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PROBLEMATIC PERIOCULAR HEMANGIOMAS - SAME TREATMENT, DIFFERENT OUTCOMES

Cristina Ioana Nisipasu¹, Doina Plesca², Ioana Stancea², C Nisipasu³, R Spataru⁴

Abstract
Hemangiomas are the most common periocular and orbital tumors of children that arise soon after birth. Some of them require early intervention to prevent serious cosmetic and functional complications. Recently, Propranolol was approved as first line therapy for infantile hemangiomas with a good safety profile. We present three different cases managed with Propranolol, with different outcomes.

Key words: hemangioma, Propranolol, early treatment, complications

Introduction
Hemangiomas are the most common periocular and orbital tumors of children that arise soon after birth. In the vast majority of cases, after an initial accelerated growth phase, they involute spontaneously. Some of them require early intervention to prevent serious cosmetic and functional complications. Periocular hemangiomas can determine amblyopia by multiple mechanisms: refractive errors, visual occlusion or strabismus. Treatment is indicated if it is a potential of vision compromise or cosmetic disfigurement. Cavernous hemangiomas in the orbit, in time, can shorten the axial length of the eye causing a gradual difference in refraction compared with the fellow eye.[1] The longer a complicated periocular hemangioma is observed, the greater the astigmatism and the harder correction it will be.[2]

Conventional therapies for infantile hemangiomas include the use of corticosteroids, laser surgery and immunomodulation therapy. Recently, Propranolol was approved as first line therapy for infantile hemangiomas. The mechanism of action remains uncertain, theories postulated include vasoconstriction, modulation of pro-survival signal transduction pathways and endothelial cell apoptosis.[3] No major adverse events have been reported, but bronchospasm, hypoglycemia, heart block, bradycardia and congestive heart failure can arise, making imperative a cardiologic exam and blood tests before treatment [4].

Case presentation
We present 3 cases of periocular hemangiomas, with different outcome of the treatment. In all cases we did an initial evaluation with complete blood tests, cardiologic exam including cardiac ultrasound, ophthalmological exam and transfontanelle ultrasound. The patients were monitored for the first 24 hours and monthly after that. No adverse events were noted during therapy.

First case
A 3 month old female patient presented with a deep hemangioma on the left superior eyelid and left frontal area affecting the opening of the left eye. The lesion appeared soon after birth and had grown fast. She received Propranolol, 2mg/kgC, for 6 months. The evolution was very good, with complete regression of hemangioma. The ophthalmological exam showed no visual impairment. The slight skin excess may improve in time. If not, it can be surgically excised. There are a few persistent telangiectasia that can be managed by laser therapy.

Second case
A 2 month old female patient, presented with a left lower eyelid hemangioma, partially obstructing the visual axis. She received Propranolol 2mg/kgC for 6 months, with regression of the deep component. Due to the persistence of superficial component, we administered Propranolol for another 2 months, with no more improvement. In this case we had a partial response to Propranolol, preserving the function of the eye. The cosmetic part remained a problem, so we referred the patient to a laser clinic for continuing the treatment.

Third case
A 5 month old female patient, presented in our clinic, with a massive compound hemangioma affecting the superior right eyelid and the right temporal area. Local examination showed almost complete visual obstruction and ocular globe protrusion. The lesion appeared soon after birth but the treatment was postponed by the general practitioner who advised the mother to wait because it will spontaneous regress. Concerned about the visual compromise the mother asked for another opinion.

Computer tomography showed the extension of the hemangioma on the superior and posterior orbital wall, pushing the ocular globe anterior and inferior. The optptalmic nerve was not affected.

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Fig. 1. Case 1 before and after therapy.

Fig. 2. Case 2 before and after therapy.

Fig. 3. Case 3 before and after therapy.
We gave her Propranolol, 2mg/kgC for 3 months, then 3 mg/kgC. After 6 months, the CT showed an important involution of the hemangioma, but with persistence in the orbit. Also, the vascularization of the tumor was significant diminished, with areas of fibro-adipose degeneration. No asymmetry in dimension or position between left and right eye. We decided to continue the treatment for another 3 months. Due to the slow improvement, and the mother request for another therapy, we administered intralesional aetoxisclerol, with visible improvement after 2 treatments at 4 weeks interval. No visual impairement at final ophthalmological exam. The asymmetry noted is due to skin excess that shall be surgically excised.

Discussions
Early treatment with propranolol is effective in treating and preventing loss of visual acuity associated with periocular infantile hemangiomas. Greater reduction was achieved when Propranolol was administered during the proliferative phase of growth but may be beneficial even in the later stage. Deeper hemangiomas have a later onset and a longer growth period than superficial ones. This is a valuable predictor in assessing the necessity and duration of treatment.[5]

In some cases, combined therapy can achieve better results. Intralesional therapy or laser therapy may be useful alternatives in the treatment of periocular hemangiomas refractory to conventional treatment modalities or for a better cosmetic result.

Residual lesions like telangiectasia, fibro-adipose tissue or skin excess can be managed secondary by lasers or surgery.

Conclusions
Propranolol is an efficient, safe treatment for periocular infantile hemangiomas, alone or in combination with other methods. Appropriate education in natural history, expected outcome and treatment update is mandatory for appropriate intervention.

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IDIOPATHIC CLUB FOOT TREATED WITH THE PONSETI METHOD. HISTOLOGICAL ANALYSIS AFTER ACHILLES TENDON TENOTOMY IN RATS WITH CLUB FOOT

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Abstract

Congenital talipes equinovarus, or clubfoot, remains one of the commonest congenital limb deformities. In most cases of clubfoot are corrected after five to six cast changes and, in many cases, an Achilles tendon tenotomy. This technique results in feet that are strong, flexible, and plantigrade.

The aim of this study is to quantify the histological modifications that occur early in the healing process of lesions made on the Achilles tendons. We made sagittal sections (without suture, with absorbable suture, with non-absorbable suture), frontal section (without suture, with absorbable suture, with non-absorbable suture), cross-section, dentate section and section into Z. For 1 month (day 7, 14, 21, 28) we studied the following histological characteristics grading it semi quantitatively: nuclear density, the amount of interstitial collagen, tendency to the parallel orientation of the nuclei of fibroblasts, granulomatous reactions.

In all evaluated sections we observed a predominantly lymphocytic and plasma cell inflammatory infiltrate, with maximum intensity on day 7 of post-intervention. The intensity of the inflammatory reaction gradually decreased to day 28. On day 7, post-intervention, we identified the presence of granulation tissue at the site of injury. From day 14 we identified a maturation of granulation tissue: the intensity of chronic inflammatory infiltrate decreases, fibroblasts becoming prevalent and producing a more obvious collagen matrix. We observed the tendency of the collagen fibers toward parallel orientation evident from day 14 for sagittal section and 21 for the frontal. By day 28, the distance between the cut ends gradually decreased with reducing the amount of fat interposed, which is absent on day 28.

Key words: clubfoot, Achilles tendon tenotomy, histological slides, section, suture, rat

Introduction

With the widespread acceptance of the Ponseti method of clubfoot treatment major surgical interventions are needed much less frequently and long-term outcomes are improved.¹ Treatment aims at correction to obtain a functional, plantigrade pain-free foot.

Long-term follow-up studies demonstrating malcorrection, overcorrection, pain, and stiffness dampened the enthusiasm for very aggressive surgery.² The main problem with surgery is that clubfoot wounds heal by a patching up process called repair.

Long-term residual deformity and pain from surgically corrected club feet still continues to occur and presents diagnostic and therapeutic challenges for the orthopedic surgeon.³

Maintenance of function without pain has been demonstrated in a 35-year follow-up study.⁴

Objective

Is to quantify the histological modifications that occur early in the healing of lesions made on the Achilles tendons.

Material and methods

We used wild-type rats, 5 rats for each section type. All rats were housed in Thoren IVC cages maintained at positive pressure with a light cycle of 14 h light, including a dusk period, and 10 h dark. The food was administrated ad libitum in pellets. The work was carried out in accordance with the Federation of European Laboratory Animal Science Associations (FELASA).

Regarding the surgical technique it was performed a longitudinal incision of the tegument in the Achilles tendon area then we made sagittal sections (without suture, with absorbable suture, with non-absorbable suture), frontal section (without suture, with absorbable suture, with non-absorbable suture), cross-section, dentate section and section into Z.

The anesthesia was inhaler using a portable anesthetic device (Harvard Apparatus Isotec 5). Isoflurane (Forene®, Abbott, Solna, Sweden) was used as anesthetic gas (2-2.5%) and 100% oxygen (the flow rate of 1 l/min) was used as vehicle. The operations were performed under non-sterile hygienic conditions.

Laboratory rats survived after interventions and then were sacrificed with an T61 intravenous injection 0.3ml.

All procedures involving animal studies were conducted with local ethics committee opinion and under the strict supervision of a veterinarian.

The tissue material harvested by surgical technique was fixed in 10% neutral buffered formalin. Histological slides were stained with hematoxylin-eosin and Gomori trichrome stain. Stained sections were then examined with a Leica DMD108 microscope.

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For 1 month (day 7, 14, 21, 28) we studied the following histological characteristics grading them semi quantitatively:
- Nuclear density (1, 2, 3)
- The amount of interstitial collagen (1, 2, 3)
- Tendency to the parallel orientation of the nuclei of fibroblasts (1, 2, 3)
- Granulomatous reactions (+, -)

**Results**

The obtained histological slides were fully evaluated. To quantify the changes that occur early in the healing of lesions made on the tendons, we restricted the quantifying area to the adjacent zone of the histologically normal tendon.

In all evaluated sections we observed a predominantly lymphocytic and plasma cell inflammatory infiltrate, with maximum intensity on day 7 of post-intervention. The intensity of the inflammatory reaction gradually decreased to day 28. Interventions which involved the suture of the tendon remains evident inflammatory infiltrate in the foreign body granulomatous reactions in the suture thread.

On day 7 post-intervention, we identified the presence of granulation tissue at the site of injury. Its quantity was reduced for interventions that involved suturing the tendon. In lesions without suture, granulation tissue occupies a large area at the interface with surrounding normal tendon histology. From day 14 we identified the maturation of granulation tissue: the intensity of chronic inflammatory infiltrate decreasing, fibroblasts that produce obvious collagen matrix becoming prevalent (Fig.1).

The orientation of the long axis of the nuclei of fibroblasts becomes perceptible from day 14, with progression to day 28. We observed also the collagen fibers tendency toward parallel orientation evident from day 14 for sagittal section and 21 for the frontal. The orientation in the direction of the force is reduced for the dentate section and for those sectioned into Z, in all four intervals, compared to the other interventions (Fig.2).

In cross-section we observed the adipose tissue interposition between the cut ends of the tendon. By day 28, the distance between the cut ends gradually decreased with reduction of the amount of fat interposed, which is absent on day 28. In the rats where the cross-sectioning of the tendon was performed, the scar tissue which is formed is more cellular on day 28, with a small quantity of collagen, a lack of orientation in the lines of force, which indicates an extended healing time for this type of intervention (Fig.3).
Fig. 2. Nuclei orientation from day 7 to day 28.

Fig. 3. Nuclear density from day 7 to day 28.
Discussions

The Ponseti method has proven to be successful around the globe, in both industrialized countries and developing nations. Radler C.\(^5\) thinks the Ponseti method has become the gold standard of care for the treatment of congenital club foot and despite numerous articles in MEDLINE reporting results from around the globe there are still crucial details of the Ponseti method which seem to be less commonly known or considered.

We found few studies about Achilles tendon tenotomy but not about healing time. Maranho DA, Nogueira-Barbosa MH, Simão MN, Volpon JB\(^7\) believe most cases of congenital clubfoot treated with the Ponseti technique require percutaneous Achilles tenotomy to correct the residual equinus. They performed a study to assess Achilles tendon repair after percutaneous section to correct the residual equinus of clubfoot treated with the Ponseti method. The reparative process was fast after Achilles tendon percutaneous section that reestablishes continuity between stumps. The reparative tissue evolved to tendon tissue with a normal ultrasonographic appearance except for mild thickening, suggesting a predominantly intrinsic repair mechanism.

Barker SL, Lavy CB\(^8\) studied the correlation of clinical and ultrasonographic findings after Achilles tenotomy in idiopathic club foot. In a study of 11 tendons in eight infants, eight tendons were shown to be clinically intact and ten had ultrasonographic evidence of continuity three weeks after tenotomy. At six weeks after tenotomy all tendons had both clinical and ultrasonographic evidence of continuity.

In our study we observed that compared to the same day in the interventions with suturing, lymphocytic and plasma cell inflammatory infiltrate is evident when using non-absorbable sutures than those absorbable.

Conclusion

We observed that the healing time is better for the sutured Achilles tendons in all evaluated sections than tendons without suture which has an extended healing time.

We thank the Department of Pathology for their support.

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PERIVENTRICULAR LEUKOMALACIA IN EXTREMELY LOW BIRTH WEIGHT NEWBORNS

Aniko Manea¹*, Boia Marioara¹, Daniela Iacob¹, Mirabela Dima¹*, Radu E. Iacob¹

Abstract
The significant improvement in the intensive care of extremely low birth weight newborn has made increased survival rates possible for these premature and, as a result, certain pathologies that had previously received little attention have become the objects of increasing interest. One of the most common cerebral injuries at preterm newborns with gestational age less than 28 weeks at birth are intraventricular hemorrhage and periventricular leukomalacia (PVL).

Periventricular leukomalacia consists of an ischemic infarction in the region of the cerebral white matter adjacent to the lateral ventricles.

The pathogenesis of cerebral leukoencephalopathy have been influenced by different perinatal inflammatory and infectious conditions interrelated with the proinflammatory cytokines: TNF-α, IL-1β, IL-6 and IL-8.

Prognosis of LPV is greatly dependent on maternal infectious history, on the time of diagnosis, type of injury, whether diffuse or focal, and also on the preventative and therapeutic measured employed during the perinatal and postnatal periods.

Key words: Extremely low birth weight, periventricular leukomalacia

Background
The significant improvement in the intensive care of extremely low birth weight newborn has made increased survival rates possible for these premature and, as a result, certain pathologies that had previously received little attention have become the objects of increasing interest. (1)

Some particular diseases through frequency and severity are caused by the plurivisceral morpho-functional immaturity: respiratory distress syndrome, apnea crisis, patent ductus arteriosus, enterocolitic ulceronecrosis and infections, but the lesion background is mostly cerebral.

One of the most common cerebral injuries at preterm newborns with gestational age less than 28 weeks at birth are intraventricular hemorrhage and periventricular leukomalacia (PVL).(2)

Up to 26% of premature infants with birth weights below 1,500 g present periventricular leukomalacia with frequent lead to cerebral palsy (CP), intellectual impairment, or visual disturbances.

Due to lower mortality rates of very low birth weight neonates, thanks to developments in neonatal intensive care units, (90% survival of the approximately 50000 infants in the United States yearly with birth weight less than 1500 g) cerebral palsy incidence increases.(3)

The prognosis and neurological outcomes are improved by prevention, diagnosis and early treatment of these neurological diseases. (4)

Periventricular leukomalacia consists of an ischemic infarction in the region of the cerebral white matter adjacent to the lateral ventricles.

The name is based on the characteristic distribution and consists of periventricular focal necrosis with subsequent cystic formation and more diffuse cerebral white matter injury (Volpe, 2008).

Less than 5% of premature newborn at whom serial ultrasonography shows only increased periventricular echogenicity without cysts will subsequently develop cerebral palsy but a significantly bigger number of them will present evidence of cognitive dysfunction.

Cerebral white matter injury is defined as at least one of the following echographic findings (3,5,6):
- The presence of cystic lesions of at least 0.5 cm in diameter. These are distributed bilaterally and located close to the external angles of the lateral ventricles.
- Image of diffuse echodensity persisting for a period of more than 14 days, without cystic formations.
- Unilateral parenchymal hyperdensity or unilateral porencephalic cyst, probably caused by ischemic and hemorrhagic infarction. There will be periventricular hemorrhagic parenchymal involvement, compromising the germinal matrix layer.

In specific literature there are several echographic clasifications of periventricular leukomalacia:

- PVL I degree-over seven days persistent periventricular echodensities
- PVL II degree- transient periventricular echodensity evolving into small, localised fronto-parietal cysts
- PVL III degree- periventricular echodensities evolving into extensive periventricular cystic lesions
- PVL IV degree- densities extending into the deep white matter evolving into extensive cystic lesions

II. Cranial ultrasound classification of PVL by Volpe (1990)(6):
- Mild- micro cysts smaller than 0.2 mm
- Moderate -cysts between 0.2 to 0.5 mm
- Severe- multiples cysts bilaterally bigger than 0.5 mm

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The Quality Standard Subcommittee of the America Academy of Neurology and the Practice Committee of the Child Neurology Society recommends the following: routine ultrasound screening should be performed on all infants with gestational age less than 30 weeks. Screening should be performed at 7 to 14 days of age and repeated at 36 to 40 weeks postmenstrual age.

Yet, several studies have shown that MRI (magnetic resonance imaging) is more sensitive than cranial ultrasound for detection of PVL especially for non-cystic form of PVL (Maalouf et al., 2001; Roelants-van Rijn et al., 2001).

Three main reasons are the base of to predominantly ischemic injuries of the periventricular white matter at premature newborn: (8,9)
- Reduced cerebral flow in the white matter
- Immature oligodendrocytes are more susceptible to damage encouraged by free radicals and certain cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1β) and tumor necrosis factor alpha (TNF-α), in addition to the greater potential for toxicity induced by glutamate, when the brain is less mature.
- Intrauterine infection (Preterm newborn babies exposed to intrauterine infection are vulnerable to pre-oligodendrocyte cell death in the face of ischemic insult)

The pathogenesis of cerebral leukoencephalopathy have been influenced by different perinatal inflammatory and infectious conditions. The inflammatory pathway, mediated by cytokines is highly involved in nervous cell death by neuronal apoptosis.(10)

The proinflammatory cytokines most described in intrauterine infections are: TNF-α, IL-1β, IL-6 and IL-8. Interleukin 6 is the best known mediator of acute inflammatory response, liberated quickly after a bacterial invasion. It is secreted by monocytes, macrophages, endothelial cells and fibroblasts in response to other inflammatory mediators such as TNF-α and IL-1β.(11 ) Interleukin 6 is also synthesized within the neurons and neuroglia and its expression is elevated in a large variety of CNS disorders, presenting neuroprotective and neurotrophic effects.(12)

Testing of IL-1-ß, TNF-α and IL-6 at a newborn babies who had had PVL listed in autopsy findings has shown significantly more elevated levels compared with those whose brains were normal on autopsy.(13)

Thus, the incidence of PVL and cerebral palsy in premature infants is increased in the presence of 1) evidence for maternal, placental, or fetal infection (14–26), 2) elevated levels of IL-6 in cord blood (27), 3) elevated levels of IL-6 and IL-1 in amniotic fluid (28), and 4) elevated levels of all interferons and IL-1 and IL-6, among other cytokines, in neonatal blood (29–31). Moreover, although potentially a secondary effect of ischemia, the demonstration of IL-6 and TNF-α within PVL lesions is also possibly supportive of a relation of PVL to intrauterine infection and cytokines (32-34).

In the figure below is shown how the action of maternal/fetal infection, inflammation, and cytokines are involved in the death of oligodendroglia (OL) precursors in LPV (Fig. 1).

![Image of the Pathogenesis of oligodendroglia (OL) death in PVL. (35)]
Consideration of the pathogenetic scheme depicted in figure 1 raises the possibility of several promising interventions to prevent PVL. Perhaps of greatest value is prevention of the cascade to OL death related to free radical attack (Fig. 1). Thus, the use of clinically safe free radical scavengers, e.g. vitamin E, could be beneficial, after further research. Maternal antimicrobials and anticytokine agents may ultimately prove valuable in preventing the injury caused by maternal/fetal infection or inflammation and cytokines (Fig. 1)

Conclusions
As a role for subclinical intrauterine infection in the genesis of neonatal brain white matter damage and permanent handicap is supported by clear evidence and there are data that strongly suggest that inflammatory cytokines participate in this damaging process.

Prognosis of LPV is greatly dependent on maternal infectious history, on the time of diagnosis, type of injury, whether diffuse or focal, and also on the preventative and therapeutic measured employed during the perinatal and postnatal periods (36)

Periodic neurological evaluation for finding behavioural and cognitive impairments is needed for giving them the best expectations in their quality of live.

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CORRELATIONS BETWEEN OXYGEN THERAPY AND RETINOPATHY OF PREMATURENESS (ROP) - STUDY OF A GROUP OF 11 PREMATURE INFANTS WITH ROP REQUIRING TREATMENT

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Abstract
Retinopathy of prematurity (ROP) is the most common ocular abnormality in premature infants. It is a neovascular disorder and its incidence increases with decreasing gestational age and decreasing birth weight. It has a multifactorial etiology, primarily due to immaturity and avascular retina.

Aim of the study: The aim of this study is to establish correlations between the forms of ROP requiring treatment as a complication of prematurity and the associated therapeutic or pathogenic factors. Regarding the used therapeutic factors we have insisted on oxygen therapy.

Material and method: 293 premature infants with gestational age less than 34 weeks, born in Maternity Hospital in Oradea in the period 01st of January 2011 – 31st of December 2013 were included in this study. All these premature infants were evaluated by an ophthalmologist at 1 month postnatal age or at 34 weeks corrected age for early detection of retinopathy of prematurity. Our study focuses on a group of 11 premature infants who experienced retinopathy of prematurity, stage 3, and required surgical correction.

Conclusions: Several risk factors have been reported as predisposing to the development of ROP: oxygen therapy, anemia, red blood cell transfusion, sepsis, and apnea. In our study proved to be significant risk factors: oxygen therapy, sepsis, congenital pneumonia and especially repeated apnea requiring treatment (81.81% in the group of infants with ROP vs. 40% in the group of infants without ROP). The variations in hemoglobin oxygen saturation, variations occurring during and after apnea, are involved in the onset and evolution of retinopathy of prematurity. The exposure to alternating hypoxia and hyperoxia increases the incidence of retinopathy and causes severe proliferative retinopathy, requiring treatment.

Key words: premature, oxygen therapy, retinopathy of prematurity

Introduction
The premature infants may show multiple abnormalities of different visual system components.1,2,3 ROP is the most common ocular abnormality in premature infants. It is a neovascular disorder and its incidence increases with decreasing gestational age and decreasing birth weight. It has a multifactorial etiology, primarily due to immaturity and avascular retina.4 Other factors, including hypoxia, hyperoxia, variations in blood pressure, sepsis, acidosis, may injure the endothelium of the immature retinal blood vessels. The retina enters a passive phase and forms a pathognomonic structure of mesenchymal cells between the vascularized and the avascular regions of the retina by 33 to 34 weeks of postmenstrual age. In some infants, this structure regresses and it remains only the vascularized retina. In other infants, abnormal blood vessels proliferate from this structure and the progressive disease can cause exudation, hemorrhage and fibrosis, with subsequent scarring or retinal detachment. The presence of plus factor, with dilated and tortuous blood vessels in the posterior pole of the eye may be associated with an adverse visual outcome.

- Stage 1: presence of a white limiting line
- Stage 2: presence of a ridge
- Stage 3: presence of an extraretinal vascular tissue
- Stage 4: Partial retinal detachment
- Stage 5: Total retinal detachment (Figure 1)

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There is much interest in the role of oxygen in retinopathy of prematurity. The optimal blood oxygen levels and hemoglobin oxygen saturation levels remain controversial.\textsuperscript{5,6,7} Excessive oxygen in the first few weeks of postnatal life represents a major risk factor for retinopathy of prematurity.\textsuperscript{8,9,10} Many studies have used protocols involving low oxygen saturation in order to decrease the incidence of ROP. The results were not statistically significant.\textsuperscript{11,12,13,14,15,16} The results of other studies have suggested that increased hemoglobin oxygen saturation at higher gestational age decreases the risk of progression of ROP.\textsuperscript{16,17} The study STOP-ROP tried to demonstrate that from a certain critical evolutionary threshold of ROP, the hyperoxia has a beneficial effect.\textsuperscript{16} Theoretically this assumption makes sense because there is a suppression of the vascular endothelial growth factor and therefore of the vascular proliferation. It was noticed that in the hyperoxia group (hemoglobin oxygen saturation = 96-99\%) the eye damage was reduced, but there were more pulmonary complications and it was significantly higher the need for oxygen therapy and hospitalization. It is interesting the fact that the infants with hemoglobin oxygen saturation above 94\%, under atmospheric air condition und that weren’t included in the study showed a favorable evolution in comparison to the infants that were included in the study and had hemoglobin oxygen saturation above 94\% under higher FiO2 conditions.\textsuperscript{15} This observation presents that the infants with spontaneous increased saturations have a protection against the side effects of hyperoxia.

**Aim of the study**

The aim of this study is to establish correlations between the forms of ROP requiring treatment as a complication of prematurity and the associated therapeutic or pathogenic factors. Regarding the used therapeutic factors we have insisted on oxygen therapy.

**Material and method**

A number of 293 premature infants with gestational age less than 34 weeks, born in Maternity Hospital in Oradea in the period 01\textsuperscript{a} of January 2011 – 31\textsuperscript{a} of December 2013 were included in this study. All these premature infants were evaluated by an ophthalmologist at 1 month postnatal age or at 34 weeks corrected age for early detection of retinopathy of prematurity. Our study focuses on a group of 11 premature infants who experienced retinopathy of prematurity, stage 3, and required surgical correction.

We obtained data from the observation sheets and monitoring sheets of the infants from the two groups: the first group consists of 11 premature infants with ROP, stage 3 and the second group consists of 15 premature infants without retinal damage and that presented similar clinical and demographic criteria:

- associated pathology – the presence of idiopathic respiratory distress syndrome, maternal and fetal infection, congenital pneumonia, cerebral hemorrhage;
- complications: apnea in premature infant, bronchopulmonary dysplasia;
- established treatment: administration of surfactant, CPAP, assisted mechanical ventilation, free-flow oxygen therapy, blood transfusion;
- days of hospitalization.

**Results and discussions**

The total number of premature infants with gestational age < 34 weeks: 342 represents 2,73\% of the total number of infants.

Infants with gestational age < 34 weeks, evaluated for retinopathy:

11 infants presented severe retinopathy requiring treatment.

The incidence of severe retinopathy was of 3,75\%, similarly to other published studies.\textsuperscript{18,19}

These 11 infants represent the first studied group. The second group consists of 15 infants, selected after similar clinical and demographic criteria and that didn’t present retinopathy of prematurity. (Table 1).
Table 1: Clinical and demographic criteria.

<table>
<thead>
<tr>
<th></th>
<th>Infants with ROP ST. III, IV-</th>
<th>Infants without retinal damage -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight (grams)</td>
<td>1064.54</td>
<td>1102.24</td>
</tr>
<tr>
<td>Average gestational age (weeks)</td>
<td>28.45</td>
<td>28.15</td>
</tr>
<tr>
<td>Average Apgar score</td>
<td>2.72</td>
<td>2.9</td>
</tr>
<tr>
<td>Sex male</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Sex female</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Several risk factors have been reported as predisposing to the development of ROP: oxygen therapy, sepsis, congenital pneumonia and especially repeated apnea requiring treatment (81.81% in the group of infants with ROP vs. 40% in the group of infants without ROP) (Figure 2, 3, 4, 5).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Infants with retinopathy</th>
<th>Infants without retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal and fetal infections</td>
<td>45.45%</td>
<td>13.33%</td>
</tr>
<tr>
<td>Congenital pneumonia</td>
<td>45.45%</td>
<td>13.33%</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>20%</td>
<td>9.09%</td>
</tr>
</tbody>
</table>

* SDRI = idiopathic respiratory distress syndrome

Figure 2: Associated pathology in the studied premature infants from the two groups.

Figure 3: Number of hours of CPAP/ Average number of hours.
The variations in hemoglobin oxygen saturation, variations occurring during and after apnea, are involved in the onset and evolution of retinopathy of prematurity (Figure 6). The exposure to alternating hypoxia and hyperoxia increases the incidence of retinopathy and causes severe proliferative retinopathy, requiring treatment. (Figure 7) These results correlate with many studies that present that the variations in oxygen saturation have adverse effects especially when hyperoxia is followed by hypoxia. It was demonstrated that the severe retinopathy is associated with a high variability of oxygen tension in the first 2 weeks of life.\textsuperscript{23} The analysis of the risk factors for retinopathy help us to understand and to prevent its development and evolution.

![Figure 4: Total number of hours of oxygen therapy/ Average number.](image)

![Figure 5: Oxygen therapy at FiO\textsubscript{2} under 40% / average number of hours.](image)

![Figure 6: Oxygen therapy at FiO\textsubscript{2} above 40% / average number of hours.](image)
The simplest and safest method to decrease the incidence of retinopathy of prematurity is the strict control of the hemoglobin oxygen saturation. This saturation should not exceed the values of 93% - 92% in extremely low birth weight infants. Despite the enormous progress in recent years, there are still many open questions that will hopefully be elucidated in the near future.

References


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PRADER WILLI LIKE SYNDROME - THE NEW MEDICAL CHALLENGE

Andreea-Iulia Dobrescu¹*, Mirela Cosma¹*,², Nicoleta Andreescu¹, Simona Farcaș¹, Radu Ștefănescu¹*, Maria Puiu¹

Abstract
PraderWilli syndrome (PWS), the most common form of syndromic obesity, is characterized by a great phenotype and genotype variability. Most cases of PWS (approximately 70%) are determinate by deletions of 15q11-13 band on chromosome 15 received from the father; 28% of cases appears due to maternal disomy. The imprinting center isolated mutations determine less than 1% of cases. There are also very rare cases with unknown cause of disease, even if the clinical score indicate a positive diagnosis of PWS. Several studies mentioned other gene mutations that mimic PWS phenotype (PraderWilli Like syndrome) without involving chromosome 15. The present study aims to present 6 patients with PraderWilli Like syndrome (PWL syndrome) and also to indicate a strategy to establish the right diagnosis for them. We selected 3 girls and 3 boys, aged between 8 and 29 years old, who presented positive clinical score for PWS according to their age and negative genetic tests for the disease. We performed clinical examination and laboratory tests for all the patients. The patients were directed to other advanced genetic tests to obtain the right diagnosis. Conclusion: those rare cases need an optimum medical strategy to improve the capacity to establish an early positive diagnosis.

Key words: Prader Willi Like Syndrome, obesity, hyperphagia, chromosome 15, uniparental disomy

Introduction
PraderWilli syndrome (PWS) is a rare genetic disorder that affects of 1:10,000 to 1:30,000 newborns, males and females, with no race particularities [1]. It is a multisystem disease with clinical, endocrine, metabolic and hormonal damage. It is the most common form of syndromic obesity. It is characterized by the clinical and genetic variability [2]. The clinical features are changing during life and they are influenced both age and early treatment. It is caused by a mutation of paternal copy of 15q11.2-13 region [3]. Approximately 70% of cases are determinate by a deletion of the specific region, 28% are due to uniparental disomy (both copies of a chromosome were received from the mother), less than 1% of cases are caused by isolated mutations of the imprinting center with high risk of recurrence [4]. Some cases (1%) have an unknown cause; the patients have a positive clinical diagnosis of PWS, without the genetic confirmation (PWL syndrome).

To obtain a positive clinical diagnose of PWS, the clinical score established by Holm and collaborators is used. It involves major criteria noted with 1 point each one and minor criteria noted with 0.5 point each [5]. A clinical score of 5 points for children younger than 3 years (at least 3 major criteria present) and 8 for children over 3 years (5 points obtained from the major criteria) is required for a suggestive clinical diagnosis of PWS. There are also some supportive criteria (no point) who strengthen the clinical score (table 1).

The clinical diagnosis needs the molecular confirmation of chromosome 15 abnormalities to establish the positive diagnosis of PWS. PWL syndrome is a particular entity. It is caused by any mutations different by those who involved chromosome 15 but determine similar clinical features. The medical attitude for those rare cases is not fully elucidated.

Aim
The study aim is to present 6 patients with PWL syndrome and also to indicate a strategy to establish the right diagnosis for them.

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Table 1: Diagnosis criteria for PWS (Holm et al).

<table>
<thead>
<tr>
<th>Major criteria (1 point each)</th>
<th>Minor criteria (1/2 point each)</th>
<th>Supportive criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal/infantile hypotonia and poor suck</td>
<td>Decreased fetal movement and infantile lethargy</td>
<td>High pain threshold.</td>
</tr>
<tr>
<td>Feeding problems and failure to thrive as infant</td>
<td>Typical behavior problems</td>
<td>Decreased vomiting</td>
</tr>
<tr>
<td>Weight gain at 1 to 6; obesity; hyperphagia</td>
<td>Sleep apnea</td>
<td>Temperature instability in infancy or altered temperature sensitivity in older children and adults</td>
</tr>
<tr>
<td>Characteristic dysmorphic facial features</td>
<td>Short stature for family by 15 years</td>
<td>Scoliosis or kyphosis (curvature of the spine).</td>
</tr>
<tr>
<td>Small genitalia; pubertal delay and insufficiency</td>
<td>Hydropigmentation</td>
<td>Scoliosis or kyphosis (curvature of the spine).</td>
</tr>
<tr>
<td>Developmental delay/intellectual disability</td>
<td>Small hands and feet for height</td>
<td>Early adrenarche (pubic or axillary hair before age 8).</td>
</tr>
<tr>
<td></td>
<td>Narrow hands, straight ulnar border</td>
<td>Osteoporosis (demineralization, or thinning, of the bones).</td>
</tr>
<tr>
<td></td>
<td>Esotropia, myopia</td>
<td>Unusual skill with jigsaw puzzles</td>
</tr>
<tr>
<td></td>
<td>Thick, viscous saliva</td>
<td>Normal neuromuscular studies</td>
</tr>
<tr>
<td></td>
<td>Speech articulation defects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin peeking</td>
<td></td>
</tr>
</tbody>
</table>

**Material and Methods**

We performed a retrospective study that analyzed data routinely collected as part of the clinical care of patients with PWS syndrome, derived from healthy non consanguineous parents. From the entire group of our department of PWS patients, we included 6 patient, 3 girls and 3 boys, aged between 8 and 29 years old. All patients had positive clinical score for PWS and negative genetic tests (FISH test, methylation test) for the disease. We excluded all patients with positive molecular tests for PWS. We performed clinical examination and laboratory tests. We did not evaluate hypogonadism in 2 girls because of their small age.

The main phenotypic features were analyzed according to the international clinical diagnostic criteria for PWS (minor criteria and major criteria)[5]. The information about the pregnancy, postnatal evolution and the onset of hyperphagia and obesity were collected from interviews with the parents. We recorded their weight and height, we calculated the body mass index (BMI) and we compared the results with the standardized values for age and sex.

The laboratory tests included a complete evaluation of the carbohydrates, lipids and proteins metabolism and hormonal status (thyroid hormones, sex hormones, insulin).

Helped by a multidisciplinary team, we diagnosed the ocular abnormalities, the intellectual disabilities, developmental delay and language disorders. We also performed the necessary tests and interviews to identify supportive criteria- scoliosis or kyphosis, osteoporosis, early adrenarche, unusual skill with jigsaw puzzles.

The polysomnography was used to identify the sleep disorders (central, obstructive or mixed apnea). It was used a mobile device who monitors the brain function, the eye movements, the heart activity, ventilatory variables and arterial oxygen saturation during night sleep [6]. All parents were informed about the procedures, the risks and benefits of each tests and they signed informed consent.

**Results**

The mean age of all patients was 16.83± 8.47 years, for girls 13.33± 9.23 and for boys 20.33± 7.57. All of them had a positive clinical score for PWS, with a mean of 9±0.89 (Figure 1).
They all had more than 5 points obtained from the major criteria. The characteristic facial features were present at all 6 evaluated patients. They had narrow bifrontal diameter, almond shaped eyes, downturned corners of the mouth and small mouth with thin upper lip (figure 2).

The patients had neonatal hypotonia according to parents’ interviews. Feeding problems appeared in 66.67% of patients. They all were obese, with a weight gain before the age of 6 years based on hyperphagia. The onset of hyperphagia was different for each patient and the parents could not correlate it with a stressful event or other causes who could modify the feeding behavior of children. It is accompanied by aggressive reactions or excessive crying if they had no access to food. Hypogonadism appeared in 4 evaluated patients, 3 boys and 1 girl; they presented delayed gonadal maturation with delayed pubertal sign. All patients had moderate mental retardation and 3 of them needed special conditions for school (figure 3).

Figure 2. PWL syndrome patients.

Figure 3: Major criteria distribution.
The minor criteria were also identified on patients. All of them had language difficulties with defects in words articulation and behavior problems. They presented aggressive, oppositional, manipulative and possessive attitude, they were stealing (especially food) and they were lying. 83.3% of patients had sleep disorders. We diagnosed obstructive apneas, central and mixed apneas and hypopneas; patients associated restless sleep, oral breathing and increased sleepiness during the day and required specialized evaluation and treatment. Thick saliva had also a high frequency in our patients (83.3%); some of them presented crusting at corners of the mouth. Infantile lethargy with weak cry was diagnosed in 66.67% of patients. We identified 3 patients (50%) with short stature according to the standardized values for age and sex. A small number of patients presented small hands and feet (16.67%) or ocular abnormalities. We did not identify osteoporosis or special skills with puzzles in our patients.

Discussions

The present study evaluated 6 patients with positive clinical diagnosis of PWS and without molecular confirmation. We searched the literature for similar cases to identify other gene mutation who can determine the same phenotype with PWS gene mutations. Izumi K et al in their paper from 2013 described the clinical and endocrine abnormalities in one patient with PWL syndrome associated with proximal interstitial 6q deletion involving Single-minded 1 (SIM1) gene [7]. They highlighted the clinical similarities between PWL syndrome and interstitial 6q deletion features and also the role of SIM 1 gene in the endocrine aspects and the importance of specific early treatment in the disease evolution.

Bonnefond et al presented the link between morbid obesity associated with PWL Syndrome and SIM1 loss of function [8]. They evaluated new mutations of SIM1 associated with chromosome 6q16 and their role in obesity from patients with PWL syndrome. Other studies who talked about the role of this gene in PWL syndrome were identified [9,10]. Those studies mentioned 6q16 deletion as a critical mutation for PWL syndrome.

Pure distal monosomy 10q26 is mentioned in the literature as a specific mutation who determined similar clinical features with PWL syndrome. The symptoms of described patient had the onset in the prenatal period with decreased fetal movements. Other features of 10q26 monosomy are: severe neonatal hypotonia, characteristic facial dysmorphism, hypogenitalism and developmental retardation [11].

Schae et al described in their paper from 2013 4 different de novo heterozygous truncating mutations in the MAGEL2 gene [12]. They described 4 boys with PWL syndrome, two of them associated autism spectrum disorders or neurological problems like seizures.

Bischof et al described the role of loss of MAGEL2 gene in the hypothalamic dysfunction. They used an animal model who presented similar clinical features to PWS if they lose the expression of MAGEL2 gene [13].

All those studies highlighted the great genetic variability of PW phenotype; even if the disease is caused by a mutation of chromosome 15, there are also many other gene abnormalities who can determine the same clinical features.

Conclusions

Even if the medical knowledge in rare diseases area has been improved, there are still a lot of cases undiagnosed. The diagnosis of PWL syndrome follows the same steps like PWS diagnosis and the patients with PWL syndrome should be treated and evaluated like PWS patients till they get a complete gene evaluation and a positive diagnosis. We need to improve our capacity to investigate gene mutations, to search and to interpret them. More advance genetic tests (arrayCGH, clinical whole-exome sequencing) should be more accessible and should be used in case of an uncertain case. We also need center of expertise for PWS and with a larger study group we could try to identify some specific PWS phenotype features who allowed us to establish a diagnosis. A personalized early treatment and restrictive diet could increase the life expectancy and complications of morbid obesity, the main feature of PWL syndrome.

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ISOLATED TRACHEOESOPHAGEAL FISTULA – A RARE CONGENITAL MALFORMATION

Niculina Bratu¹, Radu Iulian Spatâru¹, Dan-Alexandru Iozsa¹

Abstract

Introduction: Isolated congenital tracheoesophageal fistula is a very rare malformation with an incidence of 1 in 50,000-80,000 births. In most of the cases this anomaly is detected in the first year of life because of the suggestive symptoms, but sometimes the diagnosis is delayed even until adulthood.

Aim: The purpose of this paper is to analyse clinical, imagistic and therapeutic sights of this malformation.

Material and Methods: We report three cases of isolated congenital tracheoesophageal fistula, diagnosed and successfully treated in our department between 2005 and 2012.

Results: The age at time of diagnosis was 3 months, 18 months, and 3 years. The lesion was revealed by contrast radiography and endoscopy in all cases. Treatment consisted in section and ligation of the fistula. In one case the intervention was performed by right cervicotomy and in the other two by right toracothomy. The postoperatory evolution was uneventful in all cases.

Conclusion: Despite its rarity, isolated tracheoesophageal fistula should be taken into account in the presence of recurrent chest infection, associated with choking and cyanosis on feeding. The surgical strategy should be adapted to the location of the lesion.

Key words: isolated congenital tracheoesophageal fistula, diagnosis, H-tracheoesophageal fistula

Introduction

Isolated tracheoesophageal fistula represents a rare type (4-5%) [1] of tracheoesophageal anomaly. It is frequently associated (30%) with other malformations, including VACTERL syndrome, CHARGE syndrome, Goldenhar’s syndrome, esophageal stenosis, syndactyly [2, 3], and exceptionally with duplication cyst with or without esophageal atresia [4].

The characteristic signs and symptoms are described as the triad of Helmsworth and Pryles, which consists of coughing and aspiration during feeding, recurrent pneumopathy, and abdominal distension [2]. The early diagnosis of this disorder is difficult and some cases may remain undiagnosed until late in infancy or childhood [5]. In addition, false-negative results of all diagnostic tools are not uncommon [6]. The first surgical repair of such a defect was reported by Imperatori in 1939 [7]. Different surgical approaches have been described for this anomaly.

Case reports

Case 1

A 3 years old girl presented with persistent coughing, associated with repeated episodes of respiratory tract infections, considered related to a gastro-esophageal reflux. Her feeding problems were especially with liquids. The clinical aspect of the child was normal. A tube esophagogram was highly suggestive for the diagnosis of isolated tracheo-esophageal fistula (Figure 1).

The child was operated on through a right thoracotomy (Figure 2). Division of the tracheo-esophageal fistula was performed without any complications and the symptoms disappeared completely.

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Figure 1. Tube esophagogram showing isolated tracheo-esophageal fistula.

Figure 2. Tracheo-esophageal fistula exposed through a right thoracotomy.
Case 2
A 18 months old male was admitted on for repeated episodes of choking and cyanosis related with feeding. The clinical features were unremarkable. Having a high index of suspicion regarding a H-type TEF, an esophagogram was performed, revealing the fistula positioned at the cervical base level (Figure 3).

The fistula was surgically divided through a right cervicotomy (figure 4). No postoperatory complications were noted.

![Figure 3. Esophagogram showing H-type TEF situated at the cervical base level.](image1)

![Figure 4. Good exposure of the eso-tracheal fistula through a right cervicotomy.](image2)

Case 3
A 3 months old was admitted in our department for severe coughing and choking at feeding. The clinical examination revealed cyanosis associated with these symptoms. The diagnosis was made by contrast esophageal X-ray and confirmed by an esophagoscopy.

We intervened by a right a thoracotomy in order to interrupt the isolated TEF. No complications in the postoperative evolution were noted.

Discussions
Isolated tracheoesophageal fistula (H-TOF) is characterized by a triad of classical signs and symptoms that are usually present from birth, but these are also nonspecific and sometimes intermittent [8].

Esophagogram is usually a reliable method for diagnosis. It is the least invasive technique for visualizing the H-type tracheoesophageal fistula, though often difficult, requiring multiple attempts before the defect is confirmed [5]. Tracheoscopy is another valuable tool, permitting the direct visualization of the fistula.

Treatment of H-TOF is surgical and should be performed as soon as possible after diagnosis [8]. For proximally located fistula the preferable approach is cervicotomy and in cases of distal fistula thoracotomy is usually performed [6]. As an alternative to thoracotomy, the thoracoscopic approach was proposed [9].

In all of our cases the diagnosis was based on esophagogram.

The surgical approach was adapted to the fistula location and it was curative.

References

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PEDiATRIC BuRNS AND SCALds - MODERN THERAPEUTIC CONCEPTS

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Abstract
Burns and scalds are the second most frequent cause of accidents in children. In contrast to adults children usually suffer from hot water scalding and not flame burns. The treatment of burn wounds is subject to a defined management which can be divided into preclinical treatment, emergency room management, and the clinical phase. The initial therapy consists of pain management and maintenance of vital functions. During the first days of further treatment of larger burns, management of the massive fluid loss due to capillary leakage is important to avoid secondary organ damage. Later, avoidance or timely treatment of bacterial infections and the management of wound healing are core issues to achieve a good outcome. The management of fluid shifts and wound treatment are significantly different for children compared to adults and considerable experience is needed to guide therapy. Optimal treatment is best achieved in centers specialized in pediatric burns. Prevention is achieved through passive measures to enhance safety and active education of parents regarding mechanisms and risks for pediatric burn accidents.

Key words: burns scalds, preclinical treatment, analgesia, pediatric burns unit, occlusive dressing, surgical treatment prevention.

Introduction
Burns and scalds are the second most frequent cause of accidents in children. In contrast to adults children usually suffer from hot water scalding and not flame burns. The treatment of burn/scald wounds is subject to a defined management which can be divided into preclinical treatment, emergency room management, and the clinical phase. The initial therapy consists of pain management and maintenance of vital functions. During the first days of further treatment of larger burns, management of the massive fluid loss due to capillary leakage is important to avoid secondary organ damage. Later, avoidance or timely treatment of bacterial infections and the management of wound healing are core issues to achieve a good outcome. The initial therapy consists of pain management and maintenance of vital functions. During the first days of further treatment of larger burns, management of the massive fluid loss due to capillary leakage is important to avoid secondary organ damage. Later, avoidance or timely treatment of bacterial infections and the management of wound healing are core issues to achieve a good outcome. The management of fluid shifts and wound treatment are significantly different for children compared to adults and considerable experience is needed to guide therapy. Optimal treatment is best achieved in centers specialized in pediatric burns. Prevention is achieved through passive measures to enhance safety and active education of parents regarding mechanisms and risks for pediatric burn accidents.

Key words: burns scalds, preclinical treatment, analgesia, pediatric burns unit, occlusive dressing, surgical treatment prevention.

About 75%-80% of burns are provoked by hot fluids. More dangerous are burns provoked by hot fat or explosions. Small children are extremely in danger because of their lower skin thickness compared to adults. A 54 °C hot fluid affects the whole depth of a small child’s skin in 10 seconds, while it needs 30 seconds to do the same damage in an adult patient.

In the presence of a child with burns/scalds there are a few criteria for transporting the patient to a specialized burn center [1,2]:
- Infants and small children with more than 5 % body area 2-nd degree burns and schoolchildren with more than 10 % body area 2-nd degree burns
- Third and fourth degree burns
- Burn which affect the head area, hands, feet or the anal/genital area.
- Electrocutions or chemical burns
- Suspicion of inhalatory trauma
- Association with other kind of trauma in the presence of polytrauma
- Child abuse

If children with severe burns and scalds are timely admitted and treated in a specialized burn centre this leads to shorter hospital stay, fewer complications and therefore a reduction in hospital stay costs [3].

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First aid

The first and most important operational maxim is self-protection. Open fire or active power supply lines jeopardize the rescue maneuver. Is it safe to rescue the injured person? If yes, is it possible to rescue the injured person and other endangered persons from the danger zone? First aid consists in taking the victim away from the accident site (dangerous zone), checking of vital signs, removal of clothes and cooling of the burned area to avoid after-burn of deeper skin layers. The cooling should be undertaken with water which has a temperature of 15-20 °C for approximately 10-15 minutes and should be done immediately after the accident (2 to 3 minutes after the accident). If the accident is more than 30 minutes away there is no reason in doing any cooling of the affected area. Cooling is especially effective in the first 20 to 30 minutes after being burned and after this only has an analgetic effect [4]. Cool-packs or even ice are unsuitable, as they can lead to a sustained and harmful decrease in capillary perfusion around the burned skin area [5,6]. An inhalation trauma is present in many patients and this alone increases the mortality rate by a factor of nine[5]. Many patients are often mistakenly cooled during the whole transport and arrive at the burn care center with greatly decreased body core temperature. Special attention should be paid to hypothermia which is especially important in newborns and infants – each grade Celsius of hypothermia increases the overall mortality with 10% [7]. Therefore one can abandon cooling in newborns, infants, patients with affected body area surface > 15% and intubated and ventilated children. After cooling the affected area should be covered with sterile drapes which will keep the body temperature constant (metallic sheet).

At the location of the accident, vital functions, i.v. catheters, fluid management, the decision for intubation, and sufficient pain control are crucial. During the first examination of the patient the following questions should be asked and answered:
- Is there a inhalation trauma present?
- Are there any circular burns or scalds on the extremities or torso?
- Are there any lesions affecting the face, eyes, ears, hands, feet or the genital area?
- Is there any chemical or electric burn?
- Is there any suspicion of maltreatment?

Initial resuscitation and analgesia

Parallel to cooling, it is necessary to prepare a venous access with as large a lumen as possible, accompanied by fluid therapy with crystalloid solutions according to Baxter (4–8 mL Ringer lactate x kgBW x BS/24 h; BW= body weight, BS= percentage of affected body surface) [8] or using more advanced calculation formulas[8]. Within 30 minutes, the water content in the burn increases by 80%, which can lead to massive redistribution of the body fluid in large burns. If early analgesia with sedation—normally with S-ketamine and midazolam—is insufficient, or the general condition of the patient deteriorates due to the severity of the inhalation trauma, quick intubation (best before transport) is sensible. The importance of inhalation trauma as a factor determining survival cannot be overstated[10]. Clinical signs for inhalation trauma (IHT) include burns in the area of the face, soot in the oral cavity and in the throat, as well as inspiratory stridor. The classification of severity of the IHT is performed bronchoscopically after admission to the burn care center. In the case of carbon monoxide intoxication, pulse oxymetry supplies falsely high values, as the device cannot differentiate between CO-Hb and oxygenated hemoglobin.

If a venous access is difficult, an intraosseous access must be established.

Analgesia can also be established by applying drugs intranasally or intrarectal. If the burned area is under 10% and the transport to a specialized burn centre will take under 30 minutes there is no need to lose precious time to establish a venous access under difficult conditions. Analgesia is usually established by the following medication:

- Ketamin i.v./intraosseous 2-4 mg/ kg
- S-Ketamin i.v./intraosseous 1,5-3 mg/ kg
- Ketamin intrarectal 10 mg/ kg
- Fentanyl i.v. 0,001-0,01 mg/ kg
- Piritramid i.v. 0,05-0,1 mg/ kg
- Midazolam i.v. 0,05-0,1 mg/ kg

If there are second degree burns and the affected body surface is <10 percent a fluid therapy is not obligatory from the accident scene. If the affected body surface is >10 percent a fluid therapy with isotone crystalloid solutions should be started in a bolus of 20 ml/kgBW. Urine output of 1-1,5 ml/kgBW/h is a good sensor of adequate fluid therapy. Volumes should be modified as necessary to maintain adequate perfusion and urine output, colloidal solutions, cortisone, diuretics and profilactic antibiotics should be avoided during the first 24 hours.

Affected body surface and degree of burns/scalds

The affected body surface area and the degree of burns is also critical to establish at the first examination of the patient.

The assessment of the affected body surface is performed by sight. This is best done using Wallace’s "Rule of Nine". Here different body areas correspond to a percentage of the body surface (arms and head 9% each, chest/abdomen/back and legs 18% each, palms, including fingers and genital area 1% each). In this context, the rule that the palm size of the patient corresponds to about 1% of his total body surface area (TBSA) is also helpful.

In small children the scheme by Lund and Browder is better suited.

The degree of burns is synthesized in the underlying Figure 1:
Even specialized plastic surgeons need many years of experience to assess the degree of burns successfully. Cone et al. reported that non-specialist physicians providing first aid wrongly assessed the degree of burns in 75% of cases, whereby in two thirds of all cases the degree of burns was classified as too deep[11]. Blistering (degree IIa), the whitish discoloration of the insensitive skin in the affected area (degree IIb/III) and black carbonization (degree IV) can help in the rough determination of the degree of burns (Figure 1).

The final degree of burns is hard to establish at first examination (Figure 2 a and b):

<table>
<thead>
<tr>
<th>Degree</th>
<th>Anatomic correlate</th>
<th>Schematic aspect</th>
<th>Clinical aspect</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Reddening, swelling, pain (epidermis)</td>
<td><img src="image1" alt="Schematic aspect" /></td>
<td><img src="image2" alt="Clinical aspect" /></td>
</tr>
<tr>
<td>IIa</td>
<td>Reddening, blistering, pain (superficial dermis)</td>
<td><img src="image3" alt="Schematic aspect" /></td>
<td><img src="image4" alt="Clinical aspect" /></td>
</tr>
<tr>
<td>IIb</td>
<td>Pallor, blister, pain (partial dermis)</td>
<td><img src="image5" alt="Schematic aspect" /></td>
<td><img src="image6" alt="Clinical aspect" /></td>
</tr>
<tr>
<td>III</td>
<td>Greyish white or black necrosis, analgesia (complete dermis)</td>
<td><img src="image7" alt="Schematic aspect" /></td>
<td><img src="image8" alt="Clinical aspect" /></td>
</tr>
<tr>
<td>IV</td>
<td>Carbonization (may extend to the bones and joints)</td>
<td><img src="image9" alt="Schematic aspect" /></td>
<td><img src="image10" alt="Clinical aspect" /></td>
</tr>
</tbody>
</table>

Figure 1. The degree of burns.

Figure 2. a – Child at admission – the burns were classified as grade I to IIb.  
b – Child at 72 hours after accident – the burns were classified as grade IIb and III.
The quantity of administered fluid is also hard to establish in regard to degree of the burns and the affected body surface and studies of Cartotto et al. und Yowler et al. [12, 13] have shown that the Parkland formula is not the ideal instrument, concluding that a close monitoring of urine output is necessary. The same conclusions arise from the study of Jester et al.[14]

After performing life-saving measures, a standardized polytrauma check must be performed while still at the site of accident, in order to be able to detect less obvious injuries.

After initial stabilization the patient should be transported by the quickest way to a specialized centre. Transfer to a center specialized in treating children with burns adheres to predetermined criteria to ensure that the patients receive appropriate further treatment.

As guidelines the following aspects apply to pediatric patients:
- Second degree burns <5% percent can be treated as an outpatient case
- The following patients need admission to the hospital:
  o Children under the age of 1 year
  o Second degree burns with BS 5-10% or third degree with BS 1-5 % (medium burns) respectively second degree burns with BS greater than 10% or third degree with BS greater than 5 % (severe burns)
  o Burns associated with inhalatory trauma
  o Electrical burns
  o Burn which affect the head area, hands, feet or the anal/genital area or respiratory tract
  o All patients with multiple trauma and burn injuries where the main injury is the burn

The admission of patients to the emergency room should be subject to a standardized protocol, which is quickly and effectively performed by an interdisciplinary team. Emergency room management consists of a mechanical cleaning and subsequent accurate assessment of the extent of the burn injury, monitoring of vital functions, diagnosis and treatment of an inhalation injury as well as associated injuries, and the appropriate care of the burn wounds.

At presentation, the burned child should be managed using a protocol which combines rapid assessment with resuscitation of life-threatening aspects of the injury, before definitive burn wound care commences (Figure 3). Anaesthesia may be required either in the resuscitation phase, in the post-resuscitation phase for debridement and grafting procedures or for plastic surgery in the long-term. Optimal anaesthetic management of these children requires detailed attention to their psychological requirements, and awareness of the influence of the pathophysiology of burns on tolerance of anaesthesia and of the special difficulties associated with airway compromise and massive haemorrhage during debridement.

The affected children should be managed in a well heated emergency room (35-38 °C).

Body temperature at admission should be recorded, a stable venous access should be established (if not already present), blood for analysis should be withdrawn and any hair that stands in the way of proper treatment should be shaved. Swabs from the affected area should be taken and send to laboratory for culture and antibiogram determination (Figure 4). Profilaxis for tetanus should be carried out if it is not present.
One specific danger is that a compartment syndrome of the extremities or the trunk may develop from deep dermal burns. For example, the abdominal compartment syndrome has a mortality of over 40%. If this seems possible, a rapid escharotomy (separation of superficial burned layers of the skin) or even a fasciectomy is carried out (separation including muscle fascia) (Figure 5).

![Figure 5 – Escharotomy for circular deep burns of the extremity.](image)

Professional intensive care therapy is a basis for further surgery therapy and plays an important role for the survival of the patient with severe burns. Controlled fluid and electrolyte management with continuous and close meshed monitoring of various laboratory parameters decreases the risk of common complications of the burn injury.

The most common complications are:

- pneumonia
- sepsis,
- lung failure, renal failure
- infection of the wound and
- acute respiratory distress syndrome (ARDS) [15]

Severe complications such as cholecystitis [16] or acute renal [17] and organ failure [18] must be detected early and treated adequately. Due to the necessary analgesia, patients often receive long term respiration. Therefore, the use of a tracheotomy tube is sensible.

In view of the greatly increased nutritional requirements of severely burned patients, appropriate nutrition must be initiated rapidly. The patient loses massive quantities of proteins as part of his burn injury—on the one hand through his burn wounds which release abundant quantities of protein into the bandages and on the other hand through the resulting consumption of available protein depots. Early and adequate provision of proteins not only improves the resulting osmotic gradients from intra- to the extravascular space but also the wound healing competence in affected patients [19]. No clear guidelines are available for the nutrition of pediatric burned patients[20]. Enteral food supply should be targeted as early as possible, in order to avoid regression of intestinal villi[21]. The capillary leak, which is responsible for the massive displacement of fluids, spontaneously ceases after 24 hours. Till then, intensive fluid therapy must be continued, in order to counteract the increased cardiac output, the reduced perfusion of the kidney, the liver and the intestine, and the rapid increases in hematocrit [5].

**Surgical therapy**

First degree burns are treated conservatively by applying locally fatty ointments, for example Bepanthen®. Second degree burns (IIa) are treated with occlusive dressings like Biatain Ag®, Briobane®, Acticoat /Allevyn®, Urgotuel S Ag®, Contreet®. Each of them has advantages and disadvantages. The dressings are changed every 3 to 4 days under mild sedation and analgesia or anesthesia depending on the extent of the burned area, the type of dressing used, the hospital protocols, etc. The cost factor of occlusive dressings is also to be considered (Figure 6, Figure 7).

For IIb degree burns dermabrasion and application of Suprathel® (polymer related skin substitute) is a good option (Figure 8). The degradation products of SUPRATHEL® stimulate the healing process by supporting the angiogenesis and the re-building of the dermis. The acidification of the wound with SUPRATHEL® has an additional bactericidal effect and thus minimizes the risk of infections. It is also resorbed in about 6 weeks.

More deeply burned areas (degree III to IV) are initially dressed in a sterile manner after cleaning and are usually treated according to the principle of early tangential excision, i.e. removal of necrotic skin (about three to four days after the accident) with wound cover as soon as possible. For scalds the time interval is 9-12 days sometimes even 21 days after the accident. Different techniques must be considered here.
More deeply burned areas (degree III to IV) are initially dressed in a sterile manner after cleaning and are usually treated according to the principle of early tangential excision, i.e., removal of necrotic skin (about three to four days after the accident) with wound cover as soon as possible. For scalds the time interval is 9-12 days sometimes even 21 days after the accident. Different techniques must be considered here.

These techniques have to be selected according to the size, texture and thickness of the defect in the soft tissue.

One possibility is to use 0.1 to 0.4 mm split-thickness skin grafts and the area of these can be increased by a lattice (the so-called mesh graft) by a factor of 1:1 to 1:6. The head is therefore an excellent donor area, because of the relative big area of the head in children and also because after growth of hair the scars are no longer visible. Another reason is the rapid healing of the donor site, so that in case of need another skin graft can be harvested from the area in 10-12 days after the primary procedure (Figure 9).
"Cultured skin" (keratinocyte transplantation) is used in special cases (burned area over 60 %) when the donor area is too small to conduct autologous skin transplantation [22,23]. As an alternative, cadaver or pig skin can be used, in order to obtain temporary cover when donor areas are inadequate. This cover can later be replaced by autologous skin grafts. This also apply to temporary coverage by use of Integra® or Matriderm®, but high expenses should be taken into consideration. Depending on depth and localization, pedicled or free tissue grafts (flaps) may be used as well[24].

On the throat, in the face, on the hands and over the joints, only cover techniques are used which later lead to satisfactory texture, color, and elasticity of the grafted skin. Thus, stigmatizing scars in visible skin areas are avoided and contractures of the scars near the joints are prevented[25].

Infections

Bacterial infection is a common complication which can endanger the burned patient and threaten his life. The partially damaged integrity of the skin allows devastating superficial infection which, however, is rarely the direct cause of death. In contrast, if bacteremia and consecutive sepsis develop, mortality greatly increases. 75% of patients with extensive burns die as a consequence of a severe infection[26]. Invasive forms of infection of subcutaneous tissue layers play an especially important role, as well as surgery-related infections and superficial wound infections. These infections, which are mostly evoked by staphylococci, streptococci and pseudomonads, must be detected without delay and aggressively treated with broad spectrum antibiotics [27,28]. In this context, enterococci of group D and the increasing common colonization with multiresistant bacteria are especially feared. Due to these multiresistant bacteria, the early use of combined broad spectrum antibiotics is necessary. These antibiotics must be administered early at high dosage, in order to protect the life of the patient [29].

Follow up and rehabilitation

After completion of the intensive care period in extensive burns/scalds, the patients are transferred in-house to a follow-up ward where further wound care, physiotherapy, ergotherapy, and psychiatric care help to maximize the patients’ autonomy. Generally, rehabilitation therapy for patients with burn injuries begins on the day of the burn. As soon as possible, rehabilitation measures should be implemented in the therapy. All physiotherapy requires adequate analgesia. Early respiration training deepens inhalation and therefore prevents pulmonary infections. Edema prophylaxis and therapy, scar care, for

Figure 9 – Intraoperative aspects of split thickness grafts from head area.
example through external agents, compression garments and
the specific prophylaxis of scarred contractures in critical
locations (throat, face, hands, and joints) are the
fundamental pillars of multimodal rehabilitation [30,31,32].
Although physical deficiencies are most important, the
diagnosis and treatment of posttraumatic stress symptoms
play a significant role in rehabilitation therapy as well [32].
Over 60% of all severely burned patients develop
posttraumatic psychological problems [33] which in puberty
can sometimes lead to suicide. Therefore, pediatric
psychiatrists and psychotherapists should be permanent
team members on burn wards.

Late complications. Secondary Therapies

Generally in severely burned patients, a
differentiation must be made between functional and
aesthetic late complications. The extensive and deep loss of
skin is the source of most problems. Scarring of areas not
given surgery, or scar formation within the graft, lead to
symptoms which can affect patients’ quality of life. If deep
dermal burns are not identified as such and are wrongly
given conservative treatment, scar contractures may form.
These contractures may lead to disfigurement and/or
functional impairment, depending on the localization.

The consequences of the loss of skin and the
resulting surgery are more severe: burns and scalds near
joints can often make them less mobile. Scarred strands
along longitudinal axes over the flexor and extensor sides of
joints cause overextension or flexion contractures,
preventing adequate mobility. Smaller joints may be
permanently and irreversibly damaged by contractures.
After the acute phase, this may have to be corrected by
plastic surgery. Numerous techniques have been described
for the prolongation of scar strands.

In some cases, it may be necessary to pre-stretch
healthy adjacent skin (expander). The resulting excess skin
can be used to replace the scar strand. As transplanted skin
often develops contractures, skin transplantation should not
be repeated, as this can lead to relapses.

Esthetic complications

In the long term, many patients suffer from their
changed appearance. Burns of the face and hands are felt as
especially disturbing, as they are continuously visible to
other people. Therefore, for example, no meshed split-
thickness skin grafts should be used on the face and hands.
The donor skin site should have the same texture as the
recipient site. For example, a donor site with low
pigmentation should be selected for a site with low
pigmentation.

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TREATMENT OF VASCULAR ANOMALIES IN CHILDREN WITH ORAL PROPRANOLOL: PROS AND CONS

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Abstract

Introduction: Most vascular anomalies are clinically easy to recognize. The age is the most prominent element to take into consideration for the diagnostic. Lesions differ by the moment of appearance: congenital hemangiomas and hemangioendotheliomas (occurred at birth); lymphatic- and venous malformations (emerged in the first week of life-unprogressive), infantile hemangiomas (emerged in the first week of life-fast evolutive) and arterio-venous malformations (appeared throughout childhood). One may diagnose up to 90% of cases based on aspect (color, depth, local temperature, presence of murmur). Doppler ultrasound and MRI may help in difficult cases. Materials and methods: We performed a prospective study of 54 cases with vascular anomalies from May 2010 to April 2013. Thirty-six girls and 18 boys treated with Propranolol – unselective beta-blocker. There were 50 vascular tumors and 4 vascular malformations. All patients underwent ECG and echocardiography before first visit. Four patients excluded based on consent withdrawal. Results: Treatment: age m=9,24 months, duration m=9,15 months and response: very good-66,66%, good-12,96%, partial-7,40%, no response-9,25% and aggravation-3,70%. As a conclusion, our results support the use of Propranolol in vascular anomalies. Key words: vascular anomalies, Propranolol, treatment, children

In the early 1960s, James W. Black\textsuperscript{3} synthesized Propranolol and ever since, it has been used extensively in pediatric cardiology on children and neonates. Forty-eight years later, in 2008, Leaute-Labreze due to an accidental association of infantile hemangiomas to Propranolol, published successful results with this association\textsuperscript{8}. Therefore, indications for Propranolol use have exceeded the spectrum of cardiology\textsuperscript{7}. The drug posology includes migraines\textsuperscript{4}, infantile hemangiomas\textsuperscript{5}, portal hypertension\textsuperscript{9}, post-traumatic stress disorder\textsuperscript{10} and cancer\textsuperscript{11,12}.

Material and methods

Fifty-four children with vascular anomalies received oral Propranolol in between May 2010 and April 2013. In all cases, an informed consent from the parents/guardians was needed. The lesions were photographed before treatment onset and at each subsequent visit. Inclusion criteria were vascular anomalies with difficult surgical approach; high functional and esthetic risk lesions and complicated vascular tumors. Exclusion criteria included children previously treated with local or systemic corticosteroids and cardio-respiratory comorbidities.

Unselective beta-blocker treatment was administered in 36 girls and 18 boys. Forty-three patients had infantile hemangiomas, 6 congenital hemangiomas, 1 kaposiform hemangioendothelioma, 3 capillary malformations and 1 venous malformation. Prior to drug administration, all patients underwent cardiologic and dermatological evaluation. ECG and echocardiography were compulsory.

Therapeutic protocol: Propranolol was initiated with 1 mg/kg/day divided into 3 equal parts - day1 and 2 mg/kg/day divided into 3 equal parts starting from day 2 throughout the rest of the treatment. We initiated the treatment in the Department of Pediatric Cardiology. The blood pressure, glycemia and heart rate were carefully monitored in order to avoid complications. If the drug was well tolerated the treatment was continued on an outpatient base.

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The patient was brought in for a first follow-up visit after a week of treatment and, each subsequent month. Monthly, we evaluated the clinical and photographic evolution of the lesions and monitored the heart rate, blood pressure, ECG and glycemia. Echocardiogram was performed, again, after 2 months of treatment. Withdrawal from study was possible whenever the patient was cured; vascular malformations were with no clinical response or in the case of refuse to continue.

The outcome of each lesion was defined by its status at the last recorded visit. Outcomes are classified as: (1) very good – final observation indicates that the lesion has more than 95% healing, (2) good – lesion with more than 75% healing, (3) partial – lesion with less than 50% healing, (4) no response, (5) aggravation-proliferation under treatment.

**Results**

Localization: facial 35,19%; thorax 16,67%; upper limb 9,26%; lower limb 12,96%; multifocal 25,93%. The treatment did not affect blood pressure and heart rate. Adverse effects were noted in 6 cases as dyspnea and cough; and one case accused sleep disorders. Thirty-six of 54 have completed the treatment (Figure 1). Four cases were withdrawn based on parental/guardian decision and 2 cases with capillary malformation were withdrawn after 3 months of treatment.

**Localization:**
- Facial: 35.19%
- Thorax: 16.67%
- Upper limb: 9.26%
- Lower limb: 12.96%
- Multifocal: 25.93%

**Overall mean age for Propranolol treatment onset:**
- 9.24 months (2 weeks-8 years) with 5.52 months for infantile hemangioma and 34.21 months for all other vascular anomalies. Main reasons for Propranolol treatment were: 44.44% esthetics, 27.78% functional, 27.78% local or general complications.

In two cases with infantile hemangioma, aggravation was encountered due to vascular proliferation. There were no side effects concerning hypoglycemia, bradycardia and electrolyte disorders.

**Figure 1. Completed treatment (36/54 patients).**

**Results:**
- In two cases with infantile hemangioma, aggravation was encountered due to vascular proliferation. There were no side effects concerning hypoglycemia, bradycardia and electrolyte disorders.

**One case, with PHACE syndrome, had a favorable outcome with healing of the lower lip ulcerated hemangioma after 1 month of treatment (Figure 2).**

**Figure 2. PHACE syndrome:**
- a – before treatment
- b – after 5 days
- c – after 6 months
Out of the 6 cases with dyspnea only two were excluded from the treatment schedule, as there was no improvement and 1 had Klippel-Trenaunay syndrome. The other 4 presented temporary dyspnea during intercurrent respiratory infections and the beta-blocker was temporarily stopped. The treatment with Propranolol was reintroduced with favorable outcomes.

All three cases with capillary malformations were unresponsive to treatment. Out of the 43 patients with infantile hemangioma 74,41% had a very good response to treatment after a mean duration of 8,16 months. There were four cases of infantile hemangioma (2 cases – no response to oral treatment, 2 cases – aggravation under treatment) and a case of venous malformation (Figure 3) that underwent surgical procedures.

Overall outcomes are: very good - 66,66%, good - 12,96%, partial - 7,40%, no response - 9,25%, aggravation - 3,70%.

Discussions

The etiology and pathogenesis of vascular anomalies together with the action of Propranolol remains unknown. New theories focus on progenitor cells, derangement of angiogenesis, mutation in the cytokine regulatory pathway, and developmental field defects. The methods of treatment for vascular malformations includes: systemic corticotherapy, bleomycin, vincristine, cyclophosphamide, interferon α, laser therapy, cryotherapy, surgical excision, radiotherapy and Propranolol. Until recently, first line therapy for complicated infantile hemangioma was systemic corticosteroids. Due to numerous complications (aseptic necrosis of the femoral head, diabetes, osteoporosis, adrenal insufficiency, cataracts, glaucoma, infection, gastric irritation, elevated blood pressure, Cushing-like aspect, and hypothalamic-pituitary-adrenal axis suppression) we exclude such therapy from our study.

We decided to use Propranolol as first step in treatment of vascular anomalies. There are some reports concerning side effects for Propranolol usage, but we had no major complications in our study.

Potential explanations for the therapeutic effect of Propranolol on infantile hemangioma include vasoconstriction, which is immediately visible as a change in color, associated with a palpable softening of the hemangioma. Laute-Labreze et al in 2008 mention that the mean age of treatment onset was of 2-6 months, whereas Sans et al 2009 reported 4,2 months and 31 months; Theletsane et al 2009-6 weeks; Mazereeuw-Hautier J et al. 2010; 4 months; Bigorre et al 2009 6 weeks-13 months; Leboulanger N et al 2010; 5,2 months Vlastarakos et al 2012; 5,1 months comparable to our results. Christine Leauté-Labrèze et al 2008 reported a treatment duration with beta-blocker of 3-10 months, period comparable to our results. Thus, diagnosis was made in an efficient manner.

Aggravation under Propranolol treatment was encountered in 2 cases, one of which the dosage was diminished by caregivers (< 1 mg/kg/day) and the other in which we found no explanation. Compared to these, Bagazgoitia et al. found a relapse of 19% after ceasing treatment with Propranolol.

Even though there are pros and cons against Propranolol, our results encourage in prescribing and using Propranolol in children.

Conclusions

For the past 40 years, the use of Propranolol has been shown to be safe in children with cardiac disease. Even though Propranolol is the first intention for infantile hemangioma and congenital hemangioma, it is not recommended for capillary and venous malformations.
RCT should be developed to compare propranolol to corticosteroid therapy. Ongoing research will bring us closer to the understanding of hemangiomas’ formation, which will provide opportunities for personalized therapies.

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SACROCCYGEAL TERATOMA SURGICAL TREATMENT - A FIVE YEARS EXPERIENCE

Radu-Iulian Spataru¹, Niculina Bratu¹, Cristina-Ioana Nisipasu², Dan-Alexandru Iozsa¹

Abstract

Introduction Sacrococcygeal teratoma represent the most common neonatal neoplasm. Females are more 4 times more likely to present this type of tumor. Altman’s classification divides sacrococcygeal teratoma into 4 types. Alpha-fetoprotein is the most common biological marker for evaluating SCT’s malignancy and follow up. Tumor removal together with the coccyx is the standard surgical procedure for SCT treatment. Aim The aim of this study is presenting our experience with SCT between 2005 and 2009. Materials and Methods Fourteen consecutive cases treated by our surgical team in 5 years are presented in this analysis. Age at presentation and age at surgery, Altman’s classification, alpha-fetoprotein levels and surgical procedure and 1 year follow-up events were parameters used in our retrospective study. Results Mean age at presentation was 12 months. According to Altman’s classification we treated 6 cases of type I, 4 cases of type II, 1 case of type III and 3 cases of type IV. In 4 cases delay of the diagnosis and treatment led to malignant transformation and subsequent chemotherapy. Among these local recurrence was noted after the oncologic treatment, these two being evaluated for further therapy. Conclusion Early diagnosis and treatment and careful postoperative follow-up are mandatory for good results in SCT treatment. Key words: sacrococcygeal teratoma, Altman classification, neonatal tumor

Introduction

Sacrococcygeal teratoma (SCT) is the most common neoplasm in the neonatal period having an incidence of 1 to 40,000 births. Its malignancy depends on the age, increasing from 10% in neonatal period to almost 70% in the second month of life. Females are 4 times more frequently affected than males [1]. Most of the SCT are present at birth as a sacral mass, but some of them – the total intrapelvic ones - can be discovered late after as a misleading presentation of urinary or intestinal obstruction [2]. In the last years, antenatal diagnosis was achieved in more than 50% of the pediatric population, because of the evolution of imagistics [3]. In 1974, Altman, et al. [4] divided the SCT, depending on the tumor localization, in 4 types: I (tumors with a predominant external component – sacrococcygeal and a minimum presacral part), II (tumors which present externally but having a large intrapelvic extension also), III (tumors who appear to be external but the dominant mass was pelvic with intraabdominal extension) and IV (tumors presenting completely presacral with no external development. Recent studies showed no link between Altman’s subtypes of SCT, their structure (cystic/solid) and the malignant potential of the tumor. [1] However, Altman’s classification remains the most known descriptive classification of teratomas. AFP levels is the most common SCT marker. Its elevated levels can also bring useful hints about tumor recurrence or malignant degeneration. In infants AFP levels are normally elevated in the first 8 months of life while the mean time required for AFP to normalize after SCT resection is about 9 months. Early excision of SCT together with the coccyx is the surgical procedure of choice for this malignancy. [5]

Aim Our aim is to determine which aspects in treating SCT could bring favorable results and prevent recurrences of the malignancy.

Materials and methods

We studied the 14 cases of SCT treated by a single surgical team between 2005 and 2009 (Table 1). Age at presentation and age at surgery were parameters included in this retrospective study. Gender was also noted. All patients were classified according to Altman’s algorithm. Alphafetoprotein (AFP) levels were analyzed before and after surgery at 1 week, 1 month, 6 months and 1 year. Surgical procedure performed, complementary oncologic treatment and recurrence at 1 year postoperative were also factors included in this report.

Results

The mean age of presentation was ~1 year and the median age was ~1 year and 7 months. Sex ratio was M:F 4:10. We performed the surgery in approximately 2 days from the admission. According to Altman’s classification 6 patients (~42%) were type I (Fig.1), 3 patients (~21%) were type II (Fig.2), 1 (~7%) was type III (Fig.3), 3 patients (~21%) were type IV (Fig.4). In Altman I type mean age at presentation was 1.8 days, while the mean age at presentation for the other types of SCT were: approximately 2 years and 2 months for Altman II and 1 year and 2 months for Altman IV.

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Figure 1. Clinical aspects in type I SCT.

Figure 2. Computer tomography aspects of type II Altman SCT.

Figure 3. a. Removed specimen of Altman III SCT together with the coccyx (note the significant intrapelvic extension). b. Postoperative view after excision.

Figure 4. CT aspect of a type 4 SCT.
AFP was detected positive in 12 out of 14 cases at admission. In 3 cases AFP was still positive 6 months after surgery. These patients were operated and diagnosed in the first 5 days of life.

In all patients tumor removal together with the coccyx was performed.

In the neonates, all of the classified into Altman I type, days spent until surgery were about 2, while in the others days passed for admission to surgery were approximately 5 (Table I).

Only 2 patients out of 14 presented 1 year recurrence after surgical treatment, one of them despite the chemotherapy performed. One of them was Altman III detected at more than 2 years old and the other one was Altman IV diagnosed at 1 year and 1 month.

None of the patients were included in Currrarino triad syndrome or associated any anorectal malformations.

Table 1. Main aspects studied in SCT series.

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>Gender</th>
<th>Days till surgery (in hospital)</th>
<th>AFP detection: admission/6 months followup</th>
<th>Altman’s classification</th>
<th>Chemotherapy</th>
<th>Recurrence 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1 day M</td>
<td>1</td>
<td>+/+</td>
<td>I</td>
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<tr>
<td>2 1 day F</td>
<td>2</td>
<td>+/-</td>
<td>I</td>
<td>-</td>
<td></td>
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<tr>
<td>3 1 day F</td>
<td>2</td>
<td>+/+</td>
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<tr>
<td>4 1 day M</td>
<td>2</td>
<td>+/-</td>
<td>I</td>
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<td>5 2 days F</td>
<td>3</td>
<td>+/-</td>
<td>I</td>
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</tr>
<tr>
<td>6 5 days F</td>
<td>2</td>
<td>+/-</td>
<td>I</td>
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<tr>
<td>7 1 year 10 months M</td>
<td>5</td>
<td>+/-</td>
<td>II</td>
<td>-</td>
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<tr>
<td>8 3 years 2 months F</td>
<td>2</td>
<td>+/-</td>
<td>II</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 2 years 1 month M</td>
<td>6</td>
<td>+/-</td>
<td>II</td>
<td>-</td>
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<tr>
<td>10 1 year 6 months F</td>
<td>4</td>
<td>+/-</td>
<td>II</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 2 years 2 months F</td>
<td>5</td>
<td>+/-</td>
<td>III</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>12 1 year 1 month F</td>
<td>8</td>
<td>+/-</td>
<td>IV</td>
<td>+</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>13 1 year 2 months F</td>
<td>3</td>
<td>+/-</td>
<td>IV</td>
<td>-</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>14 1 year 4 months F</td>
<td>4</td>
<td>+/-</td>
<td>IV</td>
<td>+</td>
<td>no</td>
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</tr>
</tbody>
</table>

Discussions
Rectal digital examination is an extremely useful step in clinical assessment of a child with chronic constipation. This easy procedure can prevent malignancy by early diagnosing presacral tumors.

All our Altman I SCTs were diagnosed immediately after birth and operated as soon as possible. There were no malignant transformation in these and no further recurrences. 50% percent of the cases diagnosed after the age of 1 year presented malignant transformation requiring postoperative chemotherapy treatment. There were no perioperative deaths in our series. We had three cases of recurrences after tumor excision without coccyx removal in other units. We performed the right excision and follow up showed good results.

Coccyx removal is a mandatory surgical step in SCT excision in order to prevent recurrences. Thorough dissection is necessary to prevent postoperative continence disorder and rectal wall injuries. Median sacral artery must be identified and carefully ligated. In the presence of an abdominal extension of the tumor, an abdomino-perineal approach is needed as we encountered in one case.

The idea stated by Altman, et al. [4] about the link between the age and SCT’s cancerous transformation is supported by more authors who recommend surgery as soon as possible after birth in order to prevent malignant transformation [6].

Conclusions
Early diagnosis and correct treatment is mandatory in order to prevent malignant transformation. A standardized follow-up protocol is recommended to early prevention of eventual recurrences. Multidisciplinary assessment of SCT – surgery, neonatology, oncology – brings excellent results in its treatment. We must emphasize that cases with no external appearance and abdomino-perineal involvement the rectal digital examination is an extremely useful tool.

References


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EFFICACY OF PROPRANOLOL IN DIFFUSE NEONATAL HEMANGIOMATOSIS WITH PREDOMINANT CENTRAL NERVOUS SYSTEM INVOLVEMENT – A CASE REPORT

Ioana-Cristina Nisipasu¹, Cosmin Nisipasu², Dan-Alexandru Iozsa³, Radu-Iulian Spataru³

Abstract
Diffuse hemangiomatosis is characterized by the presence of multiple mucosal and visceral hemangiomas. Usually, these are benign, but some of them can be harmful by their hemodynamic impact.

We present a rare case of neonatal diffuse hemangiomatosis with predominant central nervous system involvement who presented intracerebral hemorrhage, successfully treated with Propranolol.

Propranolol is a recently approved medication for infantile hemangiomas. In our case the treatment was successful and propranolol brought good results in treating malignant hemangiomas of the central nervous system.

Key words: neonatal diffuse hemangiomatosis, intracerebral hemorrhage, Propranolol

Introduction
Diffuse neonatal hemangiomatosis is a rare condition, defined by the presence of at least 5 cutaneous hemangiomas, under 5 mm diameter, that can be present at birth or appear in the first weeks of life. The clinical evolution is similar of infantile cutaneous hemangiomas. There are two subtypes: diffuse and benign. The diffuse hemangiomatosis is characterized by mucosal and visceral involvement (hepatic, central nervous system, gastrointestinal tract, lungs, eyes, etc.). The benign hemangiomatosis can have mucosal or visceral involvement, but without hemodynamic impact. Visceral involvement can lead to hemorrhagic complications, consumptive coagulation or congestive heart failure, being associated with high mortality [1]. Propranolol, a nonselective betablocker, has recently became the first line systemic therapy for infantile hemangiomas, due to it’s high efficacy and low risk of secondary reactions [2].

We present a case of neonatal diffuse hemangiomatosis with predominant central nervous system involvement successfully treated with Propranolol.

Case report
A 12 days old male, presenting with about 30 small cutaneous hemangiomas (Figure 1 and Figure 2), with diameter between 0,3 and 1 cm, bright red in color and a 0,5 cm gingival hemangioma. The lesions appeared soon after birth. The baby is from a twin pregnancy, his brother is perfectly healthy, without any cutaneous lesions.

Figure 1 and Figure 2. Five months infant presenting hemangiomatosis.

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Transfontanelle ultrasound reveals multiple nodular tumors (>10) with increased echogenicity, spreaded bilaterally in the white matter, with the highest diameter of 8 mm. Similar images can be seen in the cerebellum and the brain stem. All the lesions are well defined, with no interior signal.

Abdominal ultrasound didn’t reveal any hepatic tumors.

At 6 weeks old, the child present with altered general status and altered respiratory function. He required intubation and mechanical ventilation followed by tracheostomy. CT and MRI revealed an intracerebral hemorrhage (Figure 4-7).

Figure 3. Transfontanelle ultrasound – sagittal section, right paramedian sagittal section – multiple intracerebral nodular tumors.

Figure 4 and Figure 5. Cerebral Computer Tomography with contrast shows multiple diffuse intracerebral nodular tumors, with high, persistent, homogenous contrast. Some of them have signs of bleeding and perilezional edema.

Figure 6 and Figure 7. MRI-multiple diffuse intracerebral nodular tumors, some with bleeding signs.
Laryngeal endoscopy doesn’t find any hemangiomas at this level. Propranolol 2mg/kgC was started. At 5 months old, the child developed gastrointestinal reflux, followed by pneumonia. Bacterial cultures showed tracheostomy colonization by Pseudomonas and Staphylococcus. Systemic antibiotherapy was started with slow improvement of status. At 6 month old is detubation is possible and at 8 months old the child was discharged from hospital. Propranolol treatment was continued for two years, with fully recovery of the patient. The intracerebral hemangiomas left nodular cavernous lesions and the cutaneous hemangiomas over 1 cm left residual fibro-adipose tissue (Figure 8-10). One year after completing the treatment, the child has no psychomotor deficit, just a slight growth delay comparing with his twin brother. No adverse effects of treatment were noted.

Figure 8 and Figure 9. Cerebral MRI 3 years old- right insular residual cavity. Multiple nodular cavernous lesions.

Figure 10. Cutaneous hemangiomas over 1 cm left residual fibro-adipose tissue.

**Discussions**

Diffuse neonatal hemangiomatosis with predominant central nervous system involvement is a rare disease, with high mortality due to hemorrhagic complications. Risk factors are unknown, male:female ratio is 2:1 and genetic transmission was not observed [1].

Propranolol is a recently approved medication for infantile hemangiomas. The mechanism of action is not fully understood. It inhibits the adrenergic response by competitive blocking beta-1 miocardic receptors and beta-2 bronchial and vascular smooth muscles receptors. Both receptors were found in cutaneous hemangiomas but the exact mechanism of action has not been identified [3].
Propranolol has also been reported to bring good results in treating hemangiomas where cosmetic surgery was difficult (like facial region) or for reduction of the tumoral mass and easier excision where dissection was difficult [4].

From our knowledge, this is the only case published of diffuse neonatal hemangiomatosis with predominant nervous system involvement treated with Propranolol.

Conclusions

Imagistic evaluation is mandatory in children with multiple cutaneous hemangiomas.

Although the skin and liver are most frequently affected by neonatal diffuse hemangiomatosis, the central nervous system involvement should be evaluated and if tumours are present, treatment should promptly be initiated in order to prevent hemorrhagic complications.

Propranolol is an efficient and safe therapeutic method for neonatal diffuse hemangiomatosis.

References


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THE IMPACT OF POLYCYSTIC OVARY SYNDROME IN ADOLESCENT GIRLS

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is a common endocrinology disorder in adolescence.

Objectives: To assess the phenotypes and biochemical parameters among adolescent girls diagnosed with PCOS and to estimate the metabolic syndrome among these cases.

Methods: Adolescent girls hospitalized in the Endocrinology Department of Children Emergency Hospital, Timisoara were evaluated clinically, anthropometric (height, weight, BMI), hormonal (estrogen, progesterone, testosterone, LH, FSH, SHBG, FAI), metabolic (glucose, oral glucose tolerance test, insulin, HOMA and lipid profile) and ultrasound (polycystic ovaries) for 3 years.

Results: According to Rotterdam criteria, 37 girl adolescents (mean age 16.7 ± 1.9 years) were diagnosed with PCOS. 88.23% of them had a body mass index higher than 75% percentiles for age. All were associated with irregular cycle, 72.97% of them with hirsutism and acne and 51.35% with polycystic ovaries. High levels of LH, testosterone and FAI and low level of FSH and SHBG were encountered. Oral glucose tolerance test was altered in 24.32% patients, hyperinsulinemia was found in 16.21% of them. Dyslipemia was identified in 10.81% patients, while the metabolic syndrome in 8.10% cases. Metformin was prescribed at adolescents diagnosed with insulin resistance (29.41%).

Conclusions: The presence of PCOS imposed extensive metabolic and hormonal tests. The lifestyle changes and metformin are the first-line intervention in obese adolescents

Key words: polycystic ovaries, obesity, insulin resistance, metabolic syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is the most common female endocrine disorder, affecting approximately 5-10% of all females and 4-6% of adolescent girls and young women\textsuperscript{1}. It can be diagnosed in all phases of life - in young girls as 8-9 years of age till post-menopausal females. According to a common view PCOS is a multifactorial and polygenic in nature, but studies failed to identify genes responsible for PCOS\textsuperscript{2}.

PCOS is a hormonal disorder that involves multiple organ systems within the body, fact that explain the great variety of clinical presentations. Overproduction of ovarian androgens, increased luteinizing hormone secretion, incomplete maturation of ovarian follicle development and insulin resistance with compensatory hyperinsulinemia are some serious reproductive and metabolic. Common clinical findings include irregular menstrual cycles with anovulation, hirsutism and acne secondary to hyperandronism and polycystic ovaries. These symptoms can be accompanied by acanthosis nigricans, important sign of insulin resistance, obesity or infertility. Patients diagnosed with PCOS are predisposed to develop diabetes mellitus, endometrial carcinoma and cardiovascular disease\textsuperscript{3,4}.

Metabolic syndrome is associated with development of hyperandrogenism and PCOS, but the question is what was at the beginning: the metabolic syndrome or hyperandrogenism.

The symptoms of PCOS usually emerge at or soon after puberty, which may, in some cases, lead to a failure of diagnosis and potentially to a delay in the initiation of treatment.

Objective

The aims of this study were to assess the phenotypes and biochemical parameters among adolescent girls diagnosed with PCOS and to estimate the metabolic syndrome among these cases.

Material and methods

We performed a cross-sectional study of 37 adolescents (13-18 years old) with PCOS admitted in the Endocrinology Department of Children Emergency Hospital Timisoara from June 2011 to June 2014. These patients attained menarche more than 2 years before the study and were diagnosed with PCOS according to the Rotterdam\textsuperscript{2} criteria.

To put this diagnosis should present at least two of the following criteria:

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1. oligo- and/or anovulation (< 6-9 menses per year or menstrual cycles more than 35 days in length);
2. clinical hyperandrogenism (acne or modified Ferriman-Gallwey scores ≥ 8 over 9 body parts) and/or biochemical hyperandrogenism (serum total testosterone ≥ 2.6 nmol/l, free testosterone ≥ 6.0 pg/ml)
3. polycystic ovaries (the presence of ≥ 12 antral follicles in one ovary measuring 2-9 mm in diameter and/or ovarian volume ≥10 cm³)

Patients with abnormal cycle secondary to the congenital adrenal hyperplasia, androgen secreting tumors, Cushing’s syndrome and hypothyroidism were excluded from the study.

All patients enrolled in the study were clinically examined and were noted down aspects suggestive for the androgen status (hirsutism, temporal recession of hair, acne) and insulin resistance (acanthosis nigricans). Ferriman-Gallwey score and acne scores were assessed and calculated by at least two observers.

Weight, height, body mass index (BMI), waist and hip circumferences and blood pressure were measured after at least two observers.

After overnight fasting, blood samples were taken from adolescents in order to measure PRL, LH, FSH, estradiol, total testosterone, sex hormone-binding globulin (SHBG), DHEAS, 17-OHP, TSH and lipid profile. An oral glucose-tolerance test using 75 g of glucose was then performed and blood samples were taken at 0 and 120 min for glucose and insulin measurement. Manufacturer’s instructions were followed for preparation, set-up, dilutions, adjustments, assay, and quality control procedures.

HOMA-IR was calculated using this formula: fasting plasma glucose (mmol/l) × insulin (mU/ml)/22.5 and insulin resistance was defined as the HOMA-IR value ≥ 95th percentile. For the calculation of the Free Androgen Index (FAI), the next formula was used: total testosterone/SHBG × 100.

For the diagnosis of metabolic syndrome is requires the presence of three of the following criteria: waist circumference ≥80 cm, serum triglyceride ≥1.7 mmol/L, serum high-density lipoprotein cholesterol <1.3 mmol/L, blood pressure ≥130/85 mm Hg and fasting blood sugar of >100 g/dL³.

The pelvic transabdominal ultrasound examination was performed by the gynecologist in order to evaluate the ovaries aspects using a mechanical 6-MHz probe.

Statistical tests were performed using SPPP version 19.00. This study was approved by the institutional review board of the Hospital and the informed consent was signed by the parents of the patients.

Results

A total of 37 patients fulfilled the inclusion study and were invited to participate to the study (Table no.1). The mean age of the patients was 16.7 (± 1.9) years, majority of them (81.08%) were from the urban area. Their mean age at menarche was 13.5 (±1.4) years and these girls were diagnosed with PCOS at 3.5 (±1.7) years after the menarche. Regarding the family history, almost a quarter of adolescent girls had their mother or sibyls diagnosed with hirsutism or PCOS.

Table no.1 The prevalence of the aspects characteristic for PCOS.

<table>
<thead>
<tr>
<th>Aspects</th>
<th>Number of patients</th>
<th>Percent of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular cycle</td>
<td>37</td>
<td>100%</td>
</tr>
<tr>
<td>Hirsutism, acne</td>
<td>27</td>
<td>72.97%</td>
</tr>
<tr>
<td>Biochemical hyperandrogenemia</td>
<td>23</td>
<td>62.16%</td>
</tr>
<tr>
<td>Ultrasound aspects of polycystic ovaries</td>
<td>19</td>
<td>51.35%</td>
</tr>
</tbody>
</table>

The duration of the cycle ranges between 35 and 43 days with a mean of 37.2±1.8 days. Acne was found in the majority of cases (64.86%) and the mean Ferriman-Gallwey scores was 13.5 (Table no.2). Among those who underwent clinical and ultrasound assessment, the characteristic aspects of polycystic ovary was detected in 51.35% patients suspected to have PCOS using Rotterdam criteria. All four signs/symptoms specific for PCOS were present in only 13.51% of the cases, 48.65% had three and majority (37.83%) had two symptoms/signs.

Table no.2 Clinical parameters of patients diagnosed with PCOS.

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>31.7 ±2.6</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>79.1±1.3</td>
</tr>
<tr>
<td>Ferriman-Gallwey score</td>
<td>13.5±8</td>
</tr>
<tr>
<td>Global acne scores</td>
<td>5.3±4.2</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>110±14</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>71±3</td>
</tr>
</tbody>
</table>
Among patients diagnosed with PCOS, 18.91% were non-obese, 29.72% cases were overweight (BMI between 75\textsuperscript{th} - 97\textsuperscript{th} percentiles) and 51.37% were obese (BMI \geq 97\textsuperscript{th} percentiles). 16.21% of adolescents had hirsutism, while 56.75% of girls presented abdominal adiposity/central adiposity. The blood pressure was higher than the 95\textsuperscript{th} percentiles for age and sex in 10.81% of cases.

In table no.3 the increased serum level of LH and testosterone and high FAI can be observed, while level of FSH and SHBG were decreased. The mean plasma glucose levels were normal in all PCOS cases except 9 patients (24.32\%), where 2 h post 75 g plasma glucose value was above 140 g/dL. Hyperinsulinemia was present among 16.21\% cases and 10.81\% had serum triglycerides above normal. Insulin resistance was encountered in 18.91\% of adolescent girls and 8.10 \% of them were diagnosed with metabolic syndrome.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
<th>Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH mIU/mL</td>
<td>3.9±1.2</td>
<td>Fasting blood sugar g/dL</td>
<td>74.2±7.5</td>
</tr>
<tr>
<td>LH mIU/mL</td>
<td>9.1±3.8</td>
<td>2-h post 75 g glucose g/dL</td>
<td>121.8±8.9</td>
</tr>
<tr>
<td>FSH/LH ratio</td>
<td>&gt;2.7</td>
<td>Insulin µU/mL</td>
<td>14.1±10.2</td>
</tr>
<tr>
<td>Testosterone ng/mL</td>
<td>0.56±0.21</td>
<td>HDL mg/dL</td>
<td>47.7±6.7</td>
</tr>
<tr>
<td>SHBG nmol/L</td>
<td>52.6±24.3</td>
<td>Triglyceride mg/dL</td>
<td>68.4±14.6</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>4.3±2.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistically, significant differences were observed between overweight and obese patients and non-obese PCOS girls regarding symptoms and biochemical and hormonal parameters. Obese and overweight girls were more hirsute (40.5\%) and hypertensive (8.10\%) and had higher mean values of post 75 g glucose and insulin and lower levels of SHBG compared with non-obese and the differences were statistically significant (p<0.05). No differences were found in the lipid profile of these two groups.

A hypocaloric diet with low carbohydrates and lipids intake was recommended for all overweight and obese girls, metformin were prescribed for all the patients with insulin resistance and oral contraceptives for the patients with polycystic ovaries.

Discussion:
The first report about seven women with amenorrhea hirsutism and bilateral polycystic ovaries was published by Stein and Leventhal in 1935\textsuperscript{7}. Since then, the definition of PCOS has undergone several changes. According to the National Institutes of Health consensus conference held in 1990, the definition of PCOS consisted in the association of the chronic anovulation with clinical and/or biochemical hyperandrogenism\textsuperscript{8}. In the year 2003, the Rotterdam European Society for Human Reproduction/ American Society of Reproductive Medicine proposed that the diagnosis of PCOS should include two of the following three criteria: oligo- and/or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovaries on ultrasound\textsuperscript{9}. More recently, in 2009, the Androgen Excess and PCOS Society defined PCOS as a hyperandrogenic disturbance which included hyperandrogenism and ovarian dysfunction\textsuperscript{10}.

We used in this study the Rotterdam criteria to define PCOS because it extended the diagnosis to women polycystic ovaries with oligo-ovulation (non hyperandrogenic), as well as to women with hyperandrogenism, fact that allows us to study a great number of patients.

Because a history of menstrual irregularity is considered normal in the first 1-2 years after menarche secondary to anovulation, we decided to analyze only adolescent girls with oligomenorrhea more than 2 years postmenarche, this period of time being considered a good screening indicator to diagnose PCOS. Acne, the first sign of hyperandrogenism manifested in the adolescent and hirsutism observed in our patients examined were suggestive for the clinical hyperandrogenism, while the biological form suggested by the increased serum level of total and free testosterone were presented in the majority of the adolescents. 51.35\% of girls were diagnosed at ultrasound with polycystic ovaries, but at 21.62\% of patients, the ovarian morphology did not corresponded to the criteria of Rotterdam regarding the size or the number of the follicles.

The disease was confirmed if all three signs/symptoms specific to PCOS were presented, fact observed in 48.65\% of cases and the diagnosis was considered when only two signs/symptoms were observed\textsuperscript{11}.

According to the medical literature, prenatal exposure to androgens demonstrated in animal studies and in daughters of PCOS mothers and peripubertal obesity are important predisposing factors, which was observed in almost 25\% of girls whose mother or sibyls had a history of PCOS and 88.23\% of them had the BMI higher than 75\% percentiles for age and sex\textsuperscript{12,13}.

Almost 80\% of our adolescent girls with PCOS were obese, although this is not a criteria required for the diagnosis. It is well known that obesity plays an important role in PCOS contributing to hyperandrogenism, anovulatory cycles and infertility. Studies demonstrated that centrally deposited fat is metabolically active, releasing inflammatory cytokines being responsible for the adverse metabolic effects\textsuperscript{14}. It worsens the underlying insulin resistance and insulin resistance-associated reproductive and metabolic features\textsuperscript{15}. The pathophysiologic mechanism is
related to hyperinsulinemia induced by insulin resistance independent of the presence of the obesity\textsuperscript{16}. In our study, the central obesity was highly associated with increased value of insulin, insulin resistance and metabolic syndrome.

PCOS can develop many complications such as insulin resistance and compensatory hyperinsulinemia, impaired glucose tolerance, dyslipidemia and metabolic syndrome. In order to prevent these serious disturbances, it is necessary to identify them as soon as possible and to take measures. Regarding the metabolic complications, we identified in this study a high prevalence of impaired glucose tolerance (24.32%), insulin resistance (18.91%), hyperinsulinemia (16.21%), dyslipidemia (10.81%) and metabolic syndrome (8.10 %). No patient was diagnosed with type 2 diabetes.

Similar prevalence of impaired glucose tolerance in obese adolescents with PCOS such as 29.6% and 27.3%, respectively\textsuperscript{17,18} have been identified in two American studies. In a study enterprise in Turkey, in which obese and non-obese adolescents with PCOS were compared, increased values of blood pressure and blood serum levels of fasting insulin, lipids and testosterone were encountered in the obese group, much alike with our study results\textsuperscript{19}.

As PCOS is associated with a 10-fold risk to develop type 2 diabetes and a 2-fold increased rate of metabolic syndrome in adulthood, it is important to treat these adolescents\textsuperscript{20,21}.

It is important to keep in mind that insulin resistance and impaired glucose tolerance are important precursors to type 2 diabetes mellitus so quick measures should be taken. Lifestyle changes are a first-line intervention in adolescents with PCOS and consisted in diet, exercise, and appropriate weight control. The medication used in PCOS consisted in Metformin and oral contraceptives. Metformin prescribe in doses varying from 1.5 to 2.5 mg/day and divided into 2or 3 doses improve insulin resistance, hyperandrogenemia, and in some cases, anovulation, while decreasing hyperinsulinemia. Contraceptives (estrogen-progestin combination pills) are used for management of oligomenorrhea or amenorrhea and good results were obtained in patients with hirsutism and acne.

Conclusions:
1. PCOS is the most frequent endocrinology disorder diagnosed in adolescent girls and should be considered when irregular menses, excess weight, acanthosis nigricans or hirsutism are presented.
2. PCOS in adolescents imposed the testing for glucose intolerance and dyslipidemia particularly in the presence of obesity.
3. Lifestyle changes are the first-line intervention in young women with PCOS, who are overweight.
4. Management of the PCOS adolescent with metformin is beneficial and well tolerated.

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LANGERHANS CELLS HISTIOCYTOSIS

– A CASE REPORT

Fuicu Păun¹, Bota Constantin², Dumitru Ionuţ-Adrian²

Abstract

Langerhans cell histiocytosis (HCL) is a disease characterized by proliferation of cells belonging to the phagocyte – mononuclear cell system. HCL is a more precise term for histiocytosis X, 'X' because the exact pathogenesis and cause of the disease is unknown. In this article we present a 16 years old patient, from rural areas that are hospitalized in our department of “Louis Turcanu” Emergency Hospital for Children Timisoara, for a tumor in the right parietal region of head, which appeared one month before admission. Results: The histopathological appearance of eosinophilic granuloma advocates for Langerhans cell histiocytosis and is confirmed by results of immunohistochemical reactions. The patient received surgical treatment consisting in ablation of the tumor until. Conclusions: The particularity of the case lies in the rarity of this disease, its unique location and a relatively short-time recovery of the patient.

Key words: histiocytosis, Langerhans cells, eosinophilic granuloma

Introduction

Langerhans cell histiocytosis (HCL) is a disease characterized by proliferation of cells belonging to the monocyte-phagocyte system. HCL term is used as a synonym for histiocytosis X. It combines several syndromes in a single entity, such as Hand-Schüller-Christian Syndrome, Letterer-Siwe disease, eosinophilic granuloma, Hashimoto-Pritzker Syndrome, purely cutaneous histiocytosis[1]. The annual incidence of this disease is estimated at about four cases per 1 million, predominantly for males. This disease can affect any age group, but most cases occur during childhood and the average age at diagnosis being 2-3 years. In general, the acute forms occur before the age of 3 years, and about half of the cases of bone lesions occur before the age of 5[2,3]. The first case was published in 1893 by Hand. In 1921, Hand reported 6 cases with bone lesions, exophthalmia and polyuria. Subsequently, Letterer (1924) and Siwe (1933) described several cases with fever, hepatomegalgy, adeno-splenomegalgy and bone injuries, with fatal outcome. At autopsy examination were discovered massive histiocytic infiltrate. In 1942 Farber describes eosinophilic granuloma of bone. Langerhans cell histiocytosis term was introduced in 1985 and reflects the essential role of these cells in disease pathogenesis[2,3].

In histopathological terms, the lesion is represented by granulomas consisting of histiocytes, lymphocytes, eosinophilic cells, neutrophilic cells and plasma. The histological appearance varies according to the different disease stage and location. The initial proliferative lesion consists mainly of histiocytes without a histological criteria of malignancy. Sometimes mitotic figures can be identified in the cytoplasm. A low percentage of histiocytes is represented by abnormal Langerhans cells[4,5]. As the lesion progresses, the granulocyte infiltration is dominated by eosinophils and areas of necrosis may occur. During the late stage, histological fibrosis and xantomatosis changes are predominant and the Langerhans cells disappear. Multinucleated giant cells can sometimes be seen in the bone or lymph node areas. The identification of those Langerhans cells, which is considered a pathognomonic sign, can in most cases be done by electron microscopy.[6,7,8]

Some immunohistochemical features for Langerhans cells, whether normal or pathological, is the existence of a positive CD1 antigen, S100 protein and the antigen 1a. In the clinical appearance, the most common areas of these cells include: skull, long bones, pelvis, ribs and vertebrae. These osteolytic lesions may be accompanied by pain, swelling of local tissues, fractures (if an affected bone) or they can be asymptomatic. If the location is the skin, the lesion is common in the acute disseminated forms.[7] The rash may be papular-crusted, scaly or pustulovesicular and it is often confused with seborrheic dermatitis. In cases of dermatitis, which do not respond to the treatment, a HCL should be suspected. Skin areas of common interest are: scalp, folds of flexion, trunk and postauriculara region. Lesions may be generalized in advanced stages. Diabetes insipidus is the most common associated endocrine disease. Although, for a definitive diagnosis, histopathological studies, including Birbeck granules and CD1a antigen are needed.[9,10]

Case presentation

Patient, R.I., 16 years old male, was admitted in our hospital for: tumor in the right parietal bone, with all common signs of local inflammation, including redness, heat, pain and swelling. We noted that the onset was sudden, about a month ago, with local inflammatory signs and a tumor in the right parietal fossa.
The family and personal history, both physiological and pathological, are insignificant. During hospital admission, the physical examination revealed a good general condition, the patient was afebrile and had a good appetite. The inspection of the parietal region revealed that the tumor is soft, elastic, about 3/2 cm, painless on palpation. The laboratory investigations showed a slight increase in Hgb (14.6 g/dl), elevated creatinine (53mg/100ml), increased uric acid (37mg/100ml) and increased alkaline phosphatase (158UI). The radiological examination (Fig.1) of the skull could identify lack of bone tissue, oval, 3/2 cm, well defined, with a moderate osteosclerotica form located in the right parietal fossa. NPI evaluation observed defects of the bone in the right parietal region and no signs of neurologic impact (ataxia, paralysis, paresthesia), the recommended affiliating treatment consisting of: Vitamin C 3x 1 capsule/day, Vitamin B6 (250 mg), following the 0-1-0 scheme, and Tarosin 3x 1 capsule/day. The thoracic radiograph did not reveal anything pathological. The positive diagnosis is supported clinical and through the laboratory findings, especially the histopathology one. A unifocal bone disease, as in this case, most often heal with or without treatment. Very rarely there is an indication for the progression of the bone lesion or for the recurrence in the other bone sites. After initial location, no other systemic relapses were reported. The differential diagnostic is made with the acute or chronic osteomyelitis, multiple myeloma, bone cyst, bone tuberculosis, malignant bone tumors or other tumors. Generally, the treatment is surgically and in this case, it consists in removal of the tumor up to the growth defect. The necessary biopsy material was collected. After the surgery was established, the patient had to undergo analgesic and anti-inflammatory treatment. The early diagnosis increases the chances of healing and ensures a good result (Fig. 2).

Fig. 1. Skull x-ray could identify lack of bone tissue, oval, 3/2 cm, well defined, with a moderate osteosclerotica form located in the right parietal fossa.

Fig. 2. Clinical appearance one month after treatment. This case has received radical surgical treatment without the need for adjuvant therapy due to its clinical and histopathological particular form; healing took place without any complications and sequelae.
Prognosis: In case of a multifocal onset of the disease, the evolution is chronic and the relapse can be unique or multiple. In these cases, the major risk of recurrence is 60% between 1 and 4 years, 20% in the first year after finding the diagnosis and 15% over four years[11]. The sequelae, which occur more frequently, are: diabetes insipidus, dental disease and chronic media otitis.

Time, age, organ dysfunction and extent of the disease are always considered important factors for the prognosis[12]. The invaded organ, which is dysfunctional, is a prognostic factor. Cytopenia, secondary to medular and liver invasion, related to jaundice is associated with a high mortality rate. If the localizations are exclusively bone or skin, whether they are single or multiple, the prognosis is extremely good.

Complications: anemia due to bone marrow infiltration, damage to the pituitary gland, causing growth deficiency, diabetes insipidus, lung problems, which may progress to severe breathing difficulties.[13]

Discussions and Conclusions
The early diagnosis of Langerhans cell histiocytosis is extremely important, especially in the acute form, because of the successful treatment, which depends on the moment of the diagnosis.

The positive diagnosis of the histiocytosis requires full clinical observation and histopathological examination. Currently, the immunohistochemical techniques give a certain diagnosis by showing the S100 protein, antigen CD1a, and Langerin in the histiocite belonging to the characteristic proliferative disease.

Sometimes, there is a discussion about the fact that the two clinical forms, the localized one and the disseminated form, received the generic name of histiocytosis and that because of the emphasis in both cases of the Birbeck granules, visible in electron microscopy and specific markers (immunohistochemical techniques)[14].

We reviewed this case because of the rarity of the disease, the unknown etiology and because the recovery was made in a relatively short period of time.

We all need to know that the symptoms are different in Langerhans cell histiocytosis (depending of its localization) and the prognosis depends on the patient's age and the number of the affected organs. In this disease there may be a single organ or system affected, but there are cases in which several organs and systems are affected, that may cause their dysfunction. The diagnosis always depends on the histopathological outcome and generally the treatment is surgical.

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CORRELATION BETWEEN REPEATED RED BLOOD CELLS TRANSFUSIONS AND SEVERE INTRAVENTRICULAR HEMORRHAGE IN PRETERM INFANTS WITH LOW BIRTH WEIGHT

Marioara Boia\textsuperscript{1,2}, Aniko Maria Manea\textsuperscript{1,2}, Mihaela Dobre\textsuperscript{1}, Daniela Cioboata\textsuperscript{1}

Abstract

Introduction: Red blood cell transfusions are extremely important in neonatal intensive care units, in many cases are lifesaving although that involves numerous risks. The literature cite increased incidence of disease forms after repeated transfusions of packed red blood cells. Some transfusion risks have been well defined; others less so and perhaps yet other risks are not even usually recognized as transfusion-related events. One of the most important life-threatening complications of RBC transfusions in premature infants is intraventricular hemorrhage, causing morbidity and mortality. Objectives: The aim of this study was to evaluate the severe intraventricular hemorrhage incidence after repeated transfusions of packed red blood cells in premature infants with low birth weight. Material and Methods: A retrospective study over a period of two years which included infants with birth weight<1500g and gestational age<32 weeks. The infants with coagulopathies and central nervous system malformations were excluded. The study group included 104 newborns divided into two groups: the study group -64 patients and control group-40 patients who had indications for red blood cell transfusions. All patients were performed transfontanelar ultrasound in dynamics. Results: Among infants who required RBC transfusions 24 patients (37.5\%) developed severe complications – worsening of intraventricular hemorrhage, ventriculomegaly, hydrocephalus, 8 of them (12.5\%) being extremely low birth weight (790-900g). These results arise a few controversial questions: are red blood cell transfusions fully responsible for the worsening of intraventricular hemorrhage? How can we differentiate IVH occurred after RBC transfusions and the IVH appeared as a complication of the associated pathology? Key words: red blood cell transfusions, intraventricular hemorrhage, premature infants

Introduction

It is well known that each transfusion administered conveys risks and benefits. Some transfusion risks have been well defined; others less so and perhaps yet other risks are not even usually recognized as transfusion – related events (1). Although the known infectious risks of RBC transfusions from each donor exposure are traditionally focused on, the infections risk are extremely small and are decreasing over time with improvements in donor screening and laboratory infection surveillance (2). Other complications of RBC transfusion can be intraventricular hemorrhage, necrotizing enterocolitis, lung injury, organ dysfunction, hemolytic transfusion reactions and transfusion related – sepsis (3). Some studies reported a higher mortality rate in children who received a transfusion compared with children and adolescents who did not received a transfusion. Many reports suggest that IVH is also associated with prematurity (4,5). After RBC transfusions, because of wide fluctuations in blood pressure and blood flow though the immature capillary beds associated withlow deformability of the erythrocytes are more likely to induce rupture and hemorrhage leading to long-term disabilities or even death.Banked RBC (even after a few days) develop “Storage Lesion” that involves less deformability and depletion of nitric oxidesynthese (6).

The incidence of the intraventricular hemorrhage is currently 15 - 20\% in infants born at<32 weeks gestational age (5). In the preterm infants IVH originates from the fragile involuting vessels of the subependymal germinal matrix, located in the caudothalamic groove. The pathogenesis of the IVH in preterm infants has been shown to be largely related to intravascular, vascular and extravascular factors (Table 1) (7).

a) The intravascular risk factors predisposing to IVH include ischemia/reperfusion, increase in cerebral blood flow, fluctuating CBF and increase in the cerebral venous pressure. Ischemia/reperfusion occurs commonly when hypotension is corrected quickly, whether due to desease or iatrogenic intervention.

Sustained increases in CBF may contribute to IVH and can be caused by seizures, hypercarbia, anemia and hypoglycemia, which result is a compensatory increase in CBF. Fluctuating CBS has also been demonstrated to be associated with IVH in preterm infants (8). Studies have showed that large fluctuations typically occurred in infants breathing out of synchrony with the ventilator.

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Table 1. The pathogenesis of the IVH in preterm infants.

<table>
<thead>
<tr>
<th>Intravascular factors</th>
<th>Ischemia/reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluctuating cerebral blood flow</td>
</tr>
<tr>
<td></td>
<td>Increase in cerebral venous pressure (high intrathoracic pressure – ventilator)</td>
</tr>
<tr>
<td></td>
<td>Platelet dysfunction and coagulation disturbances</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular factors</th>
<th>Tenuous, involuting capillaries with large luminal diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extravascular factors</td>
<td>Deficient vascular support</td>
</tr>
<tr>
<td></td>
<td>Excessive fibrinolytic activity</td>
</tr>
</tbody>
</table>

b) **Vascular factors** that contribute to IVH include the fragile nature of the involuting vessels of the germinal matrix. There is no muscularis mucosa and little adventitia in this area of relatively large diameter, thin-walled vessels. Capillaries in the germinal matrix of the VLBW brain are particularly susceptible to rupture because they lack supportive cells (pericytes). RBC pass through capillary spaces smaller than themselves. This can only occur because RBC deform and because they release nitric oxide thereby dilating the capillaries. Banked RBC have a time – associated reduction in deformability as part of the “Storage Lesion”. Transfused RBC with poor deformability and lacking nitric oxide synthase can clog capillaries. All of these factors make the vessels susceptible to rupture.

c) **Extravascular risk factors** for IVH include deficient extravascular support and likely excessive fibrinolytic activity in preterm infants.

**Objectives**

The evaluation of the severe intraventricular hemorrhage incidence after repeated transfusions of packed red blood cells in premature infants with low birth weight and the differentiation prevalence of severe intraventricular hemorrhage in premature infants transfused with or without severe pathology associated.

**Material and Methods**

A retrospective study conducted over a period of two years, from January 2011 to December 2013 which included infants admitted to Neonatal Ward of "Louis Turcanu" Children’s Emergency Hospital of Timisoara. The study group included 104 newborns divided into two groups: the study group -64 patients with gestational age <32 weeks and weight <1500g and control group- 40 patients who had indications for red blood cell transfusions. The infants with coagulopathies and central nervous system malformations were excluded. They also had associated pathology: respiratory distress syndrome, sepsis, necrotizing enterocolitis, pneumonia. All patients were performed transfontanelar ultrasound in dynamics. Were extracted demographic data (gestational age, sex, birth weight), clinical and laboratory results for each newborn (hemoglobin level, number of transfusions received, transfontanelar ultrasound, histopathological examination).

**Results**

Both groups showed similar gestational age, birth weight, sex, hemoglobin levels. Among infants who required blood transfusions 24 patients (37.5%) developed severe complications – worsening of intraventricular hemorrhage, ventriculomegaly, hydrocephalus, 8 of them (12.5%) being extremely low birth weight (790-900g). The control group did not experience worsening of existing intraventricular hemorrhage. Patients with most transfusions received (3,4) are those who have developed an increase in the severity of IV hemorrhage: to 9 of them the form of the IVH increased from II to III degree, to 11 of them IVH increased from I to III degree and 4 of the infants developed IV degree IVH. In severe forms of the disease, those who required red blood cells transfusion had an increase in both the form of IV hemorrhage and the corresponding neurological syndrome. Although we could not make a clear distinction between worsening of the IV hemorrhage after red blood cell transfusion or due to the complications of the associated pathology, we did make some observations: from the study group, those 24 patients (37.5%) who developed severe complications, 10 of them did because of the associated pathology and in others 14 patients we did noticed worsening of the intraventricular hemorrhage and the corresponding neurological syndrome, ventriculomegaly and hydrocephalus.

**Discussions**

Although the numbers of transfusions administered to preterm infants remains significant, they have decreased over the last 20 years, primarily due to the institution of restrictive transfusion guidelines in conjunction with the study of erythropoietin administration to preterm infants (4). Efforts have been made to limit transfusions and consequent donor exposures to the fewest number possible. If RBC transfusions is causally-liked with IVH in some cases, successful efforts to eliminate (or reduce) early RBC transfusions should diminish the incidence of IVH. The latest studies have showed that stripping (milking) the umbilical cord blood of small preterm infants before the cord is clamped and cut and also drawing baseline NICU blood tests from fetal blood in the placenta (thus initially drawing no blood from the newborn) do have a lot of benefits:

- more normal blood pressure
- less vasopressor use
- fewer early transfusions
- lower incidence of IVH. It was established cord milking reduces the need for red cell transfusions in VLBW neonates with 50% and also the IVH is reduced with 50%.
Conclusions
Repeated transfusions of packed red blood cells is a cause of worsening the intraventricular hemorrhage in preterm infants with low birth weight (23%) compared with controls.
Prematurity itself can be a cause of severe anemia corrected only by red blood cell transfusion.

Severe associated pathology increases the degree of the anemia and also the incidence of IV hemorrhage in this category of infants.
Repeated transfusions of packed red blood cells is a cause of worsening of IV hemorrhage in VLBW neonates.

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GENETIC POLYMORPHISMS AND RETINOPATHY OF PREMATURE	

Florina Stoica1*, Nicoleta Andreescu1, Gabriela Olariu2, Gabriela Jianu3, Maria Puiu1

Abstract
Retinopathy of Prematurity (ROP) represents a major health issue in the modern society, being the main cause for blinding in children all over the world.

We analyzed the results of a retrospective study performed on a 6-year period (2009-2014), within the Neonatal Unit of the County Emergency Hospital from Timisoara. We assessed 1948 premature infants with GA < 35 weeks and BW < 1500 grams (GA = gestational age; BW = birth weight). Incidence of retinopathy in the study group was 48.55% (945 infants). Laser therapy was applied to 155 of these (7.95%). The disease evolution was favourable in 143 infants (86.5%). The unfavourable evolution in one eye, yet favourable in the other eye, was noticed in 14 of the assessed children (9%), and the severe loss of the visual acuity / blindness was noted in 7 cases (4.5%).

The screening of ROP is essential for a timely diagnosis, allowing the application of a therapy at the right moment. The examination is performed by the ophthalmologist, upon request from the neonatologist. Finding an alternative screening method (telemedicine, the study of genetic polymorphisms), which is much easier to perform, would allow a more efficient selection of infants at a risk for severe ROP.

Key words: retinopathy of prematurity (ROP), screening, genetic polymorphisms

Introduction
Retinopathy of prematurity (ROP) is a proliferative disease that affects retinal vasculature in the eyes of premature babies. It can lead to severe visual impairment or even to blindness. The quality improvement in the medical care of premature infants has allowed the survival of children with extremely low gestational age and birth weight. However, because of premature birth, the normal development of retinal vasculature (process starting in the 16th week of pregnancy) stops. The later fibrovascular proliferation results in haemorrhages, traction on the retina and, finally, retinal detachment [1].

The international classification of the retinopathy of prematurity was established in 1984, when the disease was described as an active process focused on two aspects: staging and localization [2].

Thus, 5 stages of the disease were described:
- stage 1 (demarcation line): a thin, well-defined, silvery-white structure, present in the retina; this structure separates the posterior vascular retina from the anterior avascular retina;
- stage 2 (ridge): the line in stage 1 engorges both in height and in width and it occupies an expanded volume outside the plane of the retina; neovascularization may be present in the posterior area of the retina.
- stage 3 (fibrovascular ridge): extraretinal fibrovascular proliferation (neovascularization) adds to the anterior aspect and retinal haemorrhage may be often present;
- stage 4: partial retinal detachment, with or without the involvement of the macular area;
- stage 5: complete retinal detachment;

The severe tortuosity of blood vessels indicates an apparent vascular incompetence. This is described as "plus disease", with the following features: arterial and venous engorgement of the posterior pole, iris vascular engorgement, vitreous haze and pupil rigidity. In the posterior aggressive form of the ROP, although there are small vascular changes at the edges of the retina, the vascular tortuosity is important, the developed vascular shunts are numerous and the disease evolves fast towards stage 5.

The disease location is done by dividing the retina into three zones:
- zone 1: it is the zone centred on the optic nerve, the radius of which extends twice the distance from the optic nerve to the centre of the macula;
- zone 2: the circular zone surrounding zone 1, with the radius equal to the distance from the optic nerve to the nasal ora serrata;
- zone 3: represents the residual temporal crescent of the retina, outside zone 2.

The circumferential extent of the disease is described in 12 equal segments, similar to the hours on the face of a clock (their sum represents the extent of the disease).

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The main risk factor for the development of retinopathy of prematurity is, first of all, the premature birth. The earlier an infant is born and the less birth weight it has, the higher the possibility to develop this disease later in life. Other factors include: oxygen therapy, mechanical ventilation, sepsis, anaemia, blood transfusion, respiratory distress, hypoxia, apnoea, pulmonary interstitial emphysema, bronchopulmonary dysplasia, surfactant administration, vitamin E deficit, patent ductus arteriosus, indomethacin administration, acidosis, bradycardia, hypotension, intraventricular haemorrhage, ulcerative hemorrhagic enterocolitis, belonging to the white race etc. The newborns with systemic conditions and an unstable clinical evolution have a higher probability of developing severe forms of the disease.

The most efficient treatment for these cases is the laser therapy. This is applied in the severe forms of the disease (stage 3, threshold/pre-threshold, or the posterior aggressive form). In stages 4 and 5, the laser therapy is applied at the same time with vitrectomy surgery.

Objectives

In this paper, we analyzed the results of a retrospective study performed on a 6-year period (2009-2014). We have assessed the incidence of severe forms of retinopathy of prematurity in infants belonging to a risk group from the western part of Romania (screening and laser therapy). The authors have analyzed the opportunity of improving the means for diagnostic and monitoring of the ROP, by the study of the VEGF (vascular endothelial growth factor) genetic polymorphisms, starting from the hypothesis that the genetic polymorphisms can be associated to the disease severity and development. Last but not least, we followed the correlation between the precocious visual stimulation and the functional result in the treated children from the study group.

Methods and material

During 2009-2014 (including September 2014), within the Neonatal Unit of the County Emergency Hospital from Timisoara, we assessed 1948 premature infants and we applied laser therapy to 155 of these (Table 1).

Table 1. Distribution per years of the assessed and treated infants.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of assessed children</th>
<th>No. of children where laser therapy was applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>322</td>
<td>15</td>
</tr>
<tr>
<td>2010</td>
<td>292</td>
<td>21</td>
</tr>
<tr>
<td>2011</td>
<td>340</td>
<td>37</td>
</tr>
<tr>
<td>2012</td>
<td>355</td>
<td>33</td>
</tr>
<tr>
<td>2013</td>
<td>366</td>
<td>26</td>
</tr>
<tr>
<td>2014 including September</td>
<td>273</td>
<td>23</td>
</tr>
</tbody>
</table>

The inclusion criteria in the study group are as follows:

- history of premature birth (GA < 35 weeks and BW < 1500 grams),
- unstable clinical evolution,
- associated risk factors (regardless of GA and BW),
- patients with a history of ROP transferred to our clinic for monitoring.

Exclusion criteria:

- full-term birth,
- existing opacities in the visual axis (e.g., congenital cataract),
- presence of major eye malformations (e.g. anophthalmia)

The first examination (screening start) was done at 4-6 weeks of chronologic age (post-birth) or at 31-33 weeks of post-conceptual age (post-menstrual age), and the classification was done in agreement with the ICROP (localization, disease expansion and development stages). The interval between 2 successive examinations varied between a few days and three weeks (Table 2). The screening is ended when the visualization of the retina is complete, the retinopathy of prematurity is completely in remission or when the laser therapy is applied.

Table 2. The rhythm of examination of premature infants.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Disease stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>a few days</td>
<td>- stage 1, in zone 1</td>
</tr>
<tr>
<td></td>
<td>- stage 2, in zone 1</td>
</tr>
<tr>
<td></td>
<td>- stage 3 in zone 2 with/without PD which does not yet require ablation</td>
</tr>
<tr>
<td>after one week</td>
<td>- zone 1 without ROP, but with immature vascularisation</td>
</tr>
<tr>
<td></td>
<td>- stage 2, in zone 2</td>
</tr>
<tr>
<td>after 2 weeks</td>
<td>- stage 1, in zone 2</td>
</tr>
<tr>
<td></td>
<td>- ROP in remission from zone 2</td>
</tr>
<tr>
<td>after 3 weeks</td>
<td>- zone 2 without ROP, but with immature vascularisation</td>
</tr>
<tr>
<td></td>
<td>- stage 1, in zone 3</td>
</tr>
<tr>
<td></td>
<td>- stage 2, in zone 3</td>
</tr>
<tr>
<td></td>
<td>- ROP in remission from zone 3</td>
</tr>
</tbody>
</table>
The examination was performed by an ophthalmologist, experienced in the management of this disease in the premature infant, by indirect ophthalmoscopy. The examination was performed one hour after feeding, in mydriasis induced with (cyclopentolate 0.5%, tropicamide 0.5% or phenylephrine 2.5%). For topical anaesthesia, propacaine drops 0.5% were administered. A blepharostat, scleral depressor and a 28-diopter lens were used.

The laser therapy performed in the Neonatal Unit was applied in severe cases of the disease (stage 3 in zone 1 or 2 for 5 continuous or 8 cumulated clock hours, with or without PD or aggressive posterior forms). This was performed within the first 48-72 hours from the diagnostic, in order to reduce neovascularization and retina damage, and prevent retina detachment and the severe loss of the visual acuity. The indirect ophthalmoscope diode laser (810 nm) was used. Peripheral retinal ablation anterior to the fibrovascular ridge of ROP was done using scatter pattern photocoagulation, with impulses placed one half width apart, resulting in moderate white laser lesions on the entire peripheral avascular retina. The set laser power varied between 150 and 500 mW, and the exposure time was of 0.2 seconds. The number of impulses placed varied between 400 and 200 for a treatment session.

The results were assessed one week from the treatment session. Disease remission involves the disappearance of fibrovascular proliferation and the vascularisation of the retina beyond the ridge, in the previously avascular area. The complete involution is defined as the absence of the active neovascular tissue, absence of vessel engorgement and tortuosity at the level of the posterior pole and absence of retina detachment [3]. The unfavourable results consist in the disease progression and the occurrence of retina detachment.

Functional results were assessed at the age of 9 to 12 months. The Cardiff Acuity tests were used. The refraction was measured with a paediatric auto-refractometer. The amblyopia and anisometropia treatment was started (where applicable), and the refraction errors (hypermetropia, myopia, astigmatism) were corrected.

Early visual stimulation in children where laser therapy was applied improves the retina functional response. This is done by introducing the child in an environment rich in visual stimuli of different sizes and intensities (visual stimulation activities using various light and non-light stimuli, e.g. torches, toys with/without lights, colour stimuli), presented in a variety of situations, provided by: the luminosity of the environment, the distance between the object and the child, presentation position, background). The child's responses were followed and recorded. The choice of visual stimuli was done according to the remaining visual function and the child's functional level, as well in consideration of any neurological conditions (e.g. epilepsy); the increase in the attention span was done by changing stimuli within the same activity; black light activities or the use of visual stimulation software may be alternatives to the moving objects following activities (vertical/horizontal movement, or within the near or farther visual field).

**Results**

The incidence of retinopathy within the study group (regardless of stage) was of 48.55% (945 infants). The laser therapy was applied in 155 of the infants (7.95%). The distribution on years of the assessed/treated children is presented in Figure 1.

The infants included in the study were weighed less than 2,000 grams at birth and their gestational age was under 35 weeks. Premature infants not complying with these criteria were also assessed, when the neonatologist deemed this examination necessary due to the unstable clinical evolution of the infants and the multiple associated risk factors.

When therapy was recommended, the disease stages were as follows: stage 3 in 112 infants (72%) - in zone 1, there were 14 cases, while in zone 2 there were 98 cases; stage 4 in 6 infants (4%) and the aggressive posterior form of the disease in 37 infants (24%) (Figure 2). The children were 37 weeks old on average when the laser therapy was applied.
Disease remission and the disappearance of extraretinal fibrovascular proliferation was noted in 143 infants (86.5%). Unfavourable evolution, with fibrous retinal tractions and retinal detachment in one eye, yet favourable in the other eye, was seen in 14 of the assessed children (9%). Unfavourable evolution, with bilateral retinal detachment and loss of visual acuity / blindness was seen in 7 cases (4.5%).

We have studied the connection between the child's age when laser therapy was applied and the favourable post-surgery evolution (Figure 3). There is no close connection between the child's age upon therapy recommendation and the favourable post-surgery evolution, although we would have expected this correlation to be a strong one, given the fact that retina vascularisation is a process which continues after premature birth until week 45 (post-corrected age).

On the other hand, the correlation is positive and very significant from the statistical point between the favourable post-surgery evolution and stage 3 of the disease at the moment the laser therapy was applied (Figure 4); there is also a positive correlation between the unfavourable post-surgery evolution and the presence of the posterior aggressive form of the disease when laser therapy was applied (Figure 5).

Discussions:
The results obtained are similar to the ones reported in the relevant scientific literature. In the United States, in a study performed in 2009, retinopathy of prematurity was diagnosed in 68% of the premature infants weighing less than 1250 grams at birth [4]. In the United Kingdom, the reported incidence of retinopathy of prematurity varied between 66 and 68% in infants with less than 1251 grams at birth [5].

The inclusion criteria in our study were more permissive (with reference to the guidelines established in the program for national screening and laser therapy of
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BRODIE’S ABSCESS – A CASE REPORT

Fuicu Păun¹, Bota Constantin², Dumitru Ionuţ-Adrian²

Abstract

Brodie abscess is a form of subacute osteomyelitis; but because the diagnostic delay ranges from a few weeks to up to several years, the distinction between subacute and chronic osteomyelitis is not clear. The term ‘Brodie’s abscess’ was applied to localized bone abscess that developed without prior systemic illness. Due to its location in the bone, Brodie’s abscess can mimic benign and malignant diseases.

We report here a case of a 14 years old boy, that was admitted in the department of pediatric surgery of the "Louis Turcanu" Timisoara Hospital for a distal radius and ulna epiphyseal take-off in his left forearm. The patient presented a bone tumor in the distal part of his left forearm accompanied by pain more severe at night, laesa functio and feeling of tension within the bone.

Differential diagnosis was made mainly between osteosarcoma, bone tuberculosis and acute monoartritic rheumatoid arthritis. Due to its location in the distal third of the ulna and its MRI aspect, Brodie’s abscess mimicked the aspect of a malignant disease.

The prognosis is excellent, and healing usually takes place without complications. After effective surgical evacuation, the bone lesion can disappear within a couple of months. The patient can be completely asymptomatic, pain-free and with no tenderness on palpitation.

Key words: Brodie abscess, subacute osteomyelitis, osteosarcoma, osseous tuberculosis.

Introduction

In general practice, serious infections in children have an incidence of 12.3 cases per 1000 patients per year, or 1 serious infection per 100 children per year. Of these, osteomyelitis affects 0.2 to 1.6 children per 1000 annually and is more common in boys than in girls (ratio, 2.5:1).¹² Osteomyelitis has historically been categorized as acute, sub-acute, and chronic.¹³ Brodie abscess is a form of sub-acute osteomyelitis; but because the diagnostic delay ranges from a few weeks to up to several years, the distinction between sub-acute and chronic osteomyelitis is not clear.⁵,⁶,⁷,⁸

Brodie abscess (subacute osteomyelitis) is an infectious disease localized in metaphyseal bone, with rapid expansion in the medullary cavity, in 95% of cases caused by Staphylococcus aureus with low virulence in a body with high immunity. The immune system fight against etiopathogenic agents quartered on bone, cause inflammatory lesions, cortical abscess with periosteal reaction with bone sequestration and limitation of abscess.

Brodie first described a localized abscess of the tibia in an amputated limb that did not produce systemic signs and developed without prior febrile illness. Subsequently, the term ‘Brodie’s abscess’ was applied to localized bone abscess that developed without prior systemic illness.⁹ Due to its location in the bone, Brodie’s abscess can mimic benign and malignant diseases.

A recent study from a university hospital found that all 23 patients with a final diagnosis of subacute osteomyelitis were first referred to an orthopaedic oncology clinic.¹⁰ Due to the diagnostic challenges of the condition, imaging modalities have been used to help confirm its diagnosis. This ranged from radiography of the affected area to magnetic resonance (MR) imaging. While osteomyelitis in its different forms may be rare in developed countries, it remains a relatively common problem in developing countries.¹¹

Although the chronic variety of osteomyelitis is common, the sub-acute type (particularly Brodie’s abscess) is rare, except in East Africa, where it is reportedly a common occurrence.¹² This may explain the paucity of reports on this variant. The disease has been described to follow an indolent course due to the interplay of host resistance combined with low virulence of the infecting organisms.¹³

The treatment of Brodie’s abscess varies. There are reports of successful treatment with antibiotics combined with cast immobilization in children.¹⁴ Curettage with postoperative antibiotics,¹⁵,¹⁶,¹⁷,¹⁸ and recently, the use of antibiotic-impregnated beads. The curettage of abscess cavity with cancellous bone grafting has been reserved mainly for those with large cavity diameters > 3 cm.

Case presentation

Patient U.D, male, age 14 y.o., from urban area, was admitted in the Department of Pediatric Surgery of the "Louis Turcanu" Timisoara Hospital in October 2011 for a distal radius and ulna epiphyseal take-off in his left forearm which receives specialized treatment. In 21 March 2012 the patient is admitted presenting a bone tumor in the distal part of his left forearm accompanied by pain most severe at night, functional impotence and feeling of tension within the bone.

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Clinical Exam:

Inspection: left forearm deformation and localized edema

Palpation: reveals 2/3 cm size tumor of the ulna which imprints an abnormal position of the left forearm and the deformation of the radio-carpal joint without loss of motility, soft and elastic sensitive to touch. The superjacent skin presents edema.

General examination revealed no pathological evidence including no documented fever.

Laboratory examination revealed a minor anemia, an inflammatory syndrome and increased alkaline – phosphatase. Arm X-ray shows a round osteolytic area with a 2/3 cm diameter located in the distal 1/3 of the left ulna. We continue the investigations with a MRI, bone marrow puncture in the right and left iliac spine and bone content sampling for histo-pathological examination.

The MRI scan revealed in the distal third of the ulna, on a length of about 9 cm, a tumor in hyper / hyposignal T1, T2 hypersignal, intramedullary, with central necrosis and osteolysis, with aggressive periosteal reaction and extension in the interosseous membrane and muscular parts (deep flexor of fingers and square pronator); the formation is adjacent to the interosseous vessels. Peritumoral edema. The tumor doesn't reach the radioulnar joint (Fig.1).

General examination revealed no pathological evidence including no documented fever.

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The result of the bone marrow puncture in the right and left iliac spine and the MRI result suggests a bone tumor, possibly osteosarcoma. Pending the histopathology results the patient is released on the 31 of March, after 10 days of treatment with the following medication: Sulperazon iv, 2x 1.5 g/day; Perfalgan 3x60 ml/day; Ketonal i.v. 3x40 ml/day.

The results of the histopathology exam are received on the 5th of April:

- Soft tissue examination: Macroscopic examination of the parts showed 2 irregular fragments of 1.6/0.8/0.6 cm and 1/0.4/0.3 cm, whitish-gray color and increased consistency. Microscopic diagnosis of the soft tissue indicated a span of the acute inflammatory infiltrate (polymorphonuclear, macrophages, adult lymphocytes, eosinophils) with necrosis, thrombosis and bleeding picture consistent with that of a phlegmon.
- Marrow examination: Macroscopic examination of the parts showed a fragment of 0.8/0.7/0.3 cm, brown colored and elastic consistency. Microscopic diagnosis of the bone marrow indicated irregular fibrocollagen fragments with span of acute inflammatory infiltrate that consists mainly from: plasmocyte, eosinophilic cells, lymphoblasts, lymphocytes, polymorphonuclear cells with large areas of hemorrhage.

The patient returns presenting a fistula of the tumor in the distal 1/3 of the left ulna on the 18th of April and admitted for specialized treatment. General examination revealed no pathological evidence. Laboratory examination revealed a minor anemia. Arm X-ray shows a round osteolytic area which suggests a tuberculous etiology. To exclude a tuberculous etiology we indicate: lung X-ray, intradermal reaction with 2 units of PPD, microscopic examination of sputum and cultures to isolate the etiological agent of tuberculosis (lung X-ray, intradermal reaction with 2 units of PPD). The Phthisiology exam showed no specific changes of tuberculosis (lung X-ray, intradermal reaction with 2 units of PPD). The patient is released on the 25th of April after treatment with the following medication: Clindamycinum i.v
tumor is a Brodie abscess based on:

Diagnosis:
Clinical and paraclinical exams state that the bone tumor is a Brodie abscess based on:
- higher frequency in men between 13 and 34 years of age
- insidious onset without fever
- recurring attacks of pain more severe at night
- feeling of tension within the bone
- left forearm deformation and localized edema
- deformation of the radio-carpal joint without loss of motility
- Arm X-ray- round osteolytic area with a 2/3 cm diameter, local thickening of the bone
- MRI scan- a tumor in hyper / hiposignal T1, T2 hypersignal, centromedular, with central necrosis and osteolysis, with aggressive periosteal reaction
- Histopathology exam: Soft tissue examination-phlegmon. Marrow examination indicated irregular fibrocollagenous tissue fragments with span of acute inflammatory infiltrate

Differential diagnosis: was made mainly between osteosarcoma, bone tuberculosis and monoarthritic rheumatoid arthritis considering clinical features that are found and against the suspected diagnosis.

Treatment
1. Surgical – excisional debridement, bone cyst removal
2. Diet – normocaloric, normoproteic, normoglucidic, normolipidic
3. Etiological – Clindamycinum capsules of 150 mg, oral 4x150mg/day, 6weeks
4. Symptomatic – Ibuprofenum tablets of 200mg, oral 2x200mg/day, at need

Evolution: Patients with Brodie’s abscess respond well to surgical curettage of the abscess, and antibiotic therapy for 6 weeks, leading to a favorable evolution. The outcome is rated as satisfactory if there was no recurrence at a minimum follow-up of two years and in cases of complete obliteration of abscess cavities with development of normal trabeculae bone pattern. Without treatment Brodie’s abscess can lead to life-threatening complications.

Complications:
- Septicemia: disseminated abscesses, infective carditis
- Septic bacterial arthritis
- Pathological fractures
- Alteration in growth rate
- Squamous cell carcinoma
- Amyloidosis

Prognosis: The prognosis is excellent, and healing usually takes place without complications. After effective surgical evacuation, the bone lesion can disappear within a couple of months. The patient can be completely asymptomatic, pain-free and no tenderness on palpitation.

Particularity of this case: Due to its location in the distal third of the ulna and its MRI aspect Brodie’s abscess mimicked the aspect of malignant disease, osteosarcoma. Due to the diagnostic challenges of the condition the positive diagnosis of Brodie’s abscess was delayed.

Discussions and Conclusions
In this case, the infection became apparent in 5 months after a distal radius and ulna epiphyseal take-off. The difficulty in this case in classifying it as subacute or chronic comes from the description of these terms. Chronic osteomyelitis often progresses from an uncontrolled acute septic infection, which does not seem to be the case with this child because the symptoms were never acute. Subacute osteomyelitis, or Brodie abscess, usually reflects a low-grade clinical course of a hypovirulent infection. This description would fit the case.

The age range for osteomyelitis is bimodal, being younger than 2 years and between the ages of 13 and 34 years old. Being 14 years old, this boy fits the general characteristics found in the literature.

This patient was treated with surgically- excisional debridement, bone cyst removal and than with antibiotics Clindamycinum capsules of 150 mg, oral 4x150mg/day, 6weeks.

This case presentation wants to be a review of the case and an alarm sign, presenting the high risk of misdiagnosing a Brodie abscess due to its capacity to mimic benign and malignant diseases. In our case the abscess was initially considered to be a osteosarcoma but histopathology exam and course of the complaint excluded this diagnosis.

For positive diagnosis, investigation and treatment, such cases require a multidisciplinary approach: pediatric surgery and orthopedics, onco-hematology, pneumohistiosiogy, imaging and laboratory cooperation.

An incorrect or delayed diagnosis can lead to systemic complications affecting ad vitam prognosis of which the most feared are septicemia and squamous cell carcinoma; these contrasting with the excellent prognosis, healing without sequelae or complications if a correct diagnosis and well led treatment is initiated.

Although, sometimes positive diagnosis is one of exclusion, this condition with rare incidence must be considered every time we face tumors that borrows characteristics of osteosarcoma and bone tuberculosis.

References

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COMPARATIVE STUDY ON COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) USE BY PHYSICIANS IN ROMANIA AND HUNGARY

Ovidiu Jupaneant¹, Gabriella Hegyi², Anca Tudor¹, Simona Dragan¹,³

Abstract

Background and aim: Complementary and Alternative Medicine (CAM), as utilized by European citizens, represents a variety of different medical systems and therapies based on the knowledge, skills and practices derived from theories, philosophies and experiences used to maintain and improve health, as well as to prevent, diagnose, relieve or treat physical and mental illnesses. The purpose of the present paper was to apply a modified version of the Wahner-Roedler questionnaire and to evaluate differences in CAM use by family medicine physicians in Romania and Hungary.

Material and method: The study included 117 Romanian and 107 Hungarian physicians, in order to compare the CAM therapies used. The data was collected from seven CAM practices in Romania and from eleven CAM practices in Hungary. All physicians completed the revised Wahner-Roedler questionnaire once, in their personal country’s language. We used the above-mentioned questionnaire having the permission of the authors of Wahner-Roedler DL et al study. Because praying for health is considered to be a very used CAM therapy in Romania and Hungary, we introduced it in the second section of the questionnaire.

Results: The percentage of physicians who talk with their patients regarding possible benefits of using CAM therapies was significantly increased in Hungary as compared to Romania (14% vs 1.7%, p=0.002). The modified Wahner-Roedler Questionnaire indicated that Chiropractic, Osteopathy, Homeopathy, Phytotherapy, Traditional Chinese Medicine (TCM) and Yoga are the most important methods with limited familiarity for Romanian comparative to Hungarian physicians. The percentage of Hungarian physicians that understand proposed medicinal use and feel comfortable counseling patients regarding Bowen therapy is significantly increased comparative to Romanian physicians (25.2% vs 9.4%, p=0.002). The analysis revealed that Chiropractic is less familiar for Romanian than Hungarian physicians, and for those who understand it, is less comfortable (p=0.024). 24.8% of Romanian physicians understand proposed medicinal use of Aromatherapy, but feel uncomfortable counseling patients as compared to 13.1% of Hungarian physicians (p=0.027). A higher percentage of Romanian physicians have limited familiarity in using Homeopathy, as compared to Hungarian physicians (45.3% vs 23.4%, p<0.001). 40.2% of Hungarian physicians understand proposed medicinal use of Osteopathy and feel comfortable counseling patients versus 24.8% Romanian physicians (p=0.014).

Conclusions: The tendency to refer a patient to a CAM practitioner for treatment documented significant differences, being extremely likely in Hungarian physicians as compared to Romanian physicians.

Key words: Complementary and Alternative Medicine, Wahner-Roedler questionnaire

Introduction

Complementary and alternative medicine (CAM) represents a collection of medical and health care systems, procedures, and products not presently regarded to be components of standard medicine (1). In the latest years, the popularity of CAM has raised, despite the fact that it is ambiguous how the new global economic recession has influenced this, considering that only few CAM methods are accessible on national health insurance coverage (2). CAM is even more preferred in nearly all developed states, in particular in North America, Europe, and Australia. In North America, more than 38.2% of adults and 12% of children utilized CAM according to latest National Health Interview Survey from 2007(3). In Europe, CAMbrella, a project funded within the Framework Programme 7 investigated the prevalence of the therapies used (4).

From the data available for Hungary, it results that about half of the population uses CAM, the most common users being women, middle-aged people, well-educated individuals, people in high positions with high income, and city dwellers. There seems to be a significant trend towards an increased use of CAM.

A questionnaire comprising the physicians’ responses to questions regarding CAM utilization and outcomes, familiarity and experience with various CAM treatments, and techniques and extent of agreement with statements regarding attitude towards CAM was tested by Wahner-Roedler et al (5).

The purpose of the present paper was to develop a modified version of the questionnaire of Wahner-Roedler and to evaluate differences in CAM use by physicians in Romania and Hungary.

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Material and method
In order to compare the CAM therapies use by physicians in both countries, a modified version of the Wahner-Roedler Questionnaire was applied on 117 Romanian physicians from seven CAM practices, and 107 Hungarian physicians from 11 practices of family medicine. The physicians received a modified version of the Wahner-Roedler questionnaire once, in their own country’s language. All the data were collected at the University of Medicine and Pharmacy Victor Babes, Timisoara, Romania. Ethical approval was obtained as necessary in Romania and Hungary.

The modified Wahner-Roedler questionnaire had four sections. In the first section, the physicians answered to questions regarding CAM utilization and outcomes. In the second section, the physicians answered to questions regarding familiarity and experience with various CAM treatments and techniques; praying for one’s health was introduced in the questionnaire, as a frequently used CAM therapy. In the third section of the questionnaire the physicians were asked about the extent of agreement with statements regarding attitude towards CAM. In the fourth section, the physicians rated the impact of various factors on their attitudes towards CAM therapies.

In June 2013 the translation of the questionnaire into Romanian and Hungarian was finished. This task has been accomplished translating from the original questionnaire language (English), into Romanian and Hungarian, and retranslation back to the original language, following the European Organization for Research and Treatment of Cancer (EORTC) procedure. The modified version of the Wahner-Roedler questionnaire was then applied to Romanian physicians during July and August 2013, and to Hungarian physicians during September, October and November 2013. The application of the modified version of Wahner-Roedler questionnaire was also performed on Hungarian physicians during the International Hungarian Acupuncture Congress in Budapest (September 2013), and during the meeting of Hungarian Medical Academy in Pecs (The 6th of December 2013). Items were translated to handle the regional difference and beliefs in treatments through the countries; e.g. ‘Chiropractic’ was translated as ‘Manual therapy’ in Romania. The most difficult term was ‘Spiritual healing’, regarded as a spiritual issue in many EU countries; therefore, where necessary, respondents were given written definitions. The physicians completed and supplied the questionnaires by hand.

Statistical analysis
Data from each participating country were collected into a single data file and the statistical analysis was realized in Excel and SPSS - version 17. Basic descriptive statistics for the entire sample and for each country separately were produced to describe the respondents’ characteristics and responses to each item on the modified version of the Wahner-Roedler questionnaire. Quantitative analysis focused on the extent to which respondents followed the instructions given in the above mentioned questionnaire and the extent of missing data. The total missing data was summed across all commensurate items within each modified version of the Wahner-Roedler questionnaire, for each different language version of the Wahner-Roedler questionnaire. For numeric variables, the central tendency and dispersion indicators were calculated, and comparisons between variables were made using the ANOVA test (in the case of comparison between multiple sets of values) and the t-test of significance for variables. Frequency tables were done for nominal variables. The comparisons and associations were done using the $\chi^2$ compliance test.

Results
The characteristics of age and sex of the study groups of physicians from Romania and Hungary that completed the modified the Wahner-Roedler questionnaire are presented in table 1.

| Table 1. Demographics of physicians’ respondents. |
|-----------------|-----------------|-----------------|-----------------|
| Age (years)     | Physicians from Romania | Physicians from Hungary | $p$     |
|                 | 42.38±9.326       | 45.00±11.020     | 0.078     |
| Sex (M/F)       | 41.9/58.1         | 46.7/53.3        | 0.502     |

Section 1: Utilization and Outcomes
The answers of physicians’ responses to questions regarding CAM utilization and outcomes are showed in Table 2. It was recorded that 33.6% of Hungarian physicians had referred a patient to a CAM practitioner as compared to 12.8% of Romanian physicians ($p<0.001$). It was noticed that the proportion of physicians from Romania who responded 0-25 was significantly higher than the proportion of HU physicians that gave the same response to the question regarding the percentage of patients that talk about possible harmful outcomes of using CAM therapies ($p<0.001$). Furthermore, the proportion of Romanian physicians who responded with 76-100 was significantly lower than those in HU ($p=0.002$) (table 2).

Section 2: Familiarity and Experience
The second section of the questionnaire comprised the physicians’ responses to questions regarding familiarity and experience with various CAM treatments, and techniques (table 3).
Table 2. The responses of physicians to questions regarding CAM utilization and outcomes.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Response of RO Physicians (%)</th>
<th>Response of HU Physicians (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) How likely is it that you would refer a patient to a CAM practitioner (if available at your Clinic) for treatment of an ailment?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) extremely likely</td>
<td>12.8</td>
<td>33.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>b) somewhat likely</td>
<td>3.4</td>
<td>11.2</td>
<td>0.045</td>
</tr>
<tr>
<td>c) neither likely nor unlikely</td>
<td>1.7</td>
<td>10.3</td>
<td>0.014</td>
</tr>
<tr>
<td>d) somewhat unlikely</td>
<td>5.1</td>
<td>13.1</td>
<td>0.037</td>
</tr>
<tr>
<td>e) extremely unlikely</td>
<td>6</td>
<td>6.5</td>
<td>NS</td>
</tr>
<tr>
<td>f) N/A</td>
<td>70.9</td>
<td>25.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(2) Have you ever referred a patient to a CAM practitioner?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) yes</td>
<td>54.7</td>
<td>57.9</td>
<td>NS</td>
</tr>
<tr>
<td>b) no</td>
<td>41.9</td>
<td>42.1</td>
<td>NS</td>
</tr>
<tr>
<td>c) N/A</td>
<td>3.4</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>(3) With approximately what percentage of your patients do you talk about possible benefits of using CAM therapies?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) 0–25</td>
<td>52.1</td>
<td>44.9</td>
<td>NS</td>
</tr>
<tr>
<td>b) 26–50</td>
<td>18.8</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>c) 51–75</td>
<td>16.2</td>
<td>15.9</td>
<td>NS</td>
</tr>
<tr>
<td>d) 76–100</td>
<td>12</td>
<td>25.2</td>
<td>NS</td>
</tr>
<tr>
<td>e) N/A</td>
<td>0.9</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>(4) With approximately what percentage of your patients do you talk about possible harmful outcomes of using CAM therapies?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) 0–25</td>
<td>72.6</td>
<td>50.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>b) 26-50</td>
<td>17.9</td>
<td>26.2</td>
<td>0.138</td>
</tr>
<tr>
<td>c) 51-75</td>
<td>7.7</td>
<td>9.3</td>
<td>0.839</td>
</tr>
<tr>
<td>d) 76-100</td>
<td>1.7</td>
<td>14</td>
<td>0.002</td>
</tr>
<tr>
<td>(5) Who usually initiates discussions of benefits and risks of a CAM therapy?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) I initiate</td>
<td>36.8</td>
<td>53.3</td>
<td>NS</td>
</tr>
<tr>
<td>b) Patient initiates</td>
<td>16.2</td>
<td>13.1</td>
<td>NS</td>
</tr>
<tr>
<td>c) Third party initiates</td>
<td>17.1</td>
<td>7.5</td>
<td>NS</td>
</tr>
<tr>
<td>d) Not applicable</td>
<td>29.1</td>
<td>26.2</td>
<td>NS</td>
</tr>
<tr>
<td>(6) To what extent do you believe that the incorporation of CAM therapies into your Clinic’s practice would result in increased patient satisfaction?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Major positive impact</td>
<td>25.6</td>
<td>27.1</td>
<td>NS</td>
</tr>
<tr>
<td>b) Somewhat positive impact</td>
<td>18.8</td>
<td>20.6</td>
<td>NS</td>
</tr>
<tr>
<td>c) Unsure</td>
<td>25.6</td>
<td>28.0</td>
<td>NS</td>
</tr>
<tr>
<td>d) Somewhat negative impact</td>
<td>23.1</td>
<td>21.5</td>
<td>NS</td>
</tr>
<tr>
<td>e) Very negative impact</td>
<td>6.8</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>(7) To what extent do you believe that the incorporation of CAM therapies into your Clinic’s practice would attract more patients?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Major positive impact</td>
<td>25.6</td>
<td>26.2</td>
<td>NS</td>
</tr>
<tr>
<td>b) Somewhat positive impact</td>
<td>21.4</td>
<td>24.3</td>
<td>NS</td>
</tr>
<tr>
<td>c) Unsure</td>
<td>22.2</td>
<td>22.4</td>
<td>NS</td>
</tr>
<tr>
<td>d) Somewhat negative impact</td>
<td>19.7</td>
<td>20.6</td>
<td>NS</td>
</tr>
<tr>
<td>e) Very negative impact</td>
<td>11.1</td>
<td>6.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

CAM, complementary and alternative medicine; NR, no response.
Table 3. The answers of physicians to questions regarding familiarity and experience with various CAM treatments, techniques and herbs.

<table>
<thead>
<tr>
<th>CAM treatments</th>
<th>Answers of RO Physicians/Hungarian physicians (%)</th>
<th>$p$</th>
<th>$p$</th>
<th>$p$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unfamiliar</td>
<td>Limited familiarity</td>
<td>Understood medicinal use, but uncomfortable counseling patients</td>
<td>Understood medicinal use and comfortable counseling patients</td>
<td>ns</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>28.2/24.3</td>
<td>NS</td>
<td>37.6/24.3</td>
<td>NS</td>
<td>14.5/21.5</td>
</tr>
<tr>
<td>Aromaterapy</td>
<td>31.6/26.2</td>
<td>NS</td>
<td>35/27.1</td>
<td>NS</td>
<td>11.1/17.8</td>
</tr>
<tr>
<td>Bowen therapy</td>
<td>52.1/30.8</td>
<td>0.002</td>
<td>27.4/27.1</td>
<td>NS</td>
<td>11.1/16.8</td>
</tr>
<tr>
<td>Chiropractic</td>
<td>39.3/22.4</td>
<td>0.007</td>
<td>29.9/30.8</td>
<td>NS</td>
<td>13.7/16.8</td>
</tr>
<tr>
<td>Metal chelating Therapy</td>
<td>28.2/31.8</td>
<td>NS</td>
<td>25.6/29</td>
<td>NS</td>
<td>22.2/11.2</td>
</tr>
<tr>
<td>Phytotherapy</td>
<td>13.7/24.3</td>
<td>0.062</td>
<td>44.4/26.2</td>
<td>0.005</td>
<td>24.8/13.1</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>15.4/26.2</td>
<td>0.067</td>
<td>45.3/23.4</td>
<td>&lt;0.001</td>
<td>23.1/11.2</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>57.3/43.9</td>
<td>NS</td>
<td>26.5/30.8</td>
<td>NS</td>
<td>6.8/10.3</td>
</tr>
<tr>
<td>Kinetotherapy</td>
<td>30.8/33.6</td>
<td>NS</td>
<td>38.5/34.6</td>
<td>NS</td>
<td>9.4/6.5</td>
</tr>
<tr>
<td>Magneto-therapy</td>
<td>40.2/34.6</td>
<td>NS</td>
<td>47.4/1.1</td>
<td>NS</td>
<td>5.1/8.4</td>
</tr>
<tr>
<td>Massage</td>
<td>14.5/17.9</td>
<td>NS</td>
<td>17.1/20.8</td>
<td>NS</td>
<td>21.4/13.2</td>
</tr>
<tr>
<td>Meditation</td>
<td>36.8/34.6</td>
<td>NS</td>
<td>32.5/23.4</td>
<td>NS</td>
<td>9.4/15</td>
</tr>
<tr>
<td>Naturopathy</td>
<td>47.9/43</td>
<td>NS</td>
<td>26.5/27.1</td>
<td>NS</td>
<td>7.7/10.3</td>
</tr>
<tr>
<td>Osteopathy</td>
<td>11/28/28</td>
<td>0.002</td>
<td>47/19.6</td>
<td>&lt;0.001</td>
<td>17.1/12.1</td>
</tr>
<tr>
<td>Prayings</td>
<td>24.8/44.9</td>
<td>0.003</td>
<td>32.5/18.7</td>
<td>0.022</td>
<td>21.4/13.1</td>
</tr>
<tr>
<td>Reflexotherapy</td>
<td>23.1/20.6</td>
<td>NS</td>
<td>35.9/22.4</td>
<td>NS</td>
<td>17.1/20.6</td>
</tr>
<tr>
<td>Reiki</td>
<td>41/32.7</td>
<td>NS</td>
<td>29.1/23.4</td>
<td>NS</td>
<td>13.7/14</td>
</tr>
<tr>
<td>Shiatu</td>
<td>28.2/30.8</td>
<td>NS</td>
<td>21.4/16.8</td>
<td>NS</td>
<td>24.8/17.8</td>
</tr>
<tr>
<td>Spiritual healing</td>
<td>29.9/34.6</td>
<td>NS</td>
<td>27.4/21.5</td>
<td>NS</td>
<td>21.4/13.1</td>
</tr>
<tr>
<td>T'ai chi</td>
<td>23.9/31.8</td>
<td>NS</td>
<td>37.6/19.6</td>
<td>0.003</td>
<td>17.1/23.4</td>
</tr>
<tr>
<td>Traditional Chinese Medicine</td>
<td>27.4/20.6</td>
<td>NS</td>
<td>39.3/25.2</td>
<td>0.025</td>
<td>17.1/22.4</td>
</tr>
<tr>
<td>Yoga</td>
<td>36.8/21.5</td>
<td>0.013</td>
<td>36.8/16.8</td>
<td>&lt;0.001</td>
<td>7.7/29.9</td>
</tr>
</tbody>
</table>

Bowen therapy is more unfamiliar to Romanian physicians compared to Hungarian physicians ($p=0.002$). Moreover, the percentage of Hungarian physicians who understand proposed medicinal use of Bowen therapy and feel comfortable counseling patients is significantly increased comparative to Romanian physicians ($p=0.002$). The analysis revealed that Chiropractic is less familiar for Romanian than Hungarian physicians, and for those who understand it, is less comfortable ($p=0.024$). Hungarian physicians are less familiar with homeopathy than Romanian physicians ($p=0.067$). A significantly increased percentage of Hungarian physicians understand proposed medicinal use of Homeopathy and feel comfortable counseling patients comparative to Romanian physicians ($p<0.001$).

The proportion of physicians from Hungary who are familiar and feel comfortable with the practice of Yoga is significantly higher than the proportion of physicians from Romania ($p=0.025$). It was observed that the proportion of physicians more familiar with the prayer was significantly higher in Romania than in Hungary ($p=0.022$). No significantly difference was observed regarding the familiarity in using Acupuncture, Reflexotherapy, Reiki, Shiatsu, Spiritual healing, T’ai chi, Traditional Chinese Medicine, Hypnotherapy, Kinetotherapy, Massage and Magneto therapy between the percentage of physicians from Romania and Hungary. A more significantly increased percentage of Hungarian physicians understand proposed medicinal use of Traditional Chinese Medicine and feel more comfortable counseling patients comparative to Romanian physicians ($p=0.006$).

Section 3: Physician Attitudes

The third section of the questionnaire comprised the physicians’ extent of agreement with statements regarding attitude towards CAM (table 4).
Table 4. Physicians’ extent of agreement with statements regarding attitude towards CAM.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Answers of RO Physicians/Hungarian physicians (%)</th>
<th>Agree</th>
<th>p</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physician knowledge of CAM practices leads to a better patient treatment</td>
<td>50.4/53.3</td>
<td>NS</td>
<td>30.8/32.7</td>
<td>NS</td>
<td>18.8/14</td>
<td>NS</td>
</tr>
<tr>
<td>2. Physician’s spiritual beliefs and practices are important for patient healing</td>
<td>30.8/47.7</td>
<td>0.01</td>
<td>17.1/10.3</td>
<td>0.141</td>
<td>52.1/42.1</td>
<td>0.132</td>
</tr>
<tr>
<td>3. Patient’s spiritual beliefs and practices are important for patient healing</td>
<td>43.6/46.7</td>
<td>NS</td>
<td>10.3/8.4</td>
<td>NS</td>
<td>46.2/44.9</td>
<td>NS</td>
</tr>
<tr>
<td>4. Physicians should have knowledge about the most common CAM therapies</td>
<td>44.4/38.3</td>
<td>NS</td>
<td>40.2/44.9</td>
<td>NS</td>
<td>15.4/16.8</td>
<td>NS</td>
</tr>
<tr>
<td>5. CAM therapy has impact on symptoms, conditions and/or disease.</td>
<td>29.1/56.1</td>
<td>&lt;0.001</td>
<td>45.3/28</td>
<td>0.008</td>
<td>25.6/15.9</td>
<td>0.074</td>
</tr>
<tr>
<td>6. Some CAM therapies hold promise for treatment of symptoms, conditions and/or diseases</td>
<td>32.5/49.5</td>
<td>0.011</td>
<td>41.9/37.4</td>
<td>0.49</td>
<td>25.6/13.1</td>
<td>0.018</td>
</tr>
<tr>
<td>7. Counseling on nutrition in order to prevent chronic diseases should be a major role of physicians</td>
<td>59.0/29.9</td>
<td>&lt;0.001</td>
<td>14.5/38.3</td>
<td>&lt;0.001</td>
<td>26.5/31.8</td>
<td>0.386</td>
</tr>
</tbody>
</table>

Moreover, it was observed that the proportion of respondents from Hungary who answered that *physician’s spiritual beliefs and practices are important for patient healing* was significantly higher than that of those in Romania (p=0.01). It was noticed that the proportion of indifferent answers to proposition that *CAM therapy has impact on symptoms, conditions and/or disease response* was increased for physicians from Romania (p=0.008) and the proportion of physicians who agree with this affirmation was significantly higher for physicians from Hungary (p<0.001). It was observed that the proportion of physicians who liked the affirmation that *some CAM therapies hold promise for treatment of symptoms, conditions and/or diseases* was significantly higher for Hungarian compared to Romanian respondents (p = 0.011). The proportion of those who believe that nutrition plays an important role in preventing disease was significantly increased for physicians in Romania than in Hungary (p<0.001).

**Section 4: Physicians’ ratings**

The fourth section of the questionnaire comprised the physicians’ ratings of the impact of various factors on their attitude toward CAM therapies (table 5).

Table 5. Physicians’ ratings of the impact of various factors on their attitude toward CAM therapies.

<table>
<thead>
<tr>
<th>Impact factors</th>
<th>Rating of impact of Romanian versus Hungarian physicians (%)</th>
<th>None</th>
<th>p</th>
<th>Minimal</th>
<th>p</th>
<th>Moderate</th>
<th>p</th>
<th>High</th>
<th>p</th>
<th>Definite</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal experience; positive results when using therapy on myself</td>
<td></td>
<td>0.9</td>
<td>5.6</td>
<td>NS</td>
<td>35.3/29</td>
<td>NS</td>
<td>19.8/16.8</td>
<td>NS</td>
<td>37.9/41.1</td>
<td>NS</td>
<td>6/7.5</td>
</tr>
<tr>
<td>Recommendations by family and friends who have tried the therapy</td>
<td></td>
<td>3.4/4</td>
<td>2.8</td>
<td>NS</td>
<td>18.1/20.6</td>
<td>NS</td>
<td>36.2/43.9</td>
<td>NS</td>
<td>35.3/29.9</td>
<td>NS</td>
<td>6.9/0.9</td>
</tr>
<tr>
<td>Recommendations by colleagues who have used the therapy on themselves</td>
<td></td>
<td>1.7/2</td>
<td>0.581</td>
<td>NS</td>
<td>18.1/23.4</td>
<td>0.317</td>
<td>36.2/22.4</td>
<td>0.028</td>
<td>28.4/43</td>
<td>0.021</td>
<td>15.5/8.4</td>
</tr>
<tr>
<td>Recommendation of a medical specialist or consultant to whom you have referred a patient</td>
<td></td>
<td>0/6.5</td>
<td>0.015</td>
<td>12.1/12.1</td>
<td>0.97</td>
<td>36.2/20.6</td>
<td>0.011</td>
<td>31.9/38.3</td>
<td>0.295</td>
<td>19.8/22.4</td>
<td>0.612</td>
</tr>
<tr>
<td>Case reports in CAM journals</td>
<td></td>
<td>16.4/16</td>
<td>NS</td>
<td>17.2/12.3</td>
<td>NS</td>
<td>16.4/11.3</td>
<td>NS</td>
<td>23.3/26.4</td>
<td>NS</td>
<td>26.7/34</td>
<td>NS</td>
</tr>
<tr>
<td>Case reports in standard medical journals</td>
<td></td>
<td>19/14</td>
<td>0.336</td>
<td>25/14</td>
<td>0.002</td>
<td>13.8/9.3</td>
<td>0.313</td>
<td>19.8/28</td>
<td>0.141</td>
<td>22.4/34</td>
<td>0.04</td>
</tr>
<tr>
<td>Retrospective case–control studies reported in standard medical journals</td>
<td></td>
<td>16.4/13.1</td>
<td>NS</td>
<td>15.5/17.8</td>
<td>NS</td>
<td>17.2/7.5</td>
<td>NS</td>
<td>21.6/26.2</td>
<td>NS</td>
<td>29.3/35.5</td>
<td>NS</td>
</tr>
<tr>
<td>Prospective randomized controlled clinical trials</td>
<td></td>
<td>18.1/13.1</td>
<td>NS</td>
<td>14.7/16.8</td>
<td>NS</td>
<td>12.1/7.5</td>
<td>NS</td>
<td>27.6/4.3</td>
<td>NS</td>
<td>27.6/8.3</td>
<td>NS</td>
</tr>
<tr>
<td>Evidence demonstrating the treatment’s physiologic mechanism</td>
<td></td>
<td>2.6/1.9</td>
<td>0.726</td>
<td>3.4/6.5</td>
<td>0.281</td>
<td>4.3/15</td>
<td>0.012</td>
<td>37.1/51.4</td>
<td>0.028</td>
<td>52.6/25.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Your clinical experience in your patient population</td>
<td></td>
<td>1.7/0.9</td>
<td>0.615</td>
<td>6/5.6</td>
<td>0.904</td>
<td>6/11.2</td>
<td>0.161</td>
<td>19.8/38.3</td>
<td>0.002</td>
<td>66.4/43.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>
It was observed that the percentage of Romanian physicians in which the recommendations by colleagues who have used the therapy on themselves had a moderate impact was significantly increased comparative to Hungarian physicians ($p=0.028$).

Case reports in standard medical journals regarding the attitude towards CAM had a more increased significant impact on Hungarian versus Romanian physicians ($p=0.04$). Furthermore, the affirmation that CAM therapy has impact on symptoms, conditions and/or disease was the agreed answer in a significantly increase percentage of Hungarian physicians ($p=0.001$). On the contrary, the impact of clinical experience in patient population had a more definite significant impact on Romanian physicians compared to Hungarian physicians ($p=0.001$).

**Discussions**

The study compared the physicians’ responses to questions regarding CAM utilization and outcomes, the physicians’ responses to questions regarding familiarity and experience with various CAM treatments and techniques, and the physicians’ extent of agreement with statements regarding attitude towards CAM. Modified Questionnaire of Wahner-Roedler indicated that Chiropractic, Osteopathy, Homeopathy, Phytotherapy, TCM and Yoga are the most important methods with limited familiarity for Romanian comparative to Hungarian physicians.

More than 100 million Europeans are using CAM, 20% of EU citizens have a clear preference for CAM healthcare, and another 20% are regular users of CAM. Though, CAM therapies still lack scientific validation and are often placed in antagonism compared to conventional medicine. This fact does not discourage patients to consult CAM therapies, sometimes without talking to their doctor (6). On the contrary, healthcare providers, generally physicians, revealed that their own lack of information about CAM and pertinent evidence-based research discourages them from commenting CAM with their patients (7).

Similar with our study, many observational survey studies evaluated the patients’ complementary and alternative medicine (CAM) use and physicians’ familiarity with particular CAM modalities in the same setting and assessed patient-provider dialogue about patients’ CAM use. An example of such a survey included a total of 69 healthcare providers and 468 patients in two Texas cities. The study revealed that CAM methods most used by the patients were not those modalities that provider’s perfect comprehended. Of the 330 patients (70%) who responded to the pertinent questions about CAM, 44.5% claimed never having talked about CAM use with their providers. Moreover, college-educated responders (adjust OR=2.8, 95%CI=1.3-6.0) and US citizens were both about three times more likely to speak about CAM than their opposites (8).

Another Web-based survey was e-mailed to 660 internists at Mayo Clinic in Rochester, MN, USA. Physicians were questioned about their perceptions toward CAM in general and their understanding concerning certain CAM therapies. By all 233 physicians involved in the survey, 76% had never referred a patient to a CAM practitioner. However, 44% stated that they would refer a patient if a CAM practitioner were available at their institution. Fifty-seven percent of physicians believed that integrating CAM therapies would have a positive effect on patient satisfaction, and 48% considered that supplying CAM would attract more patients (9).

With enhanced patient’s use of CAM methods, it is acceptable to anticipate that healthcare providers will become more familiar with different CAM techniques. Therefore, motivating healthcare providers to start discussions about CAM use with their patients it is an essential step in instructing patients regarding the safety, precautions and efficacy of non-practitioner based CAM therapies.

**Conclusions**

Modified Questionnaire of Wahner-Roedler indicated that Chiropractic, Osteopathy, Homeopathy, Phytotherapy, TCM and Yoga are the most important methods with limited familiarity for Romanian comparative to Hungarian physicians.

**Conflicts of interests**

No conflicts of interests are to be declared by the authors.

**Aknowledgements**

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**References**


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MANUSCRIPT REQUIREMENTS

The manuscript must be in English, typed single space, one column on A4 paper, with margins: top – 3 cm, bottom – 2,26 cm, left – 1,5 cm, right – 1,7cm. A 10-point font Times New Roman is required.

The article should be organized in the following format: Title, Names of all authors (first name initial, surname), Names of institutions in which work was done (use the Arabic numerals, superscript), Abstract, Keywords, Text (Introduction, Purpose, Materials and Methods, Results, Discussions and/or Conclusions), References, and first author’s correspondence address.
ERRATUM

Erratum to JURNALUL PEDIATRULUI – Year XVII, Vol. XVII, Nr. 65-66, January-June 2014:

• Pp 2, line 14, Article No. 6, Authors: Zeno A must be replaced with: Andrei Gheorghe Zeno

• Pp 29, line 3, Authors: Zeno A 1,2 must be replaced with: Andrei Gheorghe Zeno 1,2,*

• Pp 29, line 47, Authors’ affiliations: 1 University of Medicine and Pharmacy “Victor Babeș” Timișoara, România must be replaced with: 1 University of Medicine and Pharmacy “Victor Babeș” Timișoara, România, *PhD Student