ascendant infection. More than 90% of women with vaginal and cervical infection during the course of the pregnancy had an increased vaginal pH value. The most frequent symptoms twomen complained about were aching in the groin or in the sacral region and temporary repeated hardening of the uterus. The majority of these women had an increased vaginal pH value (88.37% and 90.48% respectively). We also noticed that most of women complained about more than two subjective symptoms. With the exception of women with multiple pregnancies, the majority of the analyzed risk factors and subjective signs correlate with increased vaginal pH (Table 1, 2), but the groups of women that these symptoms were registered in were too small to lead to conclusions. Since this analysis is a part of an ongoing larger study, we hope to get exact results and make accurate conclusion based on the greater number of examined women.

Vaginal pH measurement is almost an ideal method for a reliable, rapid 'bed-side' risk assessment. It is an easy and efficient screening procedure. For the intervention to be effective, it is important to start testing of pH early in pregnancy (up to the 16th gestational week), as proposed by WAPM. Another important element for the intervention to be effective is appropriate medical treatment if bacterial vaginosis does occur. Bacterial vaginosis has a prevalence of between 10% and 30% during pregnancy and there are studies suggested that it precipitates preterm labor.

According to the latest proposals of WAPM, clinically simple strategies to identify patients at risk (e.g. vaginal pH testing to identify dysbiosis) and specific

interventions to prevent preterm birth, deserve systematic and urgent rigorous testing due to their promise to achieve a dramatic and rapid reduction in the rate of this adverse pregnancy outcome.

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РАДИОИЗОТОПЕН МЕТОД ЗА ОДРЕДУВАЊЕ НА ЖЕЛУДОЧЕН ТРАНЗИТ НА ЦВРСТА ХРАНА

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Извадок

Желудочниот дисмотилитет е чест проблем во секојдневната пракса, на кој честопати не се обрнува доволно внимание. Желудочниот мотилитет може да се иследува со радиографски, ултрасонографски, електрогастрографски и скинтиграфски методи.

Целта на овој труд е стандардизација на радиоизотопниот метод за следење на желудочниот транзит на цврст оброк и одредување на нормалните вредности за параметрите кои ја карактеризираат оваа студија.

Иследувањето опфати 20 здрави испитаници. Користејќи компјутеризирана гама камера по консумација на стандардизиран радиоактивен тест оброк беше направена серија од скенови во АП и ПА позиција во одредени временски интервали. Параметрите кои го карактеризираат гастричното празнење беа одредени со цртање на регии од интерес врз желудникот. Со овој метод може да се одредат полувреме на празнење, почетен индекс, β и рата на празнење за целиот и проксималниот желудник, додека за дисталниот желудник може да се одреди време на максимално полнење, полувреме на празнење и рата на празнење.

Клучни зборови: радиоизотопен метод, желудочно празнење

RADIONUCLIDE TECHNIQUE FOR THE ASSESSMENT OF GASTRIC TRANSIT OF SOLID MEAL

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Abstract

Gastric dismotility is problem frequently encountered in everyday practice, although very often underestimated. The gastric motility can be studied by radiographic, ultrasonographic, electrogastrographic and scintigraphic methods.

The objective of this study was standardization of the scintigraphic method for gastric emptying of a solid meal and determination of normal values for the parameters that characterize this study.

The research included 20 healthy volunteers. Using a computerized gamma camera, after the consumption of the standardized radioactive test meal a series of scans in AP and PA position in predefined time intervals were made. The parameters used for the observation of the gastric transit were determined by drawing regions of interest above the stomach. Emptying half-time, starting index, β and the rate of emptying for the whole and proximal stomach, and maximal filling, Emptying half-time and emptying rate for the distal stomach can be determined by this method.

Key words: Gastric emptying, scintigraphic method

Introduction

Gastric dismotility is problem frequently encountered in everyday practice, although very often underestimated. The patients complaints include nausea, bloating, vomiting, early satiety and epigastric pain. The cause of these complaints might be gastric dismotility caused by variety of conditions and diseases. Gastric dismotility may be a transitory disorder caused by drugs, electrolyte disturbances or acute infections. Chronic disturbances of gastric motility may occur in the course of some endocrine, autoimmune and neurologic diseases. Table 1 represents some of the conditions and diseases that represent with gastric dismotility.

The gastric motility can be studied by radiographic, ultrasonographic, electrogastrographic and

scintigraphic methods. The scintigraphic method is considered the gold standard for the evaluation of gastric emptying time (1). Even though it is accepted as gold standard there is no standardized protocol for the procedure of scanning and the quantification method, nor normal reference range.

The aim of our study was to introduce the radionuclide technique for the estimation of transit of solid meal as a routine method at our Institute. The standardization of the method is very important for the successful radionuclide determination of gastric transit of a solid meal and therefore we set a goal to standardize the test meal, acquisition and data processing protocol, and to establish the reference range of normal values for all the parameters of gastric transit included in the study.

Table 1. Causes for gastric dismotility**Delayed gastric emptying**

- diabetes
- idiopatic
- post operative
- gastroesophageal reflux
- sclerodermia
- dermatomyositis
- amyloidosis
- Duchenne-ova muscular dystrophy
- Spinal injuries
- hypothyreosis
- neoplastic diseases
- diseases of the central nervous system

Accelerated gastric emptying

- post operative
- Zollinger - Ellison syndrom
- duodenal ulcers
- diabetes
- hyperthyreosis

Materials and methods

Normal values for our laboratory for the various parameters of the gastric transit were set on the basis of results obtained from 20 healthy volunteers, (10 men and 10 women, ages 24-60 years) with average body mass index 24.32 kg/m². There was no evidence for gastrointestinal and endocrinologic disease in subjects.

The gastric emptying study of the solid meal with radionuclide method was performed at the Institute of Pathophysiology and Nuclear Medicine (IPNM), at the medical faculty in Skopje.

The subjects in our study were relatives, friends and the employees of IPNM who showed great enthusiasm and understanding for our project. The procedure was performed in the morning. Food, drink and smoking were prohibited for 12 hours before the procedure.

Test meal

The test meal used in our study consisted of one radiolabeled egg, 25gr of toast bread, and 120 ml of water. The whole egg was labeled with 0.5mCi ^{99m}Tc sulfur colloid. The egg was well beaten and than cooked on a non-adhesive pan without oil. The added sulfur colloid

does not cause any changes in the appearance, taste or smell of the egg.

The test meal standardized in this way is composed of proteins, fats and carbohydrates with energy value of 1000KJ.

Stability of binding

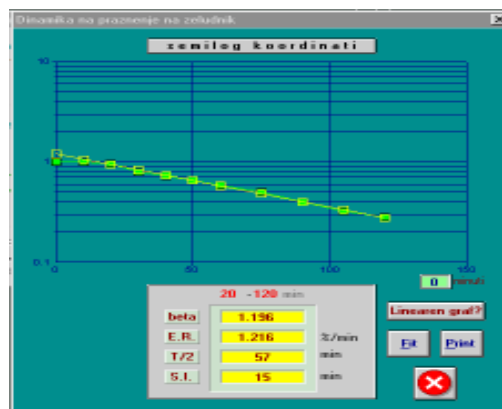
After the standard preparation the egg was cut into small pieces and divided in four tubes with 10 ml of water and 0.5 ml of 1molar HCL. The tubes were set on a mixer with slow movements in order to achieve continuous mixing of the meal. The percentage of radioactivity bound to the solid portion of the tube content was measured every 30 minutes from the samples obtained from one of the tubes. After 30 minutes the percentage of the radioactivity in the egg was 98.1%, after 60 minutes 97.6%, after 90 minutes 95.6%, and after two hours 92.8%.

Acquisition protocol

The radioactive test meal was consumed within 5 minutes, and immediately after the ingestion of the meal the first sequences were taken. The scanning was performed on a computerized planar gamma camera (Siemens - ZLC750). A series of 60 seconds static scans were obtained on a 8 bit matrix with format of 256x256 pixels. The scans were obtained every 5 minutes in the first 30 minutes, at 10-minute interval for the next 30 minutes, and at 15-minute interval until the 120 minutes. Every set of scans was obtained in AP and PA position. During the scanning the subjects were in standing position. Between the scans they were sitting near the camera in a quiet and relaxed surrounding.

Data processing

A region of interest (ROI) was drawn around the tracer activity in the stomach. The integral amount of registered radioactivity (IAR) was calculated in the region. The radioactive test meal transits from the upper region of the stomach (fundus) toward lower anterior portions (antrum). This implies that in different time points of the scanning the test meal is located at different depths within the abdomen, which results in different grade of attenuation of the gamma emission during the scanning procedure. Therefore the IAR is calculated as a geometric mean from the IARs in AP and PA position. From the IARs

**Fig. 1.** Normal gastric emptying time-activity curve

at all scanning time points the time-activity curve is produced (fig. 1).

There are two phases in the time-activity curve of gastric emptying of solid meal. The first phase is known as a lag phase and starts from the first scanning time and ends when the first significant amount of radioactivity enters the duodenum. The lag phase represents the movement and redistribution of the meal from the fundus to the distal stomach, and in the reverse direction (2). This phase is characterized with the starting index (SI).

The second phase is represented with a monoexponential correlation between the residual activity in the stomach and the time. The graph exhibits excellent linearity in a semi log coordinates with a slope that allows determination of the gastric emptying half-time (T/2) and gastric emptying rate (ER)(1).

The time-activity curve is best approximated with the following function:

$$y = (e^{-\kappa t})^{-\beta}$$

where y is representing the emptying rate, κ is the slope of the curve, β is the intersection of the extrapolated linear phase of the curve with the y axis, and τ is time. If the maximum value of the curve is normalized to 1 then when the gastric emptying is fast and the lag phase does not exist the parameter β has value <1, and if the lag phase exists then $\beta > 1$. The intersection of the extrapolated curve with the maximum value of the IAR normalized to 1 represents the SI.

For the purpose of calculations in our study a software was created using the Misrosoft –Visual basic 3.0 where a special algorithm based on the linear least-square method allowed calculation of the parameter κ , SI and T/2 in minutes, ER as % of radioactivity in minute and β as a positive number.

All these parameters were determined for the whole stomach, and for the proximal stomach. The parameters determined for the distal stomach were maximum filling (MF) which represents the time point when the maximum radioactivity is achieved in the distal stomach, emptying rate (ERd) and emptying half-time (T/2d) of the distal stomach from the moment of MF.

Statistics

Normal values for all the parameters of the gastric transit were determined according to the values gathered from the subjects in our study. The reference range was described as +/- 1 standard deviation (SD) from the arithmetical mean. Considering that the values didn't have normal distribution the 95% confidence limits of standard deviation were set according to following formula(3):

$$(N-1)SD^2/P-0.025 < SD^2 < (N-1)SD^2/P-0.975$$

N- number of subjects

P-0.025- values from the X2 table for N-1 degree of freedom
P-0.975

Results

The next three tables represent the values for the parameters of the gastric transit of the solid meal through the whole, proximal and distal stomach.

Table 2 represents the statistical parameters for the transit of the solid meal through the whole stomach. The normal values for the gastric emptying half-time are between 48 and 76 minutes, for the SI between 8 and 27 minutes, for the β from 1.17 to 1.61, and 1.40 to 2.17%/min for the emptying rate.

Table 3 represents the statistical parameters for the transit of the solid meal through the proximal stomach. The range of normal values for T/2p is from 23 to 45

Table 2 . Parameters for gastric emptying of the whole stomach

| | T/2 | SI | b | ER |
|------------|-------|-------|------|------|
| Mean | 57.58 | 14.05 | 1.27 | 1.65 |
| Median | 56.00 | 15.00 | 1.28 | 1.68 |
| Mode | 48.00 | 6.00 | / | / |
| SD | 12.14 | 8.39 | 0.21 | 0.35 |
| Range | 40.00 | 32.00 | 0.89 | 1.39 |
| Maximum | 80.00 | 32.00 | 1.87 | 2.30 |
| Minimum | 40.00 | 0 | 0.97 | 0.90 |
| Mean - 1SD | 48.40 | 7.85 | 1.17 | 1.40 |
| Mean+1SD | 75.90 | 26.71 | 1.61 | 2.17 |

Table 3. Parameters for gastric emptying of proximal stomach

| | T/2p | SIp | β p | RPp |
|------------|-------|-------|-----------|------|
| Mean | 38.1 | 4.31 | 1.00 | 2.12 |
| Median | 39.00 | 1.50 | 1.01 | 2.11 |
| Mode | 24.00 | 0.0 | / | 2.11 |
| SD | 9.66 | 5.58 | 0.30 | 0.44 |
| Range | 29.00 | 17.00 | 1.04 | 1.58 |
| Maximum | 52.00 | 17.00 | 1.55 | 2.90 |
| Minimum | 23.00 | 0.00 | 0.51 | 1.32 |
| Mean - 1SD | 23.2 | / | 0.0 | 1.46 |
| Mean + 1SD | 45.21 | 12.7 | 1.69 | 2.44 |

able 4. Parameters for gastric emptying of distal stomach

| | MP | T/2d | RPd |
|------------|-------|-------|------|
| Mean | 22.82 | 55.46 | 1.58 |
| Median | 25.00 | 49.00 | 1.67 |
| Mode | 30.00 | 32.00 | / |
| SD | 8.84 | 25.26 | 0.58 |
| Range | 21 | 77.00 | 1.74 |
| Maximum | 30 | 109 | 2.38 |
| Minimum | 9 | 32 | 0.6 |
| Mean - 1SD | 9.22 | 16.46 | 0.68 |
| Mean + 1SD | 29.35 | 74.06 | 2.01 |

minutes. The lag phase did not exists in some of our subjects therefore 0 is set as a lower range for the SI even though according to the statistic this value is supposed to be bellow zero. The upper limit of the first phase is 13 minutes. The situation is similar with the parameter β . Lower limit is set at 0.99 while the upper limit is 1.69. The normal range for emptying rate is from 1.46 to 2.44%/minute.

Table 4 represents the parameters for the emptying of the distal stomach. Normal values for MF are between 9 to 29 minutes, for T/2d from 16 to 74 minutes, and ERd from 0.68 to 2.01%/minute.

Discussion

There are many studies published in the literature where the gastric transit of a solid meal is determined with the radionuclide method. The appearance of the curve and the reference range vary widely depending on the test meal and the mode of acquisition and data processing. Very good example of the variability of normal values in

correlation with the volume of the test meal is the study of Christian et al. where the test meal used was chicken liver labeled with ^{99m}Tc sulfur colloid with weight 300, 900 and 189 grams. The gastric emptying half-time for the first test meal was 77 minutes, for the second 146 minutes, and for the third one 277 minutes (4). The normal values of gastric transit are influenced by the volume, energy value, relative percentage of the fats, proteins and carbohydrates in the meal, type of the proteins, consistency of the meal, temperature, etc (5). Therefore the test meal should be standardized in every laboratory.

The stability of binding of the radionuclide in the test meal is also very important. If the stability of binding is not achieved, during the study part of the radioactivity from the solid test meal will transit into the fluid which is always part of the test meal and the data from the scanning will represent the transit of the solid meal and the liquid as well.

The stability of binding of the ^{99m}Tc sulfur colloid to the solid part of the meal in our study was 98% after 30 minutes, and 92% after 120 minutes. These data are comparable with the percentage of binding reported by other authors and allows precise performance of the study (6).

The mode of acquisition can affect the appearance of the time – activity curve.

When the acquisition protocol requires scanning the patient every 15 minutes there is a high possibility that the lag phase will be missed. Departments with two headed gamma camera record data continuously for two hours with 60 second sequences (7). The acquisition protocol used in our study with frequent scans in the first thirty minutes allowed a good representation of both phases in the time-activity curve.

The lag phase corresponds to the period of mixing and grinding of the food in the stomach before the first morsels enter the duodenum. Various parameters are described in the literature for the first phase. Our study investigated the SI and β . SI proved to be more convenient in everyday practice. The values for SI correlate very well with visual assessment of the entrance of radioactive test meal in the duodenum. Our normal values for SI from 8 to 28 minutes are similar to those obtained by Ziesmann et al (7) where test meal was very similar to the one used in our study. There are studies that define the lag phase as the time point of maximum filling of the antrum (2). Our study demonstrated that this is not a good definition considering that in few of our subjects the MF was not established because the food descends from the proximal stomach, and exits the antrum at the same time.

There are studies that showed different gastric emptying in men and women. Bennik et al noted slower gastric emptying in women (8). Our study did not show any differences in gastric transit between males and females.

Conclusion

Radionuclide method for the study of gastric transit of a solid meal is a useful method that enables evaluation of gastric dismotilities from different etiologies

and understanding of the pathophysiology of the gastric dismotility which allows better clinical solutions of the problem.

The good interpretation of the data from this method requires standardized test meal, standardized acquisition and data processing protocol. All of those criteria were met in our study, so the radionuclide method for gastric emptying can be used further for the evaluation of gastric dismotility in various patient groups.

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НАДОПОЛНУВАЊЕ НА РАЗЛИЧНИ ДНК МЕТОДИ ВО ИДЕНТИФИКАЦИЈА НА ЧОВЕЧКИ ОСТАТОЦИ

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Извадок

Анализата на дезоксирибонуклеинската киселина (ДНК) има голем број предности во споредба со традиционалните идентификациони методи какви што се форензичната антропологија, отпечатоците од прсти и одонтологијата. Таа е важна алатка во анализата на значително распаднатите човечки остатоци. ДНК идентификацијата се изведува со споредба на ДНК профилот од човечките остатоци со ДНК профили од претпоставените биолошки роднини на лицето чиј идентитет се испитува, со користење на различни методи, какви што се типизација на кратките повторливи секвенци (СТР) на автосомните хромозоми, а во случај на машки ДНК профил, употреба на дополнителна СТР типизација на X хромозомот. Анализата на митохондриската ДНК (мтДНК) може да се користи како алтернативен метод доколку човечките остатоци се многу стари или доколку се следи мајчината линија на наследување.

Во последните 5 години во нашата лабораторија успешно беа решени десет случаи на идентификација со користење на методи за добивање ДНК профил, вклучувајќи осум случаи на идентификација на човечки остатоци од исчезнати лица, најдени во променета форма или распаднати и два случаи на напуштени бебиња со непознат идентитет. Во овие случаи, други методи за идентификација (препознавање преку карактеристики на лицето или посебни обележја на телото како што се лузни или тетоважи, или преку карактеристики на забалото) беа недоволни за позитивна идентификација. Оттука, целта на студијата беше да се евалуираат идентификационите техники базирани на анализа на ДНК и нивното дополнување при користење на различни ДНК методи, какви што се типизација на автосомните и X хромозоми и секвенционирање на мтДНК.

Клучни зборови: идентификација на човекови остатоци, СТР типизација, секвенционирање на мтДНК

COMPLEMENTATION OF DIFFERENT DNA METHODS IN IDENTIFICATION OF HUMAN REMAINS

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Abstract

Deoxyribonucleic acid (DNA) analysis has a number of advantages compared to traditional identification methods such as forensic anthropology, fingerprint and odontology. It is a critical tool in analysis of severely fragmented body remains. DNA identification is made by comparing DNA profiles from human remains to DNA profiles from supposed biological relatives of the tested person, using different methods for DNA profiling, such as short tandem repeat (STR) typing of autosomal chromosomes and, in case of male profile, additional Y STR typing. Mitochondrial DNA (mtDNA) analysis can be used as an alternative method if tested human remains are very old or if the maternal lineage of the deceased is followed.

In the last 5 years ten cases of identification using DNA profiling methods were successfully solved in our laboratory. There were eight cases of identification of body remains from missing persons, found in changed or decomposed form, and two cases of left babies with unknown identity. In these cases, other methods used in identification (facial recognition or recognition of special features of the body such as scars, or tattoos, or dentition) were insufficient for positive identification. Thus, the aim of the study was to evaluate the identification techniques based on the analysis of DNA and their complementation, when using different DNA methods, such as autosomal and Y STRs typing, and mtDNA sequencing.

Key word: human identification, STR typing, mtDNA sequencing

Introduction

Short tandem repeats (STR) typing of DNA is a powerful tool for human identification since its first use in the forensic case investigation by Jeffreys et al.¹ Various forensic techniques are used for identification of human corpse, such as recognition by the living person who knew the deceased, anthropology, matching fingerprints,

radiology and odontology, but DNA analysis is the only method of choice in some circumstances and in some state of the remains. DNA identification is particularly useful when the person has been burned in a fire or the body is decomposed or fragmented. In such circumstances, other methods are often not accurate or impossible and DNA provides the only means of establishing the identity of

body remains. The analysis involves comparing of DNA profile of the remains with DNA profile of known relatives of the deceased or comparison with in life left biological samples on personal objects from deceased person. The preferred method of DNA testing is analyses of nuclear DNA by typing of autosomal STRs loci² and additionally typing of Y STRs loci³ in samples of male gender. In some cases of highly decomposed human remains, when nuclear DNA is highly degraded, identification is performed by mtDNA sequencing.⁴ The aim of the study was to evaluate the identification techniques based on the analysis of DNA and their complementation, when using different DNA methods, such as autosomal and Y STRs profiling, and mtDNA sequencing.

Materials and methods

Materials

-DNA sources

Tissues from the body and body parts were collected during autopsy. One or two samples from each were collected during autopsy as follows: from three cases of burned bodies, a piece from right quadriceps femoris muscle and a piece from liver; from one case of putrid body, a piece from lungs; from three cases of skeletal remains, bone fragments from femur and in one case of skeletal remain where only skull was found, a piece from the skull; and from babies, few milliliters of blood. In all of these cases, blood samples were obtained from the supposed relatives of the deceased, as reference samples.

Methods

-DNA extraction

Extraction of DNA from soft tissues and bones was performed by phenol-chloroform method. Bones were firstly treated with UV light and then reduced into mineralized powder using Mixer Mill and liquid nitrogen, in order to let decalcification go faster. The bone powder was then incubated at 37°C over night with TBE buffer containing 10 mM TRIS-HCl, 10mM EDTA, 100mM NaCl, 39mMDTT, 2%SDS and 1mg of Proteinase K. Phenol-chloroform extraction followed and purification of the DNA in centrisep columns. DNA from blood samples was extracted using QiAamp DNA Mini kit-Qiagen or Chelex 100 method.

-Polymerase chain reaction amplification

PCR amplifications of STRs were performed using AmpFISTR Identifiler and Y-Identifiler kits (Applied Biosystems), and Power Plex 16 and ESX-17 kits (Promega), according to the manufacturers' protocols. PCR products were separated on a polymer substrate by capillary electrophoresis with ABI 310 DNA Genetic Analyzer.

-DNA extraction, polymerase chain reaction amplification of mtDNA and sequencing

Extraction of mtDNA from bones and blood was performed by the phenol-chloroform method. PCR amplifications of mtDNA, using 5 ng of template DNA, were carried out in a total volume of 25 µl, consisting of 2.5 µl GeneAmp 10xPCR Gold Buffer, 1.5 µl 25mM MgCl₂, 2µl 2.5 mM dNTP mix, 2µl 5µM forward amplification primer, 2 µl 5µM reverse amplification primer and 0,5 µl of AmpliTaq Gold DNA polymerase. The PCR primers and

reaction conditions for hypervariable region I (HV1) and hypervariable region 2 (HV2) have been described previously.⁵ To ascertain amplification, the PCR products with each primer set were separated in 2% agarose gel and stained with ethidium bromide. Sequencing was performed with forward and reverse primers, using BigDye Terminator Cycle sequencing kit v.1.1. Sequencing results from human remains and supposed relatives were compared with each other and with the Anderson's sequence⁸ using SeqScape sequencing software.

-Statistical analysis

To determine the real belonging of the dead subjects to the respective supposed families, a calculation for "kinship" with different scenarios using DNA View software was performed. DNA View software is specialized software for forensic DNA analysis, which calculates the frequency of analyzed STR alleles of the samples in comparison to frequency of STR alleles in Macedonian population and accordingly different statistical percent is obtained, which is always over 99.9% in cases of positive identification.

Results

In nine of ten cases, nuclear DNA was analyzed, and the amplification was performed using AmpFISTR-Identifiler kit (Applied Biosystems) or Power Plex 16 kit (Promega) (Figure 1). In all of these cases, blood samples from supposed relatives were analyzed using the same method and kits for DNA amplification. In eight of these nine cases, including one putrid body, three cases of burned bodies, one baby and three cases of skeletal human remains, DNA identification was positive, with accuracy of more than 99.9%, so the identity of the unknown deceased person was proved; only in one case of unknown baby, the supposed mother was not the mother of the baby, and the identification was negative. In three cases where DNA profile of the human remains showed male profile and the relatives for comparison were also male, additional Y STR typing was performed (Figure 2): in the first case, DNA profile of the body was compared to DNA profile of the supposed brother of the deceased and the statistical analysis of their connection showed 99.9% probability. Y STR profiles were identical; in the second case DNA profile was compared to DNA profile of the brother and father of the deceased and the statistical value for the probability of their connection was 99.9999%, their Y STR profile was the same; in the third case DNA profile was compared to DNA profile of the brother and father of the deceased and the statistical value for the probability of their connection was 95.1 % and with additional Y STR typing the statistical value for their connection was 99,98%.

In one case of identification DNA profile of the body which showed female profile was compared to the supposed parents. From 15 analyzed loci with AmpFISTR-Identifiler kit, there was a difference between the mother and the daughter in one locus. Even though the statistical value for connection between the daughter and her parents was high, another kit for amplification of autosomal



Fig. 1. Amplification of DNA extracted from 2-year-old bone from a man who was killed and buried in the forest. DNA was amplified with the PowerPlex 16 kit.

Fig. 1. (continued)



Fig. 2. Y STR profile from the same bone remains

STRs with additional five loci was included (ESX-17, Promega). The connection was proved.

In another case, where nuclear DNA was highly degraded, mtDNA was extracted from bone sample of the femur and mtDNA sequence was compared to mtDNA sequence from blood sample of the presumptive mother. Mother-child relationship was confirmed. In comparison with Anderson’s sequence, three substitutions were observed for hypervariable region 1 (HV1) (**Table 1**).

For hypervariable region 2 (HV2), in comparison to Anderson’s sequence, two substitutions, one deletion and one insertion were observed (**Table 2**).

Table 1. Mitochondrial DNA sequences: Hypervariable region 1 (HV1)

| | HV1 (base position 15997-16401) | | |
|----------------------|---------------------------------|-------|-------|
| | 16223 | 16298 | 16327 |
| Anderson’s reference | C | T | C |
| Bone sample | T | C | T |
| Presumptive mother | T | C | T |

Table 2. Mitochondrial DNA sequences: Hypervariable region 2 (HV2)

| | HV2 (base position 29-408) | | | |
|----------------------|----------------------------|-----|-----|-------|
| | 73 | 249 | 263 | 315.1 |
| Anderson’s reference | A | A | A | - |
| Bone sample | G | X | G | G |
| Presumptive mother | G | X | G | C |
| X, deletion | | | | |

Discussion

Common methods for identification of human corpses, such as forensic anthropology, fingerprint and odontology, were insufficient for identification in our presented cases because of the state in which the bodies were found (burned, decomposed or skeletal remains); hence, identification based on the analysis of DNA was a method of choice. The results obtained showed that statistical calculation in most positive identification was with high probability (more than 99.9%). Statistical accuracy depends on available relatives used for comparison and their genetic connection to the deceased. If they are first degree relatives and if more than one relative is used for comparison, then statistical value for likelihood ratio of their connection will be higher. But in some cases, where a mutation in one locus is considered, DNA typing with different kits, including additional loci are preferred, so the accuracy of the results is increased. Or, if the tested sample for autosomal STRs shows male profile and if the comparison is made with male relatives, then Y-STR typing could be used to assist in establishing kinship with bigger probability of connection. In one of the presented cases, using autosomal STR profiling for identification, statistical value for probability of connection was 95.1%, because the percentage also depends on the frequency of the tested alleles in the allele pool of the population. By including Y STR typing, it was increased to 99.98%. Additional identification technique based on analysis of DNA is mtDNA typing, which advantage over nuclear DNA typing is the high copy number of mtDNA per cell⁷. Therefore, it is a method of choice when the amount of extracted DNA from a sample is extremely low or when the extracted DNA is significantly degraded, as was in one of our cases. The conclusion is that DNA profiling is a supreme technology in human identification, and with complementation of different DNA methods the accuracy of the results is higher.

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ПРОГНОСТИЧКА МОЌ НА НОРМАЛНА СПЕКТ МИОКАРДНА ПЕРФУЗИОНА ТОМОСЦИНТИГРАФИЈА КАЈ ПАЦИЕНТИ СО И БЕЗ КОРОНАРНА АРТЕРИСКА БОЛЕСТ

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Извадок

Миокардниот крвен проток може да се зголеми од базичните нивоа во ситуации на зголемена побарувачка, или при зголемената понуда. Зголемување на миокардната кислородна побарувачка може да е провоцирана со напор или инотропични агенси-добутамин. Друг начин е зголемување на миокардното снабдување со кислород, со користење на коронарна вазодилататори: аденозин и дипиридамол.

Способност за зголемување на протокот на крв на миокардот е резултат на постоењето на коронарната проточна резерва (CFR) - капацитетот на коронарната циркулација да се шири при зголемување на миокардните метаболни потреби, а може да се изрази како разлика помеѓу протокот при максимална хиперимија и протокот во мирување (базални услови).

Постојат неколку инвазивни и неинвазивни методи на одредување CFR. Доплеровата техника на “жица” е првата инвазивна метода која нашла клиничка примена. ПЕТ-позитрон емисионата томографија е златен стандард што може да обезбеди апсолутно мерење на протокот на крв на миокардот на одмор и за време на максимална хиперимија. Ехокардиографските техники, како што се: контрастната ехокардиографија, Доплер “harmonic imaging” (HPDI), магнетна резонанца (МРИ), и вазодилаторните миокардно перфузиони студии (МПС СПЕКТ), претставуваат дел од палетата на неинвазивни методи на визуелизација кои овозможуваат увид во миокардниот крвен проток и коронарната проточна резерва. Но сепак, не постои лесно применлива, широко распространета клинички достапна метода за мерење на коронарната проточна резерва.

Мерење на CFR е важно (мерење со вазодилаторен СПЕКТ МПС), бидејќи овозможува неинвазивна проценка на коронарната проточна резерва и дава зголемувачка дијагностичка и прогностичка вредност на дијагностички и прогностички вредност на податоците за регионалниот миокарден крвен проток.

Во клиничката пракса често наидуваме на ситуации каде СПЕКТ МПС студијата е нормална, а постои тешка повеќесадовна ангиографски потврдена коронарна артериска болест (КАБ), и наспроти тоа, ситуации во кои детектуваме перфузиони абнормалности на СПЕКТ МПС студијата, а пациентите се без значајна ангиографски дефинирана КАБ. Како можеме да ги интерпретираме овие наоди?

Клучни зборови: коронарен крвен проток, коронарна проточна резерва, миокардна перфузиона томосцинтиграфија

PROGNOSTIC POWER OF NORMAL SPECT MUOCARDIAL PERFUSION TOMOSCINTIGRAPHY IN PATIENTS WITH AND WITHOUT SIGNIFICANT CORONARY ARTERY DISEASE

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Abstract

Myocardial blood flow can be increased from the baseline levels in the situations of increased demand, or by increased supply. Increasing of myocardial oxygen demands may be provoked by *exercise or inotropic agents-Dobutamine*. Other way is to increase myocardial_oxygen supply, using *coronary vasodilators: adenosine and dipyridamol*.

Capability for increasing of myocardial blood flow is a result of existence of coronary flow reserve (CFR) - the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands and can be expressed by the difference between the hyperaemic flow and the resting flow.

There are several invasive and noninvasive methods of determining CFR. The Doppler wire technique was the first invasive method used clinically. PET-positron emission tomography is the gold standard that can provide absolute measurements of myocardial blood flow at rest and during hyperemia. There are also echocardiography-based techniques such as intravenous myocardial contrast echocardiography with harmonic power Doppler imaging (HPDI), Magnetic resonance imaging, and vasodilator MPI SPECT. But steal; there isn't any easy to use, widespread, clinically available method for measuring of CFR.

Measuring of CFR is important (measurement with vasodilator SPECT MPI), as it provides noninvasive assessment of CFR and adds incremental diagnostic and prognostic value to the information already provided by the assessment of regional myocardial perfusion?

In the clinical practice there are often situations of normal perfusion scans in patients with severe multivessel coronary artery disease (CAD), and as opposite to this, situations in which perfusion scan abnormalities were found in patients without angiographically significant CAD. How can we interpret these findings?

Key words: coronary flow, coronary flow reserve, myocardial perfusion tomoscintigraphy

Introduction

Normally, coronary blood flow can increase approximately four-to-six fold to meet increasing myocardial oxygen demands. This effect is mediated by vasodilatation at the arteriolar bed, which reduces vascular resistance, thereby augmenting flow. **The coronary flow reserve (CFR) represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands, and can be expressed by the difference between the hyperaemic flow and the resting flow (figure 1).**

In 1974, Lance K Gould proposed the relationship between the anatomic condition and behaviour of coronary hyperaemic flow (*figure 2*), whereby an inverse curvilinear relationship exists between the narrowing of lumen of coronary artery and hyperaemic capability, up to a completely abolished coronary reserve for stenosis >90%. Similar condition is present in highly selected series of patients with single vessel disease, no myocardial infarction, no coronary collateral circulation, normal baseline function, no left ventricular hypertrophy, without evidence of coronary vasospasm, and off therapy at the time of testing. Such situation rarely can be found in everyday clinical practise, where many variables can modulate the imperfect match between epicardial coronary artery stenosis and coronary flow reserve, such as: the geometric characteristics of the stenosis, the presence of coronary collateral circulation, the micro vascular component of coronary resistance, the presence of left ventricular hypertrophy modulating the myocardial extra vascular component of coronary resistance, the viable or necrotic state of the myocardium distal to the stenosis, the presence of coronary macro vascular or micro vascular spasm, and, last but not least, the presence of concomitant anti-ischemic therapy. (1, 2)

Fig. 1. Schematic representation of coronary flow velocity profile obtained with transthoracic Doppler of distal left anterior descending coronary artery: in diastole the flow velocity is higher than in systole. Rigo Cardiovascular Ultrasound 2005, 3:8. doi:10.1186/1476-7120-3-8

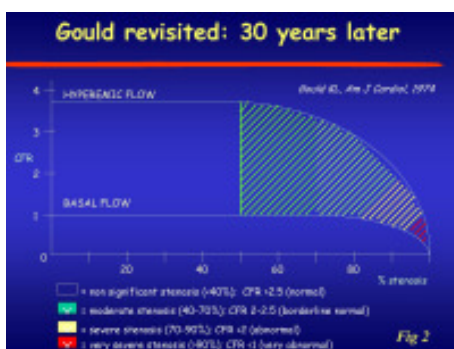


Fig. 2. Relationship between the true increments of the flow signal obtained with the currently available imaging techniques. Modified from Gould KL, ref.1. On the abscissa is represented different narrowing of the coronary vessel. Rigo Cardiovascular Ultrasound 2005 3:8; doi:10.1186/1476-7120-3-8

Myocardial blood flow can be increased from the baseline levels in the situations of increased demand (more physiological way), or by increased supply. Myocardium is extremely efficient in extracting oxygen from blood. The increase in myocardial oxygen demand and consumption leads to increase of myocardial blood flow and hyperemia. **Increasing of myocardial oxygen demands** may be provoked by *exercise or inotropic agents*-Dobutamine. Other way is to **increase myocardial oxygen supply**, using *coronary vasodilators*: adenosine and dipyridamol.

Since 1970s and 1980s, when researchers proved that vasodilators increase coronary blood flow 3 to 5 time above baseline in normally perfused myocardium, these agents were and are widely used as pharmacologic stressors in myocardial perfusion tomoscintigraphic studies (MPI SPECT).

While the mechanism of inducing ischemia by effort (or pharmacologic mimicking of effort), is well known, there are several possible mechanisms of ischemia induced during vasodilator infusion. (3, 4, 5)

Mechanisms of ischemia during pharmacologic vasodilator stress

✓ Coronary steal

In patients with severe coronary artery disease (CAD), development of collateral vessels provides maintenance of resting blood flow. Vasodilator causes

paradoxical ischemia in the territory of significant coronary stenosis when the myocardium is dependent on collateral flow. It's a situation in which regional myocardial blood flow decreases below the baseline level because of vasodilator-induced fall in pressure and resistance in the conductance arteries that supplies the collateral vessels.

✓ **Relative coronary steal**

This is a situation of decreased endocardial to epicardial flow ratio, because of the absolute decrease of the blood flow in subendocardial layer, as the result of the much greater vasodilator capacity in the epicardium.

These are the two mechanisms of induced ischemia during vasodilator infusion in the presence of collaterals. Other mechanism is occurrence of ischemia without overall reduction in transmural flow, probably as a result of abnormal flow reserve in the absence of significant stenosis. (5)

Coronary flow reserve (CFR)

Coronary flow reserve is the amount of additional blood flow that can be supplied to the heart over baseline blood flow (coronary flow in basal resting conditions).

There are several terms used to describe CFR:

- ✓ **Absolute flow reserve** is the ratio of blood flow during maximal hyperemia in a stenotic artery to blood flow in the same artery during resting conditions.
- ✓ **Relative flow reserve** is the ratio of hyperemic flow in a stenotic artery to hyperemic flow in another normal artery.
- ✓ **Fractional flow reserve** is the ratio of hyperemic flow in a stenotic artery to the maximum achievable flow in the same artery if it was normal. (1,6)

Methods of determining CFR

There are several invasive and noninvasive methods of determining CFR. The Doppler wire technique was the first invasive method used clinically, and there is also the pressure-derived fractional flow reserve. PET-positron emission tomography is the gold standard that can provide absolute measurements of myocardial blood flow at rest and during hyperemia. There are also echocardiography-based techniques such as intravenous myocardial contrast echocardiography with harmonic power Doppler imaging (HPDI), Magnetic resonance imaging, and vasodilator MPI SPECT. But steal; there isn't any easy to use, widespread, clinically available method for measuring of CFR. (1, 6)

Why measure of CFR is important (measurement with vasodilator SPECT MPI)

Does the noninvasive assessment of CFR provide incremental value to the information already provided by the assessment of regional myocardial perfusion?

In the clinical practice there are often situations of normal perfusion scans in patients with severe multivessel coronary artery disease (CAD), and as opposite to this, situations in which perfusion scan abnormalities were found in patients without angiographically significant CAD. How can we interpret these findings? (7)

Ragosta refers 18% of 143 patients with angiographically confirmed three vessel disease who have had normal MPI perfusion finding. It is well known fact that SPECT MPI techniques are based on the principle of relative flow reserve so the absence of normal vascular territory will lead to **balanced ischemia**. In such situations measurements of the coronary flow reserve (CFR) should clearly be abnormal. Other, not less important reason is **the use of antianginal medications**. Their use lead to reduction of ischemic burden, and therefore it may be the reason for diminish sensitivity of the MPI perfusion study.

Coupling of perfusion and CFR assessment may also identify patients with abnormal flow reserve resulting from **abnormalities of the coronary microcirculation** in the absence of an epicardial coronary stenosis. Such conditions can result in anginal syndrome as well as lead to ventricular dysfunction, and abnormal MPI study in the absence of angiographically significant CAD.

There are several situations that can result in **abnormal CFR** in the absence of angiographically significant CAD such as: after myocardial infarction, left ventricular hypertrophy, hypertensive heart disease, end stage renal disease and diabetes mellitus. These are situations with confirmed existence of endothelial dysfunction, which may be the reason for finding MPI perfusion abnormalities in the absence of angiographically significant CAD. (7) Reduced coronary flow reserve is one of the earliest abnormalities associated with coronary artery disease. The same situation can be found in hypertensive patients with or without left ventricular hypertrophy, even in asymptomatic middle age hypertensive patients without left ventricular hypertrophy. Also, reduced coronary flow reserve is well known in patients with traditional risk factors, especially dislipidemia and diabetes. Patients with micro vascular dysfunction such as those with dilated and hypertrophic cardiomyopathy have impaired CFR. An impairment of CFR allows us to identify those patients with a worsening outcome and therefore represents an important guide to the efficient management of these patients. (1, 3)

Prognostic implication of normal MPI study in patients with angiographically documented CAD

We will focus our attention to situations with preserved CFR and normal MPI perfusion studies in the presence of documented pathologic result of coronary angiography. As we know this method is a benchmark for evaluation of other noninvasive diagnostic techniques, because it gives not only diagnostic information, but also, what is more important prognostic information. Schulman find that the number of diseased coronary vessels predicts survival during long-term follow up. Randomized trials as Veterans Administration Cooperative Study of Coronary Artery Surgery (CASS) and European Coronary Surgery Trial demonstrated that the effectiveness of medical treatment and benefit of CABG in patients with CAD could be predicted with coronary angiography. We now know that MPI SPECT can give us same, if not better prognostic information than coronary arteriography. Introduction of MPI SPECT in 1980s in the so cold diagnostic era was in

the purpose of diagnosing CAD. Prognostic application of the method was introduced with its further technical development, especially since 1990s with ECG-gating of the studies what allowed same time evaluation of myocardial perfusion and left ventricular function in resting and stress conditions. Long-term follow up studies have showed the lowest risk of cardiac death (CD) and myocardial infarction (MI) in patients with normal perfusion findings (<1% CD/MI early), even in the presence of angiographically documented CAD. With the increasing of the abnormality of the study, there was increased incidence of major (CD/MI) and minor (revascularization etc) cardiac events. Authors like Abbott, Klodas et al., tried to identify the reasons for different prognosis inside the group of patients with normal MPI study, and to find out whether there is other prognostic information that may identify patients with CAD in this group, who are candidates for adverse cardiac events. Eagle concludes that patients at highest clinical risk remained at high risk even in the absence of reversible perfusion defects. Patients, who were enabled to perform optimal exercise, had anginal pain during the test or had achieved low workload, had worse prognosis than others. Patients who undergo vasodilator stress testing because of inability to perform exercise are patients at higher risk. In the study of more than 10000 patients with MI treated with thrombolysis, the six-month mortality rate was 0,9% in patients with normal and 1,5% in patients with abnormal maximal test, and 7,1% in those who couldn't perform exercise. Between patients with normal vasodilator stress MPI SPECT study, those who were in high risk group by clinical risk assessment before MPI, had 2-3 times higher rate of CD/MI. This means that clinical data are powerful prognosticators. In different studies Abbot and Klodas found similar results. Patients with ischemic ECG changes after vasodilator infusion were predominantly elderly women with angina, diabetes and other risk factors for CAD. Although an ischemic ECG response to vasodilator stress with normal MPI was uncommon, occurring in 0, 9 to 2% of patients, these patients were found to have increased risk for CE. During the mean follow up of 2-3 years, the rate of CD/MI was 4 to 5% per year. In the group of age and gender matched patients with normal MPI and without ischemic ECG response, Abbott found less than 1% of CD/MI early. In his study, one quarter of this group of patients underwent coronary angiography and significant CAD was found.

There are other studies that support the concept that high-risk patients (patients with angina and diabetes, older patients) with normal MPI perfusion study remain in moderate risk. Hachamovitch found that patients with normal exercise had 0, 3% annual risk of CD/MI if they have low or intermediate Duke Treadmill score. He also found early risk for CD/MI of 0, 5% in patients with normal MPI study and without ischemic response, is up to 2, and 5% in patients with combination of CAD, anginal pain and resting ECG abnormalities. (10)

Calnon, in the study with Dobutamine SPECT MPI found 1,5% early risk for CE in high risk patients with normal MPI and ECG response, while events rate increased

up to 7,8% in group of patients with ischemic ECG response.

Myocardial perfusion SPECT is useful for further risk-stratification of patients with suspected CAD. The abnormal scan result (SSS > 3) is discriminative for subsequent cardiac events only in the groups with an intermediate to high pre-test probability of CAD. The salient result is that normal scan results portend a benign prognosis independent from the pre-test probability of CAD. (8)

Both exercise MPI and exercise echocardiography has high NPVs for primary and secondary cardiac events. The prognostic utility of both modalities is similar for both men and women. (9)

These findings leads us to conclusion that in the presence of high clinical risk for CAD and adverse reactions and ischemic ECG response to exercise or pharmacologic stress, there is high probability of CAD even in the presence of normal MPI perfusion finding.

But, we also mustn't forget other non-perfusion parameters acquired from MPI SPECT gated study as: dilated ventricular cavity, reduced left ventricular ejection fraction in rest, and further decrease after stress (reduced contractile reserve), increased left ventricular end-systolic volume, increased lung uptake, that are strong indicators of severe CAD in the presence of normal MPI perfusion study. (7, 8, 9, 10)

Instead of conclusion: Clinical implication and prognostic role of coronary flow reserve

The additional diagnostic value of measurement of coronary flow reserve with different diagnostic methods is represented by the possibility of monitoring different heart pathologies objectively and thereby obtaining important functional information over time in patient follow-up. Although the importance of the prognostic role played by stress-echo in patients with coronary artery disease has been demonstrated, there has also been emphasis on how the presence of ant ischemic therapy at the time of testing can heavily modulate the predictive value of pharmacological stress-echo. In fact, a positive test in therapy is more prognostically malignant, and a negative test less prognostically benign. The potential prognostic role of coronary flow reserve has recently been tested in predicting different clinical situations through invasive and non-invasive approaches. In particular, it has been demonstrated that the patency over time of coronary vessel disease after coronary angioplasty (PCI) can be accurately predicted by evaluating the functional status of the revascularized coronary artery just after the procedure. Recently, we have emphasized the added prognostic role of an impairment of CFR despite normal wall motion contractility during combined dipyridamole stress-echo: these patients showed a worsening outcome during a mean follow-up of 24 months.

A further important application of CFR is as a good predictor of adverse events regarding the relationship with left ventricular remodelling after anterior

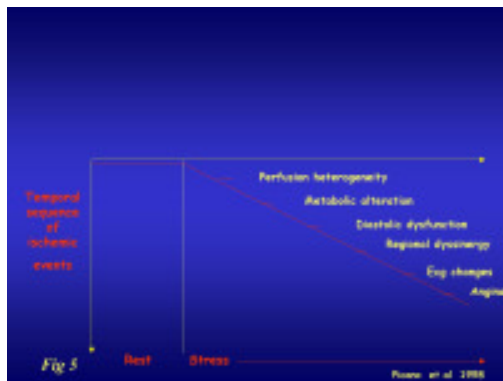


Fig. 3. The classical ischemic cascade, triggered by coronary vasospasm and/or epicardial stenosis. The various markers are usually ranked according to a well-defined time sequence.

Rigo Cardiovascular Ultrasound 2005 3:8. doi:10.1186/1476-7120-3-8

myocardial infarction treated with coronary angioplasty. In patients with coronary microvasculature dysfunction such as dilated and hypertrophic cardiomyopathy, an impairment of CFR allows us to identify those patients with a worsening outcome and therefore represent an important guide to the efficient management of these patients. Theoretically, and on the basis of the classic and alternative cascade (*figure 3*), coronary flow reserve information can be especially helpful for mild to moderate stenosis (capable of reducing flow reserve, but to sub ischemic levels) and in identifying patients with micro vascular disease (reduced flow reserve and normal coronary arteries).

Coronary flow reserve: a new diagnostic power

When evaluated with intravenous myocardial contrast echocardiography with harmonic power Doppler imaging, the use of CFR as a “stand-alone” diagnostic criterion suffers from so many structural limitations as to make it little more than an academic somersault: firstly, only LAD is sampled (when echocardiography is used); secondly, the coronary flow reserve cannot distinguish between micro vascular and macro vascular coronary disease. Therefore, it is much more interesting (and clinically realistic) to evaluate the additive value over conventional wall motion for LAD detection. The assessment of CFR adds sensitivity for LAD disease – with a modest loss in specificity. In reality, the inherently quantitative information of LAD flow reserve allows a stratification of the response, integrating many different tests into one: greatly reduced CFR (<1.5) yields extraordinary specificity whilst mildly reduced CFR (<2.0) offers outstanding sensitivity.

When evaluated with vasodilator MPI SPECT again distinction between micro vascular and macro vascular coronary artery disease can't be accomplished.

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ГЛОМЕРУЛАРНИ БОЛЕСТИ КАЈ ДЕЦА ВО РЕПУБЛИКА МАКЕДОНИЈА ДОКУМЕНТИРАНИ СО БУБРЕЖНА БИОПСИЈА

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Скопје

Извадок

Цел: да ја утврди честотата и структурата на гломеруларните заболувања кај детската популација во Р.Македонија, формирајќи база на податоци кои би се користеле во понатамошни истражувања.

Материјал и методи: Со оваа студија беа евалуирани пациенти на детска возраст кои во периодот од јануари 1996 до декември 2008 година беа лекувани на Универзитетската Клиника за детски болести под дијагноза гломерулонефритис, документиран со бубрежна биопсија. Децата со гломеруларна болест исклучиво се реферираат на Универзитетската Клиника за детски болести во Скопје која е единствен, специјализиран, терциерен центар за педијатриска нефрологија на територијата на Република Македонија. Одтука, прикажаните резултати во оваа студија се референтни за целата територија на нашата земја. При изработката на студијата ги користевме податоците од историјата на болеста, хистолошкиот и имунопатолошкиот наод од бубрежната биопсија.

Резултати: Со оваа студијата беа обработени вкупно 82 пациенти до 15 годишна возраст, со средна вредност 8.59 ± 3.9 години. Примарни гломерулонефритиси регистриравме кај 65 (79%) деца, а секундарни кај 17 (21%) деца. Најчест патохистолошки наод кај примарните гломерулонефритиси беше нефритисот со минимални промени пројавен кај 35% пациенти. Потоа следеа пациентите со мезангиопролиферативен гломерулонефритис (17%), имуноглобулин А нефропатија (14%), фокална и сегментална гломерулосклероза (12%), мембранозен гломерулонефритис (8%), мембранопролиферативен гломерулонефритис (3%), кресцентен гломерулонефритис (3%) и постинфекциозен гломерулонефритис регистриран кај 8% пациенти, ако го вклучиме во групата на примарни гломерулонефритиси. Најчест патохистолошки наод кај секундарните гломерулонефритиси беше Ноеноч Schonlein синдром/нефропатија пројавен кај 59% пациенти, а потоа следеа лупус нефропатија (29%) и Алпорт синдром (12%).

Заклучоци: Податоците кои се презентирани во оваа студија ги отсликуваат спецификите на гломеруларните заболувања кај детската популација во нашата земја. Овие наоди беа споредени со наодите презентирани во други епидемиолошки студии, и истите покажаа сличност во зачестеноста кај едни студии, а разликност кај други студии. Претпоставуваме дека тие различности најверојатно се должат на постоењето на различната селектираност на пациентите, односно на постоењето на различни критериуми за реализирање на бубрежната биопсија. Оваа студија ја покажува важноста од постоење на регионален регистар за гломеруларни заболувања кај детската популација.

Клучни зборови: епидемиологија, гломерулонефритиси, регистар, деца, бубрежна биопсија

BIOPSY-PROVEN CHILDHOOD GLOMERULAR DISEASE IN REPUBLIC OF MACEDONIA

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Abstract

Objectives: This study aimed to determine glomerular disease frequencies in Macedonian children and it represents the basis for future studies.

Methods: All native renal biopsies (January 1996 to December 2008) were reviewed, but only glomerular diseases were analyzed. The diagnosis of each case was based on histological, immunopathological and clinical features. As University Pediatric Clinic in Skopje is the only pediatric nephrology centre in the country, the results of this study relate to the whole country.

Results: A total of 82 patients under 15 years of age (mean age $8.59 \pm 3.9\%$) were included in the study. Primary glomerular diseases were diagnosed in 65 biopsies (79%) and secondary in 17 (21%). The most common primary diseases were minimal change disease (35%), mesangioproliferative glomerulonephritis (17%), immunoglobulin A nephrotathy (14%), focal and segmental glomerulosclerosis (12%), membranous glomerulonephritis (8%), membranoproliferative glomerulonephritis (3%), crescentic glomerulonephritis (3%). Postinfectious glomerulonephritis represented 8% of the diagnoses if included primary glomerulonephritis. In the group of secondary glomerulonephritis

was Henoch Schonlein nephritis corresponded to 59% of the entire series and lupus nephritis to 29% . Alport syndrome was found in 12%.

Conclusions: The distribution of glomerular diseases in the pediatric age group in R. Macedonia is similar to that described in other countries with some differences. This study illustrates the importance of having a regional register for renal diseases in children.

Key words: epidemiology, glomerulonephritis, Register, children, renal biopsy

Introduction

In the last few years the knowledge of glomerular disease as heterogenic group of diseases where the glomeruli are primarily affected are improved because of renal biopsy. It enable to make possible to learn more about the structure of glomerular disease that has diagnostic, prognostic and therapeutic significance^(1,2,3).

Classification of World health organization (WHO) based of the structure alteration of glomerular disease divide them in two groups: primary disease (where the kidney is only affected organ with pathological process) and secondary disease (where the kidney in one of the most affected organs in multisystemic diseases)⁽³⁾.

Aim of the paper

Table 1. Classification of primary glomerular disease (WHO, 1982)

- Primary glomerulonephritis
- Minimal change disease
- Focal and segmental glomerulosclerosis
- Diffuse glomerulonephritis Membranous glomerulonephritis
- Proliferative (mesangioproliferative, membranoproliferative type 1,2,3, crescentic glomerulonephritis)
- Nonclassificate glomerulonephritis

Table 2. Classification of secondary glomerular disease (WHO, 1982)

- Secondary glomerulonephritis
- Glomerulonephritis of systemic disease
- Glomerulonephritis of systemic infection
- Glomerulonephritis of vascular diseases (Henoch Schonlein nephritis, Periarteritis nodosa, Wegener granulomatosis, HUS, Skleroderma, Nephroskleroza, Glomerular tromboza)
- Glomerulonephritis of metabolic diseases (Diabetic nephropathy, Amiloidosis)
- Hereditary nephropathy (Alport syndrome, Congenital nephrotic syndrome, Syndrome of teen glomerular basal membrane)

The aim of this paper is to determine the pathohistological characteristics of glomerular disease in childhood.

Methods

This retrospective study a total of 82 patients-children aged up to 15 and suffering glomerular disease who, within the period 1996-2008 were treated at the nephrology department at the University Paediatric Clinic. We used data of medical history (detailed anamnesis, clinical examinations, biochemical investigation) and histopathological findings of kidney biopsy. The histological diagnosis was established by kidney biopsy done at the Clinic of nephrology controlled by ultrasound. The biopsy material was examined at the institute of Pathology using the method of light microscopy and immunofluorescence, but in few cases we used electron microscopy. Indication for kidney biopsy we observed the recommendations of the European Society for pediatric nephrology.

The diagnosis of each case was based on histological, immunopathological and clinical features. As University Pediatric Clinic in Skopje is the only pediatric nephrology centre in the country, the results of this study relate to the whole country.

For statistically analyze we applied the methods of descriptive statistics and Chi-square test for one exemplar to correlate the observed and theoretic frequency. Statistical significance was established set up for $p < 0.05$ and $p < 0.01$ levels. These data are shown in tables and graphs.

Results

A total of 82 patients less than 15 years of age (mean age 8.59 ± 3.9 year) were included in the study. Primary glomerular diseases were diagnosed in 65 biopsies (79%) and secondary in 17 (21%). The most common primary diseases were minimal change disease (35%), mesangioproliferative glomerulonephritis (17%), immunoglobulin A nephropathy (14%), focal and segmental glomerulosclerosis (12%), membranous glomerulonephritis (8%), membranoproliferative glomerulonephritis (3%), crescentic glomerulonephritis (93%). Postinfectious glomerulonephritis represented 8% of the diagnoses if included primary glomerulonephritis. Statistical analysis showed the dominance of the minimal change disease in the group of primary glomerular diseases with statistical significance ($p < 0.01$).

of female sex in patients with mesangioproliferative glomerulonephritis is statistically significant ($p < 0.01$).

Fig 1. Distribution of patients with primary glomerulonephrites

MCD- minimal change disease
 FSGS - focal and segmental glomerulosclerosis
 MGN - membranous glomerulonephritis
 IgAN - immunoglobulin A nephrotathy
 MezPGN- mesangioproliferative glomerulonephritis
 MPGN - membranoproliferative glomerulonephritis

Fig.2 shows the distribution of patients with secondary glomerulonephritis: Henoch Schonlein nephritis corresponded to 59% and lupus nephritis to 29%. Alport syndrome was found in 12%. Statistical analysis showed the dominance of Henoch Schonlein nephritis in the group of secondary glomerular diseases with statistically significance ($p < 0.05$).

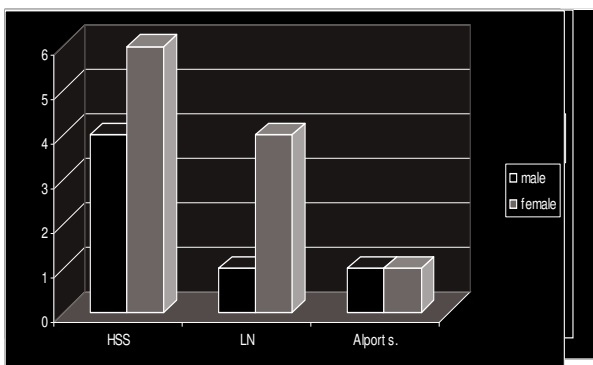


Fig 2. Distribution of patients with secondary glomerulonephrites

Henoch Schonlein nephritis
 LN - lupus nephritis
 Alport s.- Alport syndrome

Fig.3 shows the distribution of patients with primary glomerular diseases according to sex. Male sex dominates at 17/23 patients with minimal change disease, 5/5 patient with membranous glomerulonephritis, 5/9 patients with immunoglobulin A nephrotathy and 2/2 patients with membranoproliferative glomerulonephritis. The female sex is prevalent in at 14/17 patients with mesangioproliferative glomerulonephritis and at 7/8 patients with focal and segmental glomerulosclerosis. Statistical analysis showed the dominance of male sex in patients with minimal change disease and the dominance

Fig 3. Distribution of patients with primary glomerulonephrites according to sex

MCD- minimal change disease
 FSGS - focal and segmental glomerulosclerosis
 MGN - membranous glomerulonephritis
 IgAN - immunoglobulin A nephrotathy
 MezPGN- mesangioproliferative glomerulonephritis
 MPGN - membranoproliferative glomerulonephritis

Fig.4 shows the distribution of patients with secondary glomerular diseases according to sex. The female sex is dominate in at 6/10 patients with Henoch Schonlein nephritis and at 4/5 patients with lupus nephritis. The patients with Alport syndrome have equal number according to sex. Statistical analysis showed that the occurrence of dominance of the female sex in patients with Henoch Schonlein nephritis and lupus nephritis is statistically significant ($p < 0.01$).

Fig 4. Distribution of patients with secondary glomerulonephrites according to sex

Henoch Schonlein nephritis
 LN - lupus nephritis
 Alport s.- Alport syndrome

Tabl 3. Distribution of patients with glomerular diseases in corelation with diferent clinical presenatations

| | ANS | NS | ANS/NS | AKI | RH | IP |
|---------|-----|----|--------|-----|----|----|
| MCD | 0 | 23 | 0 | 0 | 0 | 0 |
| MGN | 0 | 3 | 0 | 0 | 0 | 2 |
| MPGN | 0 | 0 | 2 | 0 | 0 | 0 |
| MezPGN | 3 | 4 | 3 | 0 | 1 | 0 |
| IgAN | 2 | 0 | 0 | 0 | 7 | 0 |
| FSGS | 0 | 5 | 0 | 2 | 0 | 1 |
| HSS | 1 | 0 | 5 | 0 | 2 | 2 |
| LN | 0 | 0 | 4 | 0 | 0 | 1 |
| Alptort | 0 | 0 | 0 | 0 | 1 | 1 |

1. ANS – acute nephritic syndrome

NS - nephrotic syndrome

ANS/NS - acute nephritic syndrome/nephrotic syndrome

AKI – acute kidney injury

RH - recidivant hematuria

IP - isolate proteinuria

2. MCD- minimal change disease

FSGS - focal and segmental glomerulosclerosis

MGN - membranous glomerulonephritis

IgAN - immunoglobulin A nephrotathy

MezPGN- mesangioproliferative glomerulonephritis

MPGN - membranoproliferative glomerulonephritis

Henoch Schonlein nephritis

LN - lupus nephritis

Alport s.- Alport syndrome

Tabl. 4 shows the distribution of patients with glomerular diseases in corelation with diferent clinical presenatations of the diseases. All (23/23) patients with minimal change disease had nephrotic syndrom as a dominant clinical presentation. Also, the nephrotic syndrom was the dominant clinical presentation in the patients with focal and segmental glomerulosclerosis (62%), membranous glomerulonephritis (60%) and mesangioproliferative glomerulonephritis (33%). The patients with immunoglobulin A nephrotathy in 80 % of the cases had recidivant hematuria as the dominant clinical presentation. But in the patients with Henoch Schonlein nephritis and lupus nephritis, nephritic syndrome combine with nephritic syndrome was the dominate clinical presentation. The most frequent clinical presentation in the patients with Alport syndrome was recidivant hematuria or isolate proteinuria.

Discussion

This study evaluated a total of 82 patients-children aged up to 15 and suffering glomerular disease who at the period of 14 years were treated at the University Paediatric Clinic. All native renal biopsies (January 1996 to December 2008) were reviewed, but only glomerular diseases were analyzed.

The midle age in the hole group of the patients was 8.59 ± 3.9 years with dominance of the older age.

According to sex, male sex dominates in the group of primary glomerular disease, but female sex dominates in the group of secondary glomerular disease. This finding is a result of dominance of male sex in the patients of primary glomerular diseases with minimal change disease and dominance of female sex in the group of secondary glomerular diseases with lupus nephritis^(5,6,7.).

We known that Alport syndrom has different hereditary (autosomal resecive, autosomal dominante and X binding). 80% of the patients have mutation in COL4A5 gene which can be hereditary with X binding. The male who have one x chromosome, one alternative copy of COL4A5 gene is able to predict kidney injury. The female (have 2 x genes) who have mutation of one copy of COL4A5 gene usualy predict hematuria. The characteristics of this hereditary is that the fathers of these females can not transmited disease to their sons⁽⁸⁾. In our study we dijagnosed only 2 cases with Alport syndrome, one boy and one girl. We dont have informations about the way of transmutation of COL4A5 gene in these families, so we can not give general conclusion for Alport syndrom according to sex.

The most frequent patohistological finding in primary glomerular disease was minimal change disease (35%). Similar finding published in the other stydies^(5,6,7.), as the study of Rivera where minimal change disease was finding in 40%⁽⁶⁾. We already known that minimal change

disease is one of the most frequent glomerular disease in childhood, but great number of the patients are not recommended for kidney biopsy. Kidney biopsy are predicted for those patients who have unconvenient prognostic score (increase values of urea and creatinin from the beginning of the disease, hypertension, hematuria, hypocomplementemia), as those who have primary or secondary corticosteroid resistance. On the other hand, Bazina and Naumovic in their studies published a different findings where mesangioproliferative glomerulonephritis dominates at 1/3 of the patients with primary glomerular disease^(9,10). Covic in his study reports of the dominance of the membranous glomerulonephritis (30%) in primary glomerulonephritis⁽¹¹⁾.

These different reports most probably result from the differences in selecting patients when setting indication for kidney biopsy^(12,13). Henoch Schonlein nephritis was the most frequent secondary glomerulonephritis (10/17) with finding of focal and diffuse mesangioproliferative glomerulonephritis on light microscopic examination. Henoch Schonlein nephritis is also frequent glomerular disease in childhood, usually with good evolution. In acute phase of disease, prognosis is determined of finding in the gastrointestinal tract, but following prognosis is determined of finding in kidney^(14, 15). In the other studies lupus nephritis dominates in secondary glomerulonephritis^(5,10,12).

In our study all (23/23) patients with minimal change disease have nephrotic syndrome as a dominant clinical presentation. Also, nephrotic syndrome dominates in the patients with mesangioproliferative glomerulonephritis (12%), focal and segmental glomerulosclerosis (8%), membranous glomerulonephritis (4.5%). Similar finding published Rivera and Rychlik in their studies. So, Rivera reports that 39% and Rychlik reports that 48% of patients with minimal change disease have nephrotic syndrome as a dominant clinical presentation^(12,13). Also, nephrotic syndrome is the most frequent clinical presentation in the patients with membranous glomerulonephritis as reports in the study of Naumovic and in 40% of the patients with membranoproliferative glomerulonephritis as reports in the study of Bazina^(9,10).

In our study 67% of the patient with immunoglobulin A nephropathy are clinically presented with recidivant episodes of hematuria. Similar finding published Rivera in his study where in more than half of the patients with immunoglobulin A nephropathy have recidivant hematuria as a dominant clinical presentation⁽⁶⁾.

Patients with Henoch Schonlein nephritis and lupus nephritis in 80 to 90% of the cases show combination of nephritic and nephrotic syndrome as a dominant clinical presentation. Different finding published Rivera in his study where nephrotic syndrome dominates at least than half of the patients with Henoch Schonlein nephritis and lupus nephritis.

Data presented in this study reflect the specifics of glomerular disease in children population in our country. This study illustrates the importance of using these results for future clinical and epidemiological investigations and

also for using them by the health authority to create preventive programs and health politics.

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Интернет:

Greenblatt DJ, Abernethy DR, Shader Jr RI. Pharmacokinetic aspects of drug therapy in the elderly (commentary). Ther Drug Monit 1986; 8 (6): 249-55. Available from: <http://www.med.monash.edu.au/medical>

Извадок

Извадокот треба да се пишува на посебна страна со не повеќе од 250 зборови. Неговата содржина треба да претставува независна целина, да се пишува во сегашно време, поделена во пет делови кои го опфаќаат следниот редослед: Цел, Вовед, Методи, Резултати, Заклучок. Се користат цели реченици. Сите податоци во извадокот треба да се пишуваат во сегашно време како и целиот текст и табелите. Да не се користат повеќе од 3 до 5 клучни зборови. Може да се користат зборови од Index Medicus. Содржината на апстрактот не треба да содржи повеќе од 50 зборови и да ја задоволи содржината на дадените табели и прикази на клинички случаи.

Корекции

Рецензираните трудови треба да се вратат во рок од 3 дена; секое задоцнување може да доведе до одложување на печатењето. Ве молиме претходно проверете го текстот, табелите, легендите и литературните податоци.

Критериуми за поднесување на труд во електронска форма

Трудот се доставува на 3,5 inch disk во MS – DOS форма.

Секоја поднесена дискета треба да е обележана со етикета на која се наоѓа име на авторот, наслов на трудот, наслов на списанието, компјутерски програм (верзија) и име на фајлот.

Ракописот даден на дискета треба да ја претставува конечната верзија и да е во согласност со материјалот поднесен за печатење. Дискетата треба да ја содржи само конечната верзија на трудот, а останатиот материјал треба да се избрише од дискетата. Ве молиме да се следат критериумите за пишување на труд дадени во “Критериуми за авторот за пишување труд”.

Текстот даден во ракопис за печатење треба да е со двоен проред, додека електронската верзија не треба да содржи форматираните инструкции.

Не се користи tabs или екстра простор на почетокот на текстот. **Не се подвлекува** во референците.

Се исклучува копчето за line spacing. **Не се** обележуваат страните.

Внесете ги коректно “еден” (1) или “el” (мало латинско л), како и “нула” (0) и голема буква “O” (O). Ве молиме следете ги усвоените правила. Користете една црта за простор пред за да го обележите знакот минус, а користете двојна црта (со простор пред и по) за да обележите долга црта во текстот и тројна црта (без простор) за да ги обележите броевите (стр. “23-45”).

Нестандарни карактеристики (грчки букви, математички симболи и др.) треба да се шифрираат во контекст на текстот. Ве молиме направете листа на користење на шифрите.

Авторите треба да се согласат со тоа што го бара издавачот за печатењето. Авторите треба да ги извршат сите мерења спрема усвоените правила на Systeme International (SI). Конвенционалните правила на користење на слики и табели треба да се дадат со легенда за користење на истите.

Во електронското пишување на текстот се препорачува **text editor** или (**editor T602**). Текстот треба да се пишува **од лево (not justified), без цртички, без точки за набројување, броеви и подвлекувања**. Еден тип на програм Word треба да се користи во целиот текст.

Табели во Word: не користете вертикални линии, освен ако тоа не е потребно. Ставете ги табелите како посебен фајл со наслов (не ги ставајте во текстот).

Графикони во Excel: ставете ги како посебен фајл во Excel.

Графикони во Word: ставете ги како посебен фајл во Word.

Легендата за табелите и графиконите ставете ја посебно на крајот од текстот.

Графиконите да бидат во црно-бела боја. **Графиконите принтани на laser или на ink printer да не се користат како templates – секогаш во оригинален електронски фајл!**

Слики: Оригинални или скенирани. Скенирање до **600 – 800 dpi!**-set to B/W or line art.

Слики- во црно-бела боја – со добар квалитет или скенирани до **350 dpi**.

Слики – во боја - со висока резолуција до **350 dpi**.

Сликите со поголема резолуција од 72 ili 96dpi нема да се печатат.

Електронски подготвените слики се примаат во Tif ili Jpg формат (со минимална резолуција).

Легендата за сликите се пишува како посебен фајл.

Не се ставаат слики во Power Point- тие се користат за презентации и не можат да се користат како документ за принтање.

Слики од дигитална камера не се ставаат во текстот. Се користат во Tif или Jpg формат (со минимална резолуција).

INFORMATION FOR AUTHORS

These guidelines are in accordance with the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals”. (Complete document available at www.icmje.org)

Manuscripts are accepted for processing if neither the article nor any essential part, tables or figures, has been or will be published or submitted elsewhere before presenting in *Acta Morphologica*. This restriction does not apply to abstracts or press reports related to scientific meetings.

The Editors will consider both invited and uninvited review articles. Authors should detail how their work differs from existing reviews on subject in cover letter.

Manuscripts/General Guidelines

The manuscript should conform the guidelines set forth in the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals”, 5th edition, *New Engl J Med* 1997; 336 (4): 309–315.

Manuscript must contain no more than 5000 words. A cover letter signed by all authors should identify the person (post address, telephone number, and e-mail address) responsible for negotiations. Each author must sign a statement attesting that he or she fulfills the authorship criteria of the Uniform Requirements. Each author must significantly contribute to the submitted work.

Form of Manuscript

Three copies of each manuscript, along with a disk (see “Instructions for Electronic Manuscript Submission”), must be submitted in English, in double-spaced typewritten form with a 5-cm (2-inch) left margin. (Do not use “erasable” bond.) The text should be written in following sequence: Introduction, Methods, Results, Discussion, Acknowledgement, References, Tables, Illustrations and Figure Legends, Structured Abstract with key words and Condensed Abstract.

Page 1 should bear an article title, name(s) of the author(s) and institution where the work was done and a person whom proofs and reprint request should be sent, with complete address (including postal codes), telephone number and e-mail address (address for correspondence).

Tables should be typed neatly, each on a separate sheet, with title above and any notes below. All abbreviations should be explained. Do not provide duplicate information in tables and figures.

Illustrations should be submitted as clear glossy prints (two duplicate sets may be photocopied), with lettering large enough to be legible if reduced. The maximal final size of any figure in the printed journal will be 20 by 28 cm (8.25x11 inch). **On the back of each figure**, the name of author and the figure number should be written, with the top indicated by an arrow. Each figure should have a separate, fully explicit legend; all parts of the figure and all abbreviations and symbols should be clearly defined. **Figure legends** should be typed on separate pages; figure numbers must follow their reference in text.

Drug names. Generic names should be used; trade names may be given in parentheses in the first mention, and generic names should be used thereafter.

Abbreviations. The list of abbreviations given in “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (section References) should be followed. For additional abbreviations, consult the CBE Style Manual (available from the Council of Biology Editors, 9650 Rockville Pike, Bethesda, Maryland 20814, U.S.A.) or other standard sources.

References

The journal complies with the reference style given in “Uniform Requirements for Manuscripts Submitted to Biomedical Journals”. References should be cited in text by number and numbered in order they are cited. The reference should be written in double-spaced form at the end of the text, following the sample formats given below. For the abbreviations of journal names, refer to the List of Journals Indexed in Index Medicus (available from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, U.S.A., DHEW Publication No. NIH 83-267; ISSN 0093-3821).

Provide all names of authors when fewer than seven: when seven or more, list the first three and add et al. Provide article titles and inclusive pages. The author is responsible for the accuracy of reference data.

Article:

1. Greenblatt DJ, Abernethy DR, Shader Jr RI. Pharmacokinetic aspects of drug therapy in the elderly (commentary).

Ther Drug Monit 1986; 8 (6): 249-55.

Book:

2. Mitchell JR, Horning MG, (editors). Drug metabolism and drug toxicity. 2nd ed. New York: Raven Press; 1984.

Chapter of book:

3. Kutt H, Pippenberg CE et al. Plasma clearance of nor-methsuximide in a uremic patient. 223-226. In: Levy RH, Pitlick WH, Meijer J, (editors). Metabolism of antiepileptic drugs. New York: Raven Press; 1984. pp-1-25.

Internet:

Greenblatt DJ, Abernethy DR, Shader Jr RI. Pharmacokinetic aspects of drug therapy in the elderly (commentary). Ther Drug Monit 1986; 8 (6): 249-55. Available from: <http://www.med.monash.edu.au/medical>

Structured Abstract

A structured abstract should be provided on a separate page with no more than 250 words, presenting essential data in five paragraphs introduced by separate headings in following order: Objectives, Background, Methods, Results, Conclusion. Complete sentences should be used. All data in the structured abstract must be present also in the submitted text or tables. Three to five key words should be added. Terms from Index Medicus should be used.

Condensed Abstract (for table of contents)

A condensed abstract of no more than 50 words should be provided for the expanded table of contents, stressing clinical implications. Do not include data which are not present in the text or tables.

Proofs

Proof must be returned within 3 days; late return may cause a delay in publication. Please check text, tables, legends, and references carefully.

Instructions for Electronic Manuscript Submission

The preferred storage medium is a 3.5 inch disk in MS-DOS compatible format.

Each submitted disk must be clearly labeled with the name of the author, article title, journal title, type of the equipment used to generate the disk, word processing program (including version number), and filenames.

The manuscript submitted on a disk must be in the final corrected version and must agree with the final accepted version of the submitted paper manuscript. The submitted disk should contain only the final version of the manuscript. Delete all other material from the disk. Please follow the general instructions on style/arrangement and, in particular, the reference style as given in "Instruction to Authors".

Note, that while the paper version of the manuscript must be presented in the traditional double spaced format, the electronic version will be typeset and should not contain extraneous formatting instructions. Do **not** use tabs or extra space at the beginning of a paragraph or for list entries. Do **not** indent runover lines in references. **Turn off** line spacing. Do **not** specify page breaks, page numbers, or headers. Do **not** specify typeface.

Take care to enter "one" (1) and lower case "el" (l), as well as "zero" (0) and capital "oh" (O) correctly.

Please note the following conventions on dashes: Use a single hyphen with space before it for a minus sign, use a double hyphen (with space before and after) to indicate a "long dash" in text, and a triple hyphen (with no extra space) to indicate a range of numbers (e.g. "23-45").

Non-standard characters (Greek letters, mathematical symbols, etc.) should be coded consistently throughout the text. Please make a list and provide a listing of the used codes.

Authors agree to execute copyright transfer forms as requested. Authors should express all measurements in conventional units, with Système International (SI) units given in parentheses throughout the text. Conventional units should be used in figures and tables, with conversion factors given in legends or footnotes.

In electronic manuscript submission **text editor Word 6 or higher** is recommended (editor T602 is possible). Text should be **aligned left (not justified), without hyphenation, without bullets, numbering and underlines**, without extra hard returns at the end of line (only at the end of paragraphs). **One type of Word paragraph** should be used throughout the text. Word graphic experiments should not be used.

Word tables : do not use vertical lines, unless it is necessary. Provide tables as a separate file (do not place in text).

Excel graphs : provide as Excel file.

Word graphs : provide as a separate Word file (do not place in text!)

Table and graph legends should be provided separately at the end of the text.

Graphs should be processed for black and white print. **Graphs printed on laser or ink printers could not serve as templates– always provide original electronic files !**

Figures : provide original or scan. Scan to **600-800 dpi !** – set to B/W or line art.

Figures – black and white photos – provide high-quality original or scan to **350 dpi !**

Figures – color photos — provide high-quality original or scan to **350 dpi !**

Figures scanned to 72 or 96 dpi are not suitable for print !

On principle, **do not place scans in text !** Always provide original figures in tif or jpg format (with minimal compression). Placing scan in Word text causes a loss of quality!

Figure legends should be provided as a separate text file.

Do not place figures in PowerPoint – this application is meant for presentations and it is not possible to use it as a template for print !

Figures from digital camera should not be placed in text. Provide them in **tif** or **jpg** format (with minimal compression)!

Transcription of Macedonian Cyrillic Alphabet into English Latin

| | | | |
|-----|-------|-----|---------|
| А а | А а | Н н | Н n |
| Б б | В в | Њ њ | Nj nj |
| В в | У у | О о | O o |
| Г г | Г г | П п | P p |
| Д д | Д д | Р р | R r |
| Ѓ ѓ | Г г | С с | S s |
| Е е | Е е | Т т | T t |
| Ж ж | Zh zh | Ќ к | K k |
| З з | Z z | У у | U u |
| С с | Dz dz | Ф ф | F f |
| И и | И и | Х х | Kh kh |
| Ј ј | J j | Ц ц | Ts ts |
| К к | K k | Ч ч | Ch ch |
| Л л | L l | Џ џ | Dzh dzh |
| Љ љ | Lj Lj | Ш ш | Sh sh |
| М м | M m | | |

On the basis of ISO Recommendation R-9-1968 International List of Periodical Title Abbreviations (1970)

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