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Editorial

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Pediatric Exposures to Persistent Environmental Chemicals

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Traditional risk factors are responsible for about 70% of the population attributable risk of Cardiovascular Disease (CVD).[1] Common environmental exposures are known to be responsible for some portion of the remaining 30%. Therefore, it is important to study chemicals like the class known as Perfluoroalkyl Chemicals (PFCs) or Perfluoroalkyl Substances (PSASs). Two of the most highly studied PFCs are Perfluorooctanoic Acid (PFOA or C8) and Perfluorooctane Sulfonate (PFOS or C8S). PFCs are persistent in the environment and associations have been shown with a whole host of negative health outcomes in laboratory animals, including endocrine-disrupting properties as well as developmental effects.[2] To make matters worse, PFCs have been detected in the blood of >98% of the US population[3] and epidemiological studies have demonstrated associations between PFOA and PFOS, and many negative health outcomes such as cancer,[4] CVD,[5] osteoarthritis,[6] hyperuricemia,[7] pregnancy-induced hypertension,[8] endocrine disruption,[9] dyslipidemia,[10,11] and reproductive effects,[12,13] often times even at baseline levels typical of the general population's exposure level.

Children are an ideal sample for studies examining the relationship between common environmental exposures and health outcomes because as a group they are largely devoid of cumulative lifestyle risk factors typically experienced by adults; this phenomenon results in associations less subject to confounding. Perhaps more importantly, pediatrics populations are one of our most vulnerable and should be studied with particular rigor in terms of health effects resulting from virtually unavoidable environmental exposures.

In this field of research, the trajectory tends to move from animal studies to occupational epidemiological studies to highly exposed community-based, to population-based, and finally to pediatrics, before possibly moving on to longitudinal study design. Although associations between PFCs and health outcomes among children have not yet been extensively studied, there is a small and growing body of existing literature in this area.

Intermediate cardiovascular disease outcomes among children are known risk factors for earlier onset of more severe forms of CVD, as well as other types of intermediate CVD that tend to cluster together.[14] In this context, Frisbee et al., using C8 Health Project data (n=12,476) noted a significant positive association among highly exposed children between PFCs and total cholesterol and Low-Density Lipoprotein Cholesterol (LDL-C).[15] Another study by Geiger et al. confirmed the associations among children using nationally representative US data, showing an overall positive, significant association between both PFOA and PFOS, and total cholesterol and LDL-C.[16] Geiger et al. also examined associations between PFCs and serum uric acid levels and results indicated a strong, significant relationship independent even after complex multivariate adjustment.[17] Finally, a cross-sectional study by Hoffman et al.[18] found a modest association between PFOA (OR 1.12; 95% confidence interval [CI]: 1.01-1.23) and PFOS (OR 1.03; 95% CI: 1.01-1.05) and attention deficit hyperactivity disorder among children (n=571).

Needless to say, more research, particularly of longitudinal study design, is needed on child exposure to this class of chemicals as well as other persistent organic pollutants such as Polychlorinated Biphenyls (PCBs) as well as semi-persistent organic pollutants such as Bisphenol-A (BPA).

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Mini Review

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Neonatal Hyperoxia and Pulmonary Hypertension

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ABBREVIATIONS: ACh: Acetylcholine; ALK: Activin-like Kinase; BMP: Bone Morphogenetic Protein; BMPR2: BMP Receptor type II; BPD: Bronchopulmonary Dysplasia; cGMP: Cyclic Guanosine Monophosphate; ETA-R: Endothelin Receptor type A; ETB-R: Endothelin Receptor type B; LRP: Low-density lipoprotein Receptor-related Protein; MYPT1: Myosin-associated Phosphatase Type I; NO: Nitric Oxide; PASMC: Pulmonary Artery Smooth Muscle Cell; PDE: Phosphodiesterase; PH: Pulmonary Hypertension; PPHN: Persistent Pulmonary Hypertension of the Newborn; RVH: Right Ventricular Hypertrophy; sGC: Soluble Guanylate Cyclase; TGF-β: Transforming Growth Factor-β; WISP: Wnt-induced Secreted Protein.

INTRODUCTION

Oxygen therapy and mechanical ventilation with hyperoxia are necessary to treat patients with respiratory distress and failure.[1] However, premature infants requiring oxygen supplementation and ventilation often develop Bronchopulmonary Dysplasia (BPD) as a chronic lung disease, and Pulmonary Hypertension (PH) occurs in 25% to 35% of premature infants with significant BPD. Recent reports indicate that the morbidity and mortality from pulmonary hypertension due to BPD is high, with up to 48% mortality 2 years after the diagnosis of PH.[2] PH is a disease of the pulmonary vasculature defined by an elevated pulmonary vascular resistance leading to right ventricular failure and ultimately death. The effects of adverse environmental factors on a newborn's lungs lead to the failure of the pulmonary circulation to fully adapt to postnatal life. This, in turn, contributes to the pathogenesis of pulmonary vascular dysfunction later in life.[3-5] There is increasing evidence in humans and experimental animal models that exposure to neonatal hyperoxia results in factors that may be linked to the development of pulmonary vascular disease and hypertension. The focus of this review is to elaborate on hyperoxia-activated key sensing molecules and signaling pathways, summarized in Figure 1 and Table 1, in neonatal hyperoxia-induced PH.

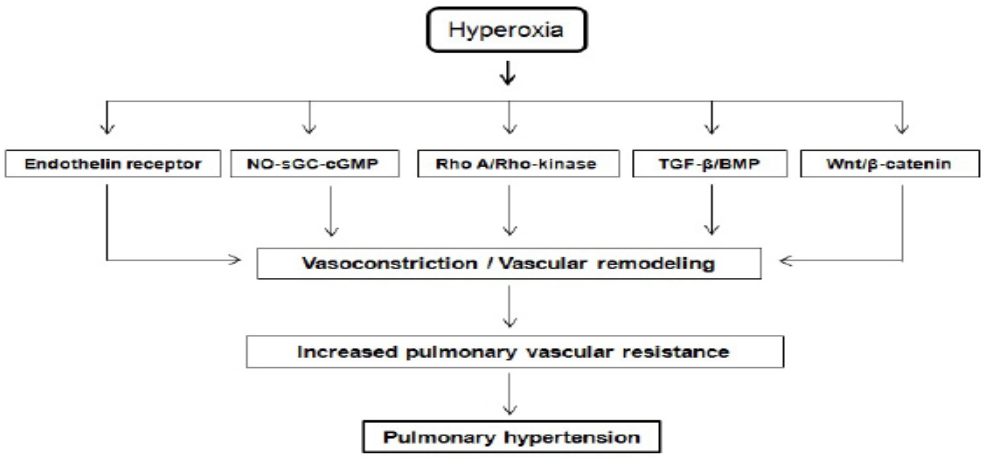

Figure 1. Neonatal hyperoxia modulates signaling pathways leading to development of pulmonary hypertension

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Protein	Signaling pathway	Major functions	Response to hyperoxia	Drug (function)	Dose (route of administration)	Experimental models	Treatment effects	Ref.
PDE5	NO-sGC-cGMP	Hydrolyze and decrease the concentration of cGMP, causing vasoconstriction	Increased expression and activity leading to increased vasoconstriciton	Sildenafil (inhibitor)	50-150 mg/kg/day (subcutaneous injection)	Neonatal rats and mice exposed to hyperoxia	Prolonged survival and reduction of RVH	9-11
PDE4				Piclamilast (inhibitor)	5 mg/kg/day (subcutaneous injection)	Neonatal rats exposed to hyperoxia	Attenuation of RVH	8
sGC	NO-sGC-cGMP	Produces cGMP from GTP, playing an important role in vasodilation	Decreased activity	Cinaciguat (stimulator)	0.05 mg/min (intrapulmonary infusion)	Intrauterine PH in sheep	Significant drop in pulmonary vascular resistance after birth compared with other conditions	11-12
Rho-kinase	RhoA/Rho-kinase	Plays a role in vasoconstriction and maintaining vascular tone	Increased activity	Y-27632 (inhibitor)	10 mg/kg/day (intraperitoneal injection)	Neonatal rats exposed to hyperoxia	Attenuation of MYPT1 phosphorylation and RVH	13-14
ETA-R	Endothelin-1	Induces vasoconstriction and proliferation of smooth muscle cells	Decreased mRNA expression	Ambrisentan (antagonist)	1-20 mg/kg/day (subcutaneous injection)	Neonatal rats exposed to hyperoxia	Attenuation of RVH, pulmonary vascular remodeling, and right ventricular pressure	15
TGF-β superfamily receptors	TGF-β/BMP	Play an important role in cell growth, differentiation, and homeostasis	Down-regulation	Not tested	Not tested	Aged mice exposed to neonatal hyperoxia	Not tested	16-17
LRP5/6	Wnt/β-catenin	Plays a role in cell proliferation and differentiation	Increased activity	Mesd (inhibitor)	(intraperitoneal injection)	Neonatal rats exposed to hyperoxia	Attenuation of RVH, right ventricular systolic pressure, and pulmonary vascular remodeling	18
β-catenin	Wnt/β-catenin	Plays a role in tissue development and remodeling	Increased expression	ICG001 (inhibitor)	10 mg/kg/day (intraperitoneal injection)	Neonatal rats exposed to hyperoxia	Reduction in pulmonary vascular remodeling and PH	19

Table 1. Proteins involved in hyperoxia and pulmonary vascular dysfunction.

NO-sGC-cGMP SIGNALING

Nitric oxide-soluble guanylate cyclase-cGMP (NO-sGC-cGMP) signaling dysregulation has been described in pulmonary hypertensive disease and is a current target of therapeutic agents in humans.[6] Hyperoxic ventilation in the management of Persistent Pulmonary Hypertension of the Newborn (PPHN) results in the formation of reactive oxygen species, such as superoxide anions, which can inactivate Nitric Oxide (NO) and cause vasoconstriction and oxidation. NO is able to act as an antioxidant and has recently been found to improve the oxidative balance in preterm infants.[7]

In the pulmonary vasculature, cGMP concentrations are regulated in part by cGMP-dependent phosphodiesterases (PDEs). PDEs hydrolyze the cyclic nucleotide second messengers of important pulmonary vasodilator agents, including prostacyclin and NO.[8] *In vitro* data have shown that hyperoxia increases PDE5 expression and activity in ovine fetal Pulmonary Artery Smooth Muscle Cells (PASMCs). Exposure of fetal PASMCs to high levels of oxygen leads to decreased responsiveness to exogenous NO. Inhibition of PDE5 activity with sildenafil partially rescues cGMP responsiveness to exogenous NO.[9] In addition, abnormal PDE5 activity has been reported in neonatal animal models of hyperoxia-induced PH. In a rat model, de Visser et al. reported that sildenafil treatment, started simultaneously with exposure to hyperoxia after birth, prolongs survival, increases pulmonary cGMP levels, and reduces Right Ventricular Hypertrophy (RVH).[10] A separate experiment in a neonatal mouse PH model also demonstrated the beneficial effects of sildenafil treatment during chronic hyperoxia or acute hyperoxia with recovery.[11] Untreated animals exhibited increased RVH and disrupted pulmonary artery cGMP signaling. Sildenafil reduced RVH and restored vascular cGMP signaling. As such, PDE5 inhibition with sildenafil has been used to treat severe PH and BPD in humans. Administration of sildenafil is associated with a significant increase in oxygenation as well as a reduction in mortality with no clinically important side effects.

In addition to PDE5, PDE4 has also been observed to play a role in neonatal hyperoxia-induced PH.[8] Although PDE4 inhibition by piclamilast does not advance alveolar development in neonatal rats with hyperoxic lung injury, piclamilast attenuates neonatal hyperoxia-induced RVH when administered either concurrently with hyperoxia exposure or only during the late injury and recovery period.

Experimental animal models have demonstrated

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that NO-responsive soluble Guanylate Cyclase (sGC) activity is decreased in chronic hyperoxia-induced PH.[11] Due to its importance in this signaling pathway, sGC has been the target of recent drug discovery efforts in pulmonary disease. For example, riociguat, a sGC stimulator recently approved by the U.S. Food and Drug Administration to treat adult patients with PH, accelerates the production of cGMP by both synergizing with endogenous NO and directly stimulating sGC independent of NO availability, which can be used to restore NO-sGC-cGMP signaling. Chester et al. have reported that cinaciguat (BAY 58-2667), another sGC activator, augments cGMP levels after oxidative stress and causes pulmonary vasodilation in sheep exposed to chronic intrauterine PH.[12] In contrast to the impaired vasodilator response to Acetylcholine (ACh), an endothelium-dependent relaxing agent, cinaciguat-induced pulmonary vasodilation was significantly increased. After birth, cinaciguat also caused a significantly greater fall in pulmonary vascular resistance compared to 100% oxygen, inhaled NO, or ACh. These data suggest that increased NO-insensitive sGC and sGC stimulators may provide favorable treatment strategies for neonatal hyperoxia-induced PH.

Rho A/Rho-KINASE

Several lines of evidence indicate that the Rho A/Rho-kinase pathway plays an important role in the progression of PH. Rho-kinase is one of several factors that contribute to the normally elevated pulmonary vascular resistance of the fetus and newborn.[13] Chou et al. have reported that neonatal hyperoxia increases Rho-kinase activity in rats, and administration of the Rho-kinase inhibitor Y-27632 effectively blocks the hyperoxia-induced Rho-kinase activity in lungs, attenuating the hyperoxia-induced phosphorylation of myosin-associated phosphatase type I (p-MYPT1) and RVH.[14] This study provides evidence that there are beneficial effects from Rho-kinase inhibitors such as Y-27632 in experimental models of neonatal hyperoxia-induced PH, which will hopefully lead to future clinical trials with new potent compounds selectively targeting this pathway.

ENDOTHELIN RECEPTOR

The development of PH is believed to arise in part from disturbances in the balance between endogenous vasoconstrictors and vasodilators. The endothelin signaling pathway is one of the known vasodilatory pathways involved in the pathogenesis and development of PH. Endothelin-1, a potent vasoconstrictor, binds to Endothelin receptor type A (ETA-R) and B (ETB-R) on PASMCs, which leads to vasoconstriction, proliferation, and migration of the PASMCs. On the other hand, vasodilation occurs due to increased production of prostacyclin and NO when endothelin-1 binds to ETB-R on endothelial cells. Therefore, specific targeting of ETA-R while preserving the potential beneficial effects of ETB-R is an important therapeutic strategy for PH patients. For example, strategies for targeting ETA-R have been used in the treatment of adult PH using ambrisentan, an ETA-R antagonist. In addition, Wagenaar et al. have demonstrated that early treatment with ambrisentan improves survival in neonatal rats exposed to hyperoxia and reduces lung fibrin and collagen III deposition, arterial medial wall thickness, and RVH.[15] When neonatal rats were treated during the late hyperoxic and recovery period, ambrisentan did not improve alveolarization and vascularization, but treatment moderated PH, RVH, and right ventricular peak pressure, demonstrating that ambrisentan prolongs survival and attenuates PH but does not affect inflammation or alveolar and vascular development. This study demonstrates that specific ETA-R antagonists like ambrisentan can diminish the adverse effects of endothelin-1, and that targeting the endothelin-mediated vasoconstriction pathway may be beneficial in treating neonatal hyperoxia-induced PH.

TGF-β/BMP SIGNALING

The importance of TGF-β/BMPR2 in PH has been supported by a number of studies in both animal models and clinical research.[16] Moreover, several studies have indicated that neonatal hyperoxia modulates TGF-β/BMP signaling, causes pulmonary vascular disease, and shortens life span in aging mice.[17] Growth and respiratory compliance are significantly impaired in mouse pups exposed to hyperoxia, and these pups also exhibit a pronounced arrest of alveolarization accompanied by dysregulated expression and localization of both receptor (ALK-1, ALK-3, ALK-6, and the TGF- β type II receptor) and Smad (Smads 1, 3, and 4) proteins. Yee et al. reported that mice exposed to hyperoxia between postnatal days 1 to 4 showed a significantly shortened life span compared to siblings exposed to room air by 67 weeks of age. Mice exposed to neonatal hyperoxia exhibited increased RVH and pulmonary wall thickness. BMP receptors and downstream p-Smad1/5/8 were reduced in the lungs of aging mice exposed to neonatal hyperoxia.[17] These data suggest that loss of BMP signaling in aged mice exposed to hyperoxia as neonates is correlated with a shortened life span, pulmonary vascular disease, and associated cardiac failure. However, there is currently a lack of studies focused on the rescuing of BMP signaling in neonatal hypoxia-induced PH.

Wnt/β-CATENIN SIGNALING

Wnt/β-catenin signaling is a key regulator of multiple aspects of embryonic development and tissue homeostasis. Elevated expression of Wnt signaling molecules is observed in the remodeled vessels of patients with idiopathic pulmonary arterial hypertension. The importance of Wnt/β-catenin signaling was also identified in neonatal hyperoxia-induced lung injury and PH. Alapati et al. have reported that inhibition of LRP5/6-mediated Wnt/β-catenin signaling by Mesd, a LRP5/6 inhibitor, attenuates hyperoxia-induced PH in neonatal rats.[18] Hyperoxia exposure markedly induced p-LRP5/6, cyclin D1, and WISP-1 expression in the lungs of animals. Administration of Mesd significantly attenuated hyperoxia-induced RVH, right ventricular systolic pressure, and pulmonary vascular remodeling. However, there was no effect on alveolarization or vascularization after Mesd administration. A further experiment by Alapati et al. demonstrated that treatment with ICG001, a pharmacological inhibitor of β-catenin, significantly increased alveolarization and reduced pulmonary vascular remodeling and pulmonary hypertension during hyperoxia.[19] Administration of ICG001 decreased PASMC proliferation and expression of extracellular matrix

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remodeling molecules in vitro in hyperoxia. Finally, these structural, cellular, and molecular effects of ICG001 were associated with the down-regulation of multiple β-catenin target genes. These data indicate that Wnt/β-catenin signaling mediates hyperoxia-induced alveolar impairment and PH development in neonatal animals, thereby suggesting a potential therapeutic target to alleviate PH in neonates with severe BPD.

CONCLUDING REMARKS

Neonatal hyperoxia elicits a distinct phenotype of compromised alveolar and vascular development. Exposure of neonates, both humans and in animal models, to high concentra tions of inspired oxygen modulates signaling molecules such as transcriptional factors, protein kinases, receptors, and pro- and anti-apoptotic factors leading to the development of PH and chronic lung disease. However, it is difficult to predict which infants are at increased risk for developing PH. In addition, studies on hyperoxia-induced PH and its treatment are limited, and it is not known why some infants with moderate to severe BPD develop PH while others do not. Furthermore, it has not yet been determined whether neonatal hyperoxia alters epigenetic gene regulation through microRNAs, histone modifications, or DNA methylation leading to PH. So far, oxidative stress due to the generation of reactive oxygen species from hyperoxia has been identified as an important pathological feature in patients with BPD. However, the role and mechanism of oxidative stress in experimental models of neonatal hyperoxia-induced PH have not been well characterized. Moreover, unlike in adult PH, neonatal hyperoxia-induced PH is also associated with impaired lung growth and alveolar development, which continue to have adverse effects later in life. Multiple approaches or combination therapy should be considered for treatment of BPD with PH. It should be emphasized that these studies were performed using preclinical animal models. Therefore, the results are dependent on the animal model chosen and may not perfectly correlate with human diseases. As such, comprehensive studies are needed to fully explore the therapeutic potential of targeting vasodilatory pathways, reversal of vascular remodeling, and regenerative strategies and further our understanding of the mechanisms and pathology of neonatal pulmonary dysfunction that lead to adult diseases.

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Review

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Infantile Hemangioma

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ABSTRACT

Infantile hemangiomas typically appear in the first few weeks of life as areas of pallor, followed by telangiectatic patches. They then grow rapidly in the first 3 to 6 months of life. Superficial lesions are bright red, protuberant, and sharply demarcated and are often referred to as "strawberry hemangiomas". Deep lesions are bluish and dome-shaped, feel like a "bag of worms", and are compressible. Infantile hemangiomas have a predilection for the head and neck region. Most infantile hemangiomas exist as solitary lesions. Infantile hemangiomas continue to grow until 9 to 12 months of age, at which time the growth rate slows down to parallel the growth of the child. Half of these lesions will show complete involution by the time a child reaches age 5; 70% will have disappeared by age 7; and 95% will have regressed by ages 10 to 12. The majority of infantile hemangiomas require no treatment. Indications for active intervention include severe or recurrent hemorrhage unresponsive to treatment, threatening ulceration in areas where serious complications might ensue, interference with vital structures, pedunculated hemangiomas, and significant disfigurement. Treatment options include systemic corticosteroids, intralesional corticosteroids, topical and oral beta blockers, pulsed-dye laser, and less commonly interferon-α or surgical resection. In recent years, propranolol, a nonselective β-blocker, has been preferentially used as a first-line treatment of problematic infantile hemangioma.

KEYWORDS: Infantile hemangioma, Involution, Propranolol, Corticosteroids, Laser, Surgical resection.

INTRODUCTION

Infantile hemangiomas are the most common tumors of infancy, yet most are not present at birth but appear as areas of pallor, followed by telangiectatic patches in the first week of life.[1-3] These lesions are characterized by a distinctive life cycle, in which proliferation is generally limited to the first year of life, at which time the growth rate slows down to parallel the growth of the child, followed by a variable involution phase over the next several years of life.[2,4]

EPIDEMIOLOGY

In the white population, infantile hemangioma affects approximately 1.1 to 2.6% of newborn infants and 10 to 12% of children by the first year of life.[2] The female to male ratio is approximately 3:1.[5,6] Other risk factors for developing infantile hemangiomas include prematurity, low birth weight, white ethnicity, multiple gestations, older maternal age, maternal history of infertility, *in vitro* fertilization, pre-eclampsia, placenta previa, maternal use of progesterone, and chorionic villus sampling.[1-3,7] There may also be a genetic predisposition as siblings of an affected patient have an increased relative risk for infantile hemangiomas.[8]

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PATHOGENESIS

Infantile hemangiomas arise from endothelial stem cells that later proliferate by vasculogenesis, with further angiogenesis. Hypoxia and estrogen are important stimuli and have synergistic effect on angiogenesis.[9,10] The genes encoding Vascular Endothelial Growth Factor (VEGF), indoleamine 2,3-dioxygenase, Insulin-like Growth Factor 2 (IGF2), angiopoietin-1, angiopoietin-2, basic Fibroblast Growth Factor (bFGF), and tyrosine protein kinase receptor (Tie2) are believed to play a significant role in the pathogenesis of infantile hemangiomas.[2,3,5]

An infantile hemangioma might result from a somatic mutation that slows the maturation of endothelial progenitor cells to endothelial cells.[2,5] Infantile hemangioma stains with a panel of immunohistochemical markers such as Glucose-Transporter-1 protein (GLUT-1), Allograft Inflammatory Factor-1 (AIF-1), Lewis Y antigen, and merosin that distinguishes it from other vascular malformations.[1-6] As these markers are expressed in placental microvasculature, infantile hemangioma might originate from embolized placental tissue or a somatic mutation which causes angioblasts to differentiate toward a placental microvascular phenotype.[4,9,10] In this regard, chorionic sampling has been associated with an increased incidence of infantile hemangiomas.

CLINICAL MANIFESTATIONS

It is generally believed that infantile hemangiomas are not clinically apparent at birth.[4,5,11] They usually appear in the first few weeks of life as areas of pallor, followed by telangiectatic patches.[12,13] In contrast, a more recent study showed that infantile hemangiomas were present at birth in 65% of patients.[14] Infantile hemangiomas then grow rapidly in the first 3 to 6 months of life (proliferative phase).[15] They continue to grow until 9 to 12 months of age, at which time the growth rate slows down to parallel the growth of the child (quiescent or plateau phase).[1] Involution begins in most cases by the time the child is 3 to 4 years old (involution phase).

Clinically, superficial lesions are bright red, protuberant, and sharply demarcated and are often referred to as "strawberry hemangiomas" or "capillary hemangiomas" (Figures 1 and 2).[1,3]

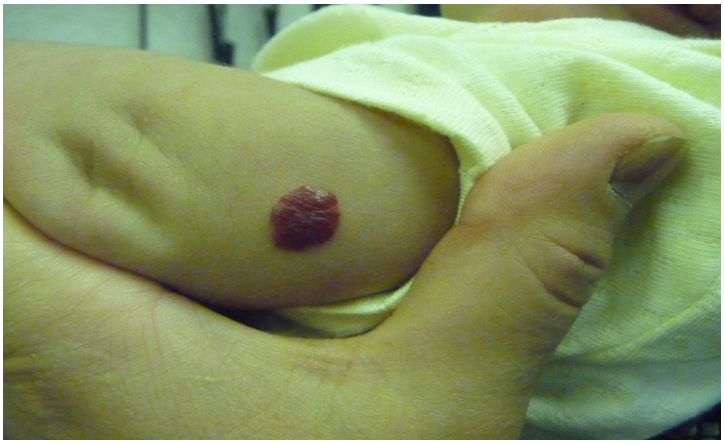

Figure 1: A 6-month old girl with a superficial infantile hemangioma on the left elbow.

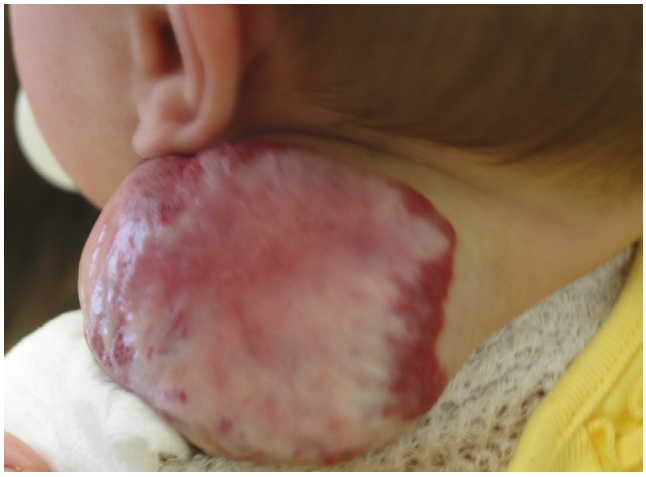

Figure 2: A 10-month old girl with a superficial infantile hemangioma on the left shoulder.

A plaque type is a distinctive variant of superficial hemangioma and is often termed "segmental".[16] A segmental hemangioma is more prone to ulceration and has a stronger association with developmental structural anomalies.[16,17] Deep lesions are bluish and dome-shaped and are noted on average 1 month later than superficial hemangiomas and reach their maximun size between 1 and 2 years of age.[18,19] Deep infantile hemangiomas feel like a "bag of worms" and are compressible.[16] Approximately 60% of infantile hemangiomas are superficial, 15% deep, and 25% mixed superficial and deep.[16] Mixed hemangiomas (both superficial and deep) may show characteristic features of both, often presenting with a red plaque overlying a bluish nodule.

Although infantile hemangiomas can appear anywhere on the skin, internal organs or mucous membrane, they have a predilection for the head and neck region.[16,20] Most infantile hemangiomas exist as solitary lesions,[4,20] although up to 20% of affected children have more than one lesion.[15,16] Infants with multiple lesions may have extracutaneous involvement.[9] Benign neonatal hemangiomatosis is characterized by multiple hemangiomas occurring exclusively in the skin.[21] In most cases, the hemangiomas resolve spontaneously during the first few years of life. In contrast, diffuse (disseminated) neonatal hemangiomatosis is characterized by multiple cutaneous and visceral hemangiomas and associated with a poor prognosis.[21]

An infantile hemangioma usually occurs sporadically and in isolation.[20] Occasionally, it is associated with PHACES syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects or Coarctation of the aorta, Eye abnormalities, and Sternal defects) and PELVIS syndrome (Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tags).[1,4] Lesions over the lumbosacral area may be associated with spinal dysraphism, urogenital abnormalities, and rectal abnormalities.[1] Segment

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al hemangiomas, multiple hemangiomas, and hemangiomas at a high-risk site are associated with a higher risk of extracutaneous anomalies and require referral to a physician or clinic specializing in the management of these lesions.[3,6,16]

DIAGNOSIS

The diagnosis is mainly clinical. Timing of appearance of the lesion, changes in size and color over time, and tactile qualities provide clues for accurate diagnosis.[15] Dermoscopy is useful for evaluating the precise vascular structure.[22] Imaging studies are usually not necessary but should be considered if the diagnosis is in doubt or an associated anomaly is suspected. Color Doppler ultrasonography, computed tomography, and magnetic resonance imaging will reveal specific characteristics of different types of vascular anomalies and delineate the extent of the lesion.[15]

DIFFERENTIAL DIAGNOSIS

Infantile hemangiomas have to be differentiated from Rapidly-Involuting Congenital Hemangiomas (RICH) and Non-Involuting Congenital Hemangiomas (NICH) which are fully formed at birth, have no sex predilection, are pink or violet in color, do not grow postnatally, and lack GLUT1 surface markers.[3,9,18] Lesions are usually noted around the elbows and knees and along the mandibular border.[18] Rapidly-involuting congenital hemangiomas typically shrink rapidly after birth and disappear by 6 to 12 months of age.[19] Non-involuting congenital hemangiomas, on the other hand, do not change after birth. Other differential diagnoses include tufted angioma, Kaposiform hemangioendothelioma, pyogenic granuloma, infantile hemangiopericytoma, glomangiomatosis, port-wine stain, salmon patch, venous malformation, and lymphatic malformation.[16,18]

COMPLICATIONS

Complications include hemorrhage, ulceration, infection in an ulcerated lesion, disfigurement, and compromise of vital functions such as airway obstruction, cardiac failure, visual impairment, and feeding difficulties.[15,16,23] In general, the risk for complications is closely related to the size of the lesion.[24] The risk is greatest in children younger than 6 months of age and in premature infants.[14,25] Incomplete involution may leave residual atrophic scars, hypopigmentation, or telangiectasia. Facial, segmental, or large-sized lesions are more likely to have incomplete involution.[19,22] The condition can be unsightly and cosmetically disfiguring, especially if it occurs on the face. The quality of life may be adversely affected due to psychosocial sequelae, although a recent study showed that affected children do not have a negative quality of life or low self-esteem.[26]

PROGNOSIS

Approximately 50% of infantile hemangiomas will show complete involution by the time a child reaches age 5; 70% will have disappeared by age 7; and 95% will have regressed by ages 10 to 12.[4,13] A central graying of the lesion and shrinkage in size are the visible stages of this process.[4] When involution is complete, the skin looks completely normal; partial involution may result in telangiectasia or an atrophic scar.

MANAGEMENT

The majority of infantile hemangiomas require no treatment.[4,23] Parents should be educated about the natural history of infantile hemangiomas. Follow-up with reassurance to the family is essential. Indications for active intervention include severe or recurrent hemorrhage unresponsive to treatment, threatening ulceration in areas where serious complications might ensue, interference with vital structures, life- or function-threatening complications such as ocular compromise and respiratory distress, pedunculated hemangiomas, and significant disfigurement.[4,6,20,23,24]

Until recently, systemic corticosteroids, mostly oral prednisolone or prednisone, were the mainstay of treatment for complicated infantile hemangiomas.[20] Treatment with systemic corticosteroids is only effective during the proliferative phase.[10,16] Presumably, corticosteroids work by down-regulating the secretion of VEGF-A by hemangioma stem cells.[27,28] The recommended dose is 1 to 3mg/kg/day, depending on whether the lesion is superficial (lower dose) or deep (higher dose).[9,28] The course usually lasts 4 to 8 weeks and an additional few weeks to taper off.[10] Response rates range from 69 to 90%.[10,29] Lesions on the tip of the nose tend not to respond well to steroid treatment.[19] Side effects are increased risk for immunosuppression, hypertension, Cushing's syndrome, adrenal suppression, cataracts, glaucoma, diabetes mellitus, gastrointestinal hemorrhage, osteopenia/osteoporosis, and growth retardation.[27] To minimize adrenal and growth suppression, it is recommended that the steroid should be given in a single dose in the morning. Expert care and monitoring is required when using systemic steroids.

Intralesional corticosteroids can be used for small, localized infantile hemangiomas.[20] Multiple intralesional injections of triamcinolone acetonide over a period of several weeks are often needed. Each dose should not exceed 3 to 5 mg/kg. Complications include bleeding, subcutaneous fat atrophy/necrosis, dyspigmentation of the skin as well as other complications associated with oral corticosteroid administration.

In recent years, propranolol, a nonselective β-blocker, has been used as a first-line treatment of problematic infantile hemangioma.[23] Propranolol-resistant infantile hemangiomas are rare.[30] With a response rate of 98% even in the most complicated cases and a favorable safety profile, propranolol has replaced former treatment options such as corticosteroids and laser therapy.[31] Lou et al performed a meta-analysis on 35 studies that estimated the efficacy of propranolol therapy involving 423 patients with infantile hemangiomas and 248 control subjects.[32] The authors found that efficacy of propranolol was

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more than other therapies in treating infantile hemangiomas (odds ratio:9.67; 95% confidence interval:6.62 to 14.12; P<0.001). In stratified analysis by sites of tumor, propranolol was more effective when compared to corticosteroids (odds ratio: 9.67; 95% confidence interval: 6.61 to 14.15; P<0.001), vincristine (odds ratio: 9; 95% confidence interval: 2.15 to 37.66; P=0.003), and laser (odds ratio: 9; 95% confidence interval:1.42 to 57.12; P=0.02) in treating cutaneous infantile hemangiomas (odds ratio: 24.95; 95% confidence interval:9.48 to 65.64; P<0.001), periocular infantile hemangiomas (odds ratio:9.39; 95% confidence interval: 3.88 to 22.71; P<0.001), airway infantile hemangiomas (odds ratio: 20.91; 95% confidence interval: 7.81 to 55.96; P<0.001), and hepatic infantile hemangiomas (odds ratio: 9.89; 95% confidence interval: 20.81 to 81.54; P=0.033). The mechanisms whereby propranolol works include vasoconstriction of the high-flow blood vessels feeding the hemangioma, suppression/blockade of VEGF and bFGF with induction of apoptosis of capillary endothelial cells, blockade of GLUT1 receptors, and accelerated adipogenesis of hemangioma stem cells.[9,33,34] Other authors suggest that propranolol does not induce apoptosis of infantile hemangioma stem cells, which is in contrast with the result of capillary endothelial cells.[35] In contrast to corticosteroids, propranolol is effective in treating hemangiomas in children of all ages, and not limited to the proliferative stage of the lesions.[36] The recommended dose is 1 to 3 mg/kg/day divided in three doses.[37] Clinical improvement is evident in the majority of patients within the first week of treatment.[32] Side effects are uncommon and include hypoglycemia, hypotension, sinus bradycardia, cold extremities, bronchial hyperreactivity, constipation, nocturnal restlessness, somnolence, seizure, and electrolyte disturbances.[9] Contraindications to the use of propranolol include hypoglycemia, reactive airway disease, significant cardiac disease (heart failure, cardiogenic shock, hypotension, second or third degree heart block), compromised renal function, central nervous system disorders, and hypersensitivity to propranolol.[10] Facial and mixed hemangiomas with both superficial and deep components tend to respond less well.[10] Rebound growth after discontinuation of treatment has been reported.[37] Expert care and monitoring is required when using oral propranolol.

Timolol maleate, a nonselective topical β-blocker, may have a role in the treatment of superficial lesions. Topical timolol has fewer side effects than systemic administration of β-blocker.[38] However, systemic absorption following topical application of timolol can occur, especially in young infants. Pruritus may occur at the application site.[38] Topical timolol may be considered in patients at risk for potential side effects from oral administration of propranolol.[39]

Interferon-α may be considered if there is no response to corticosteroid or propanolol. The mode of action can be attributed to its anti-angiogenesis and bFGF inhibition properties. The recommended dose is 3 million IU/m2/day. The medication is usually given subcutaneously for a few months.[19] Neurotoxicity such as spastic diplegia and developmental delay occurs in 10 to 30% of patients.[24] Other side effects include fever, irritability, depression , anemia, neutropenia, thrombocytopenia, hypothyroidism, and hepatotoxicity. Interferon-α is best avoided in infants as they have a higher risk for complications.[24]

Treatment with pulsed-dye laser with a wavelength of 595-nm, typically performed by a dermatologist, may be useful in the treatment of superficial infantile hemangiomas.[40] Pulsed-dye laser works by targeting intravascular hemoglobin resulting in vascular injury. Early treatment is associated with better cosmetic results. Pulsed-dye laser may also be used to reduce the telangiectasia that may occur after the involution phase. Adverse effects include hypopigmentation, skin atrophy, ulceration, and scarring.[40] A recent study showed that facial-segmental infantile hemangiomas treated with propranolol and pulsed-dye laser displayed more rapid and complete clearance and required a lower cumulative propranolol dose to achieve near-complete clearance.[41]

Surgical excision is indicated for function- or life-threatening or disfiguring lesions when pharmacologic agents are contraindicated, not tolerated, or fail. It may also be considered for lesions on the tip of the nose or eyelid, pedunculated lesions, ulcerated lesions, and lesions with a thick dermal component.[10]

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Case Report

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Giant Scrotal Hernia in a Tiny Male Infant

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ABSTRACT

Inguinal hernia is a common diagnosis in children. A real scrotal hernia is less common and underreported in medical textbooks. In this case a tiny Libyan boy was admitted with a big swelling of the left groin and hemiscrotum. His clinical findings have been mistaken for a longer time, until the definitive diagnosis has been made. During surgery a giant real scrotal hernia has been dissected and successfully repaired. All specific findings in this special case of infant scrotal hernia are discussed in front of a literature review.

KEYWORDS: Scrotal hernia; Infants.

INTRODUCTION

Inguinal hernia is one of the most common finding and subsequent reason for surgery in infants and children. Approximately 60% of inguinal hernias are located on the right, 25% on the left side, and 15% are found bilateral. Inguinal hernia is predominant in boys over girls (80:20).[1,2]

The diagnosis of a scrotal hernia instead is less common. Therefore, reports on definite scrotal hernias in children are found only sparsely in medical textbooks and literature reviews. By definition, a scrotal hernia is characterized by a large indirect hernia running through both, the internal and external inguinal rings, carrying the contents of the hernia sac deeply into the scrotum.[2]

Besides inguinal hernia, strangulated or not, a hydrocele, an incarcerated ovary, a varicocele, or inflammatory and neoplastic groin and scrotal masses, and last but not least the whole entity "acute scrotum" have to be considered in order to find the final diagnosis.[1,2]

In this brief case report a tiny boy suffering from a giant scrotal hernia is presented, and his diagnosis discussed in front of the current literature available at hand.

CASE PRESENTATION

A Libyan mother presented her 1½ year old son with a giant swelling of his scrotum. The swelling of the left scrotum was constantly increasing since birth. Otherwise the boy was healthy and showed a regular development. However, because of this "giant mass" he was unable to walk freely.

During clinical examination a giant, soft, non-tender, but easily reducible swelling in the left groin and hemiscrotum could be detected (Figure 1). Both testicles, epidydymes and spermatic cords were easy palpable, painless, with no signs of inflammation. No enlarged lymph nodes were detectable in the groin. Regular male genitalia, no signs of a varicocele. Diaphanoscopic illumination of the scrotum for hydrocele testing was negative. A wide open inguinal ring was present. The protruding hernia sac was filled with

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bowel, that could be easily reduced from the scrotum back into the abdomen (Figure 2).

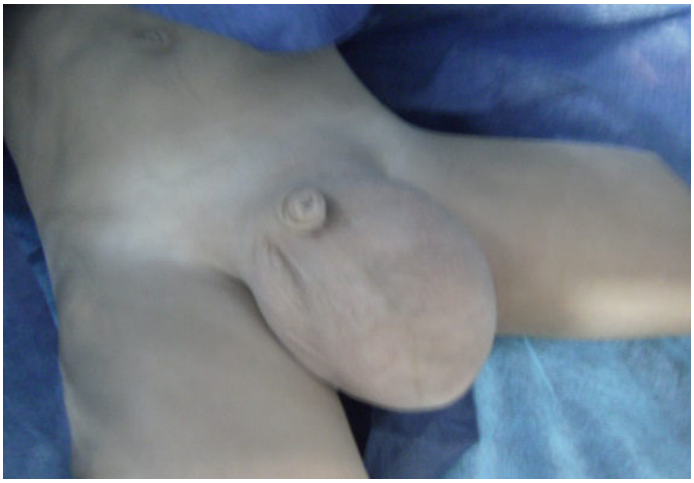

Figure 1: Giant scrotal hernia on the left side.

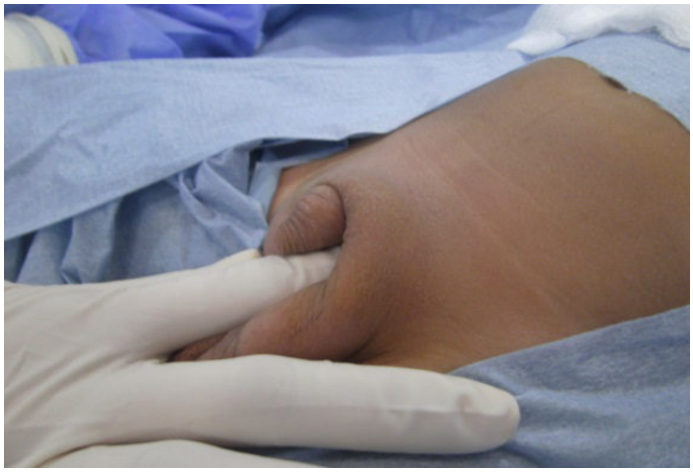

Figure 2: Giant scrotal hernia reduced back through the inguinal canal into the abdominal cavity. scrotal hernia on the left side.

The ultrasound scan of the scrotum and groin revealed no hydrocele or varicocele formation. No echogenic irregularities on the testis or testicular appendages become visible. No scrotal edema. During dynamic examination a small bowel loop with regular peristalsis could be detected, running straight through the inguinal canal. No enlarged lymph nodes could be visualized further up in the groin. No free fluid or air in the lower abdomen was visible. After voiding the urinary bladder was empty.

A few days later elective open surgery was performed *via* the left inguinal approach. After splitting the external oblique aponeurosis, the thickened and huge hernia sac was protruding immediately out of the inguinal canal. The roof of the sac was incised and a 1m (!) long small bowel loop was reduced slowly back from the bottom of the scrotum back into the abdominal cavity. Following the spermatic cord, the entire scrotal part of the hernia sac, the testes, together with the edematous scrotal coverings were brought smoothly back into the incision site (Figure 3). After that, the entire sac was carefully dissected step-by-step from the spermatic cord and the inner scrotal wall under meticulous bipolar coagulation. The base of the sac was twisted at the level of the abdominal transversus muscle, closed by a pursestring suture, than resected, before the base was fixed in Bastianelli-technique to the inner abdominal oblique muscle. The small left testis was brought back into the scrotum and fixed by its gubernaculum after checking for a Morgagni hydatide. Finally, the surgical site was closed according to Grob with fine absorbable sutures.

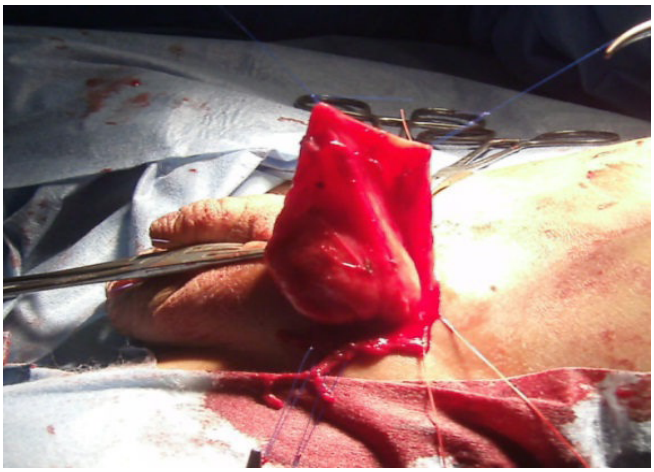

Figure 3: Entire hernia sac brought into the incision site.

The postoperative course was uneventful. The boy was discharged the following day with a moderate swelling. At 1 week follow-up no signs of infection were noticed, and the swelling has had markedly decreased. Shortly after, the boy started to stand and tried to walk freely.

DISCUSSION

Acute painful scrotal swelling in children and infants is a common entity that requires prompt, accurate and appropriate therapy. The etiologies of these symptoms can range from benign self-limited conditions to more serious organ threatening problems like testicular torsion,[3,4] or torsion respectively strangulation of the hernia sac.[3-7] In these cases usually urgent surgical intervention is necessary.[1-7]

In this case the swelling was chronic and always pain-free, but progressive over the time. Maybe the civil war setting forced his caregivers to take it less seriously under such circumstances.

Since they are placing a considerable economic burden on their countries` health care budgets, a larger number of papers on “hernia in combination with groin and scrotal diseases” in adults and children do exist. While, when searching the common medical literature and textbooks specifically for the term “scrotal hernia”, only sparse information will be found.[8-10] And, usually these authors refer much more to the “inguino-scrotal” hernia” or the “acute scro

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tum" entity, than to the well defined "scrotal" hernia as already mentioned in the previous paragraphs.[1-2]

Nevertheless, strangulated inguino-scrotal hernias are a clinical entity, that must be included in the differential diagnosis of a "real" scrotal hernia. Here, Eriki et al. presented a series of patients with an average age of 1.9 years (range 22 days - 10 years), with half of their patients presenting as soon as in the newborn period. In the majority of cases the hernias were right - sided.[4] Several other authors presented cases of indirect hernia sac torsions,[3,5,6,7,11] with their results being comparable to Eriki et al' s findings. Khozeimeh et al. presented an extraordinary case of a newborn with giant bilateral inguinal hernias complicated by in utero perforation and meconium peritonitis.[12] Authors from Brazil, finally, reported a case of a child with a ventriculo-peritoneal shunt, where the tip migrated into the scrotum mimicking a scrotal hernia.[13] Indian authors, indeed, reported a case where a huge anterior urethral diverticulum was presenting as an inguino-scrotal swelling.[14]

Thus, to the best of our knowledge we did not found any comparable cases of true, well defined scrotal hernia with this search strategy in our literature review. We are unsure, why the scrotal hernia is of less interest in the pediatric surgical community. For sure, every pediatric surgeon can handle any kind of hernia, but it should not be forgotten that giant scrotal hernia can pose a considerable challenge on the less experienced one.

Based on history and physical examination, and with the selective use of ultrasonography, inguinal hernias, all types of hydrocele, and scrotal masses can be differentiated in almost all cases. Especially, ultrasound is well suited for the study of all pathological conditions of the scrotum in children. Because, ultrasonography provides excellent anatomic details, dynamic mode, is bed-side available, cheap and lacking of irradiation harms.[15,16] Like in our case, where bed-side US scans visualized the small bowel loop within the semi-scrotum and confirmed the final diagnosis.

In medical textbooks usually two inguinal rings are defined: internal and external. Several authors introduced a third one, the "secondary internal ring", located more deep to the classical internal one. Respectively a fourth one, named the "secondary external ring". Embryologically, this ring may be formed by evagination of the Scarpa fascia during testicular descent. Its anatomic position is 2cm below the pubic tubercle. It is formed by Scarpa fascia that covers the spermatic cord anteriorly. Medial and lateral fascial reflections delineate the ring and form the spermatic cord canal. The cord is attached to the posterior wall of the canal, and the canal ends at the entrance of the scrotum, where Colles` fascia fuses with the coverings of the cord. Surgically, an inguino-scrotal hernia passes (in addition) through this secondary external ring and obtains an extra outer layer by entering the spermatic cord canal. Underdevelopment of this ring may lead to incomplete testicular descent or ectopic testis.[17]

The huge hernia sac and the extremely wide "classical" rings and inguinal canal found and dissected in this case might have been representatives of such a second external ring and/or spermatic cord canal. However, since only a surgical and not a histological dissection has been performed this question will be left unanswered.

Mirilas et al. recommend to reconstruct the Scarpa`s ring after all orchidopexies and herniotomies in children, while Okoro et al. found no demonstratable advantage or disadvantage in closing the spermatic fascia after every herniotomy in children. Therefore, the decision to close or not to close should be at the discretion of the individual surgeon.[17,18]

In this case, the spermatic fascia was closed after tailoring by the intention to prevent seroma formation better.

CONCLUSION

Since there is only scant information about scrotal hernias in infants and children available in medical literature and textbooks, their management might be challenging especially for the junior pediatric surgeon on call.

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Mini Review

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Are We All Talking about the Same Thing? Heterogeneity and Nomenclature in Description of Natural Health Products

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ABSTRACT

The use of Natural Health Products (NHPs) in pediatrics is becoming increasingly common. NHPs are often referred to by a variety of different names, which may lead to parental/patient confusion when asked to disclose their use. The aim of this paper is to determine what terminology is cited throughout the literature to describe NHPs. This review reveals that there is significant heterogeneity in the literature used to describe NHPs. Nurses need to be aware of the diverse terminology used to describe or define NHPs, so that further delineation can be attempted while assessing for their use among their patients. Clear communication is pertinent to the delivery of safe patient care, so that all medicinal products can be accounted for, regardless if they are classified as "natural" or otherwise.

KEYWORDS: Natural Health Products (NHP); Communication; Terminology.

BACKGROUND

Throughout the world Natural Health Products (NHPs) are referred to in the same spoken language with different terminology. Just as it is pertinent to understand homonyms in medicine (such as "lyse", to break something open, and "lice", a parasite) it is also important to understand how language used to describe NHPs can contribute to miscommunication in assessment and patient care. The World Health Organization recently reported that natural products are widely valued and utilized globally, and their use is anticipated to continually grow.[1]

The term NHP was coined in Canada and includes vitamins and minerals, herbal, homeopathic, and traditional medicines (such as Chinese medicines), probiotics and other products such as amino acids and essential fatty acids.[2] In the United States (US), NHPs include these same products although are considered "food products" intended to supplement the diet, hence, the term dietary supplement.[3] Due to the author's belief that NHPs are medicinal, rather than nutritional, the term NHP is used throughout this paper.

The term "natural" does not necessarily mean a therapy is safe; this is illustrated with the natural leaves of the Erythroxylum coca bush that pose serious health risks when produced into the illegal street drug, cocaine.[4] In addition, almost 25% of NHPs are comprised of natural plant substances and can have the same biological effects on patients as other prescription medications.[5] Globally, some NHPs are placed under strict government regulations, and others are easily accessible as over the counter products. A good example of this is melatonin. In the US, melatonin is considered a dietary supplement, in Canada, a NHP, and in Australia, it is available only as a prescription medication. The aim of this review is to investigate the different terminology used throughout the literature to describe NHPs.

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METHOD

Two bibliographic databases were searched for discovery of utilized terminology in March 2014. Inclusion criteria were peer-reviewed article titles, with human health science research, published within the past five years. The first database, PubMed, was chosen for its wide access to biomedical literature from the US National Library of Medicine. Results revealed citations for the term dietary supplements (245 articles), botanical (111 articles), complementary and alternative medicine (661 articles), nutraceutical (76 articles), NHPs (22 articles), natural medicine (8 articles) traditional medicine (115 articles) and herbal medicine (297 articles).

Despite PubMeds global access, a second search was performed using Scopus in effort to limit cultural confounding. Scopus reports they are the largest biomedical database of peer-reviewed literature, abstracts, and citations, and place emphasis on the inclusion of global research. Using the same inclusion criteria as the prior search, the author found dietary supplements (331 articles), botanical (64 articles), complementary and alternative medicine (673articles), nutraceutical (50 articles), NHPs (22 articles), natural medicine (21), traditional medicine (718) and herbal medicine (370 articles).

Title Term Searched	PubMed	Scopus
Botanical	111	64
Dietary Supplement	245	331
Complementary and Alternative Medicine (CAM)	661	673
Nutraceutical	76	50
Natural Health Product (NHP)	22	22
Natural Medicine	8	21
Traditional Medicine	115	718
Herbal Medicine	297	370

Table 1: Natural Health Product Terminology: Displays search results for terminology used to describe natural health products in PubMed and Scopus. CAM and traditional medicine were found the most, and natural medicine was found the least.

FINDINGS

Search results imply that there is wide nomenclature and heterogeneity in the literature when describing NHPs. It appears that bibliographic databases produce a variety of citations, favoring the terms complementary and alternative medicine or traditional medicine. Policies and product regulations within different countries often bind terminology used among their health care agencies. The worldwide diversity in the terminology utilized to describe similar products could potentially lead to decreased access to evidence based literature among health care professionals, hasten confusion among patients and peers, and finally, limit the dissemination of knowledge.

DISCUSSION

Despite the common use of NHPs, it has been reported that there is little acknowledgement between families and providers when discussing the care of a child. Approximately 37% of clinicians ask about NHP use, and up to 72% of patients don't spontaneously disclose using it.[6] Families do not report using NHPs because they assume their medical provider has no knowledge of NHPs, the provider never asks, or they fear a negative response.[7]

Open communication about all medical therapies is paramount to the delivery of safe patient care. Certain NHPs put patients at risk for potential drug-herb interactions. Liver enzymes, such as CYP450, can be altered by the use of an NHP, and as a result, render a prescription drug more toxic or ineffective. In addition, co-administration of NHPs with prescription medications is common.[8] If a parent/patient fails to disclose NHP use (either by failure to report or by failure of being asked) the risk of drug-herb interactions increases greatly.

Goldman and associates conducted a study in a pediatric emergency room department in 2008 and found that concurrent drug-NHP use was documented in every fifth patient, and 15% of NHP users were receiving more than one NHP simultaneously. One quarter of those paired medication-NHP or NHP-NHP could have potentially caused adverse interactions, with bleeding being the most common.[9] The importance of this can be illustrated with patients taking high doses of fish oil supplements. Omega fatty acids can produce an antithrombotic effect, increasing the risk of bleeding. Disclosing the use of this NHP would be significant for a provider who was evaluating a patient who had received a traumatic head injury.

Children are more susceptible to adverse NHP effects because of the differences in their metabolism, physiology, and dose per body weight. If a provider is not aware a child is taking an NHP, he/she cannot give recommendations on its safety or efficacy. A study in 2011 discovered approximately 9% of infants were given NHPs, most commonly "gripe water", within the first year of life.[10] Parents reported that their sources for information on this NHP came from friends, family, or media. Parents reported receiving the least amount of information from their health care provider, who is arguably in the best position to provide such advice.

IMPLICATIONS/CONCLUSIONS

To the author's knowledge, this is the first known scholarly review to evaluate the literature surrounding the

terminology of NHPs. Despite what terminology is used to describe a NHP, health care providers need to be aware of their use so they can provide appropriate medical care. The results of this review suggest natural medicines and substances are called by many different names. While keeping up to date with all possible labels assigned to NHPs is prudent for clinicians, so is understanding confusion and misconceptions are likely among patients. It is plausible to consider that allotting more time to further define what NHPs are (naming them individually; vitamins, minerals, herbs, amino acids, essential fatty acids, probiotics, and traditional medicines), will yield greater disclosure of their use among patients. Once patients and providers can agree they are talking about the same thing, important health information can be elicited for all medicinal products patients are consuming. Full product disclosure enables clinicians to provide more comprehensive, holistic, and safer patient care.

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Review

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Pediatricians and Pediatric Nurses in the Delivery of Culturally Competent Care: A Scoping Literature Review to Investigate Progress and Issues around Culturally Diverse Care in Pediatrics

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ABSTRACT

The demographics in the United States are rapidly changing. In 2012, 47.2% of the children who lived in the United Stated were of color. However, three out of four physicians identified themselves as White non-Hispanic and approximately 83% of nurses are White, non-Hispanic. The changing demographics and increasing diversity of the population has an impact on care and quality of care being delivered by pediatric healthcare providers to children and their families. In 2005, The Office of Minority Health reported that the main ingredient in closing the gap in health care disparities is cultural competency. This scoping literature review investigated how pediatricians and pediatric nurses were progressing with their delivery of culturally competent care. The studies in the review revealed that the delivery of culturally competent care by pediatric health care providers has been a slow and difficult process and that there are identified areas of improvement. Pediatricians, pediatric nurses, other pediatric health care providers and families whose children received health care services from these providers were participants in the studies reviewed. Health care providers reported that more cultural competence training and education was necessary. Families in several studies identified communication/linguistics and the provider's ability to be more open and aware as areas where more cultural education and training are needed.

KEYWORDS: Cultural competence; Diversity; Pediatrician; Pediatric nurses; Health disparity; Communication; Openness.

INTRODUCTION

Limited research has been found in the literature to inform pediatric health care providers, specifically physicians and nurses on their progress of delivering culturally competent care to their patients and families and what are the issues that arise when they are caring for diverse patient populations. However, a vast amount of literature exists stating why it is important and necessary to provide culturally competent care for all patient populations. A key factor in the necessity to provide culturally competent care is the rapidly changing demographics across the United States. According to Humes, Jones, and Ramirez[1] data from the 2010 Census revealed a 32% increase since 2000 in people reporting they belonged to two or more race categories. Two races that reported the greatest growth in ten years were the Asian and the Hispanic populations. The Asian population experienced the fastest rate of growth that increased 43.3% from 2000. Today, the Asian population comprises almost 5% of the total population in the United States. The Hispanic population grew by 43% between 2000 and 2010, accounting for approximately half of the total population growth in those ten years and comprising 16%

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of today's total population. The White only population experienced the slowest rate of growth, with only 1.2% increase between 2000 and 2010. The overall population of those reporting White only decreased from 69% to 64% in that ten year period.

In 2012 there were 73,728,088 children who lived in the United States.[2] Of those children 47.2% were of color. The largest percentages reported being Hispanic children (23.9%), Black children (13.9%) and Asian children (4.6%). Additionally, 3.9% of children reported being of two or more races.

While the demographics of the population in the United States are rapidly changing, the demographics of nurses and physicians do not reflect this rapid change. Findings from the "2008 National Sample Survey of Registered Nurses"[3] reported that the population of nurses from minority racial/ethnic groups has increased by 54% between 2000 and 2008. However, even with the 54% increase, minority racial and ethnic nurses only comprised 16.8% of the total nurse population in the United States. According to the "2008 National Sample Survey of Registered Nurses", 5.8% of nurses stated they were Asian and 3.6% of nurses stated they were Hispanic. An overall, 83.2% of nurses reported being White, non-Hispanic, an indication that nurse represented a primarily homogeneous workforce.

In examining physician demographics, The Center for Studying Health System Change[4] reported that "three out of four physicians identified themselves as white, non-Hispanic, while 3.8 percent were black, non-Hispanic, 5.3 percent were Hispanic, and 17.2 percent were Asian or other races. Among physicians under age 40, about two-thirds were white and 33 percent were minority - black (4%), Hispanic (5.4%), and Asian or other race (24%)".[4]

In Pediatrics, the Official Journal of the American Academy of Pediatrics, Goodman[5] stated that one of the challenges facing pediatric healthcare providers is that it still fails to reflect the growing racial and ethnic diversity of the United States even with strategies in place to expand medical school opportunities for underrepresented minority groups including black, Hispanic, and American Indian/Alaska Natives. Additionally, "the disparity in race and ethnicity is anticipated to grow substantially by 2025, reflecting the combination of high minority population growth rates and an assumption of slow increases in enrollment rates of individuals of minority groups in medical education".[5]

The changing demographics and increasing diversity of the population has an impact on care and quality of care being delivered by healthcare providers.[6] In 2005, The Office of Minority Health[7] reported that the main ingredient in closing the gap in health care disparities is cultural competency.

Cultural Competency

The National Center for Cultural Competence (NCCC) as cited in Ahmann,[8] stated one of the important reasons for promoting culturally competent care is to improve the quality of services and health outcomes. Furthermore, OMH[7] reported that "health care services that are respectful of and responsive to the health beliefs, practices, and cultural and linguistic needs of diverse patients can help bring about positive health outcomes". Additionally, culturally competent care provided by health care providers increases the satisfaction of the person and family receiving the services and lends itself to a more rewarding interpersonal experience. In order to provide culturally competent health care services critical factors must be included:

- An understanding of the beliefs, values, traditions and practices of a culture.
- Culturally defined, health related needs of individuals, families, and communities.
- Culturally- based belief systems of the etiology of illness and disease and those related to health and healing.
- Attitudes toward seeking help from health care providers.[8]

Many health care institutions and academic settings (schools of medicine, nursing and health related science schools) provide training and include curriculum around cultural competence, but limited research was located focusing on pediatric physicians and nurses and if strides have been made in delivering culturally competent care to their patients and families.

Review of the Literature 2005-2014: Methods

The literature review presented here uses a scoping review methodology as described by Armstrong, Hall, Doyle and Waters.[9] A scoping method was used to identify research gaps and to summarize findings of research. Standage and Randall[10] stated a "scoping review allows for a broader approach and attempts to capture all the literature irrespective of the quality of the data or method".

The two research questions guiding this literature search were: Are pediatric physicians and nurses delivering culturally competent care to their patients and families? What do pediatric physicians and nurses report are the issues related to providing culturally competent care to their patients and families as addressed in the research between the years 2005-2014? The data bases used were CINAHL, ERIC, and Academic Search Premier. The English language and published research relevant to the research question was included. The keywords used were cultural competence, children, pediatric nurse, pediatrician, pediatric health care providers and health care providers. Forty-five were retrieved, of which 35 were rejected because they did not contain methodologically based research. Eight of the rejected articles detailed programs on how to provide cultural competence training; another 20 articles did not include pediatric patients, health care providers or cultural competence; five articles detailed methods to do research or suggestions on how to capture culturally competent care; three articles were either letters to the editor,

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Author	Country Based	Method	Data Collection	Participants	Key Findings
Berlin, Nilsson, &Tornkvist (2010)	Sweden	Quantitative	Survey questionnaire	51 Swedish Pediatricnurses who worked at a primary child health-care center: 24 nurses in theintervention group received cultural competence training 27 nurses in the control group did not receive training	Statistically significant improvements in the areas of cultural knowledge, cultural skill, and cultural encounters in the intervention group participants following training. Additionally 92% of the intervention group participants increased their desire to learn more about culturally competent health services
Davies, Larson, Contro, & Cabrera (2011)	USA	Qualitative	Interviews	13 Mexican-American Families whose children were treated for a life-limiting illness at two children's hospitals in Northern California	Participants perceived discrimination across a variety of settings (including the two hospitals in the study, other hospitals and community clinics) where their children received care.
Johnson, Clark, Goree, O'Connor, & Zimmer (2008)	USA	Qualitative	Focus Groups	38 Healthcare Providers: 13 WIC Educators, 9 Registered Nurses, 8 Medical assistants, 3 WIC Dieticians, 3 Pediatricians, Physician Assistants who worked in well-established Mexican American communities and newer Mexican immigrant communities in the Denver metropolitan area.	Five overarching themes were identified that represented provider's perceptions of Mexican American families' practices as related to early weight and growth and a sixth theme identified providers' reflections about their practice with this population: 1) a chubby baby is a healthy baby 2) Complementary foods are introduced earlier than recommended 3) Extended family influences feeding practices 4) Mothers offer high-calorie, low-nutrient dense food choices 5) Mothers delay weaning from the bottle 6) What's a provider to do? Role confusion
Kerfeld, Hoffman, Ciol, &Kartin (2010)	USA	Quantitative	Survey questionnaire	750 Families who had Children with Special Health Care Needs	Patients who were White non-hispanic perceived the providers of healthcare for their Child with Special HealthCare Needs as providing more culturally competent care compared to other race/ethnic group. Forgone/delayed care was more often reported by White Hispanics, followed by Multiple/Other Hispanics and Black Hispanics
Pergert, Enskar, & Bjork (2008)	Sweden	Qualitative	Interviews	12 Swedish Pediatric Nurses who worked on a pediatric oncology unit	Pediatric hospital nurses who were faced with overwhelming emotional expressions by families with a foreign background were found to override their professional preparedness on account of a distinguishing difference between the expression and the norm.
Tavallali, Kabir, &Jirwe (2014)	Sweden	Qualitative	Interviews	14 Swedish Parents with a child in the hospital who had minortity/ethnic nurses	Nurses' ethnicity did not have much impact on parents' satisfaction related to the care of their child. Parents attached great importance to the nurses' language skills, to their adaptation to and awareness of the Swedish culture and to their professional knowledge and personal attributes.
Whitman, Davis & Terry (2009)	USA	Quantitative	Survey Questionnaire	1,429 Rural and urban public school nurses in Alabama	Participants located in both urban and rural areas of Alabama have witnessed an increase in the number of English-as-a-second-language (ESL) students and a third have experienced difficulty communicating with these children. Over half have experienced difficulty communicating with the parents of the ESL students. Use of the student as a translator when speaking to parents was reported in over half of urban schools and nearly 47% of rural schools.

Table.1: Selected papers in scoping literature review

editorials or briefs; and two articles were literature reviews. The remaining seven articles formed the basis of this review (Table. 1).

Literature Review 2005-2014: Findings

Of the seven studies reviewed three used a quantitative research design in corporating survey questionnaires. The other four studies utilized a qualitative research design incorporating focus groups or interviews. Participants from four of the studies were pediatricians, pediatric nurses, or other health care providers who worked with children. The participants from the remaining three studies were families whose children had received care in hospitals or community settings. Three of the studies were performed in Sweden and four were performed in the United States.

Thematic analysis of the data produced the essential theme that pediatric health care providers are still lacking in cultural competence and significant progress still needs to be made in this area when caring for children and their families. In the studies, specific cultural competence issues were seen around communication/linguistics (including language barriers) and provider openness and awareness. Strategies that were identified in the studies that would possibly increase cultural competence are: training, education and increased resources.

Communication: Research done by Betancourt, Green and Carrillo[11] found that the "provision of culturally competent care may be hindered because of (a) nurses' own linguistic and culturally diverse backgrounds (b) hospitals' poorly designed patient support systems for culturally diverse patients an (c) providers' poor communication skills". Four of the studies in this literature review cited at least one of these factors as a hindrance in providing culturally competent care.

In the research done by Tavallali, Kabir, and Jirwe[12] Swedish parents reported communication between them

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and the minority ethnic nurse was one of the most important aspects and a key indicator of good, quality nursing care. All of the parents in the study expressed the importance of the minority ethnic nurse having Swedish language skills and lack of this language skill reduced parents' satisfaction with the care provided by the minority nurse. Kerfeld, Hoffman, Ciol and Kartin[13] supported this thought in their study of dissatisfaction with care among parents of Children with Special HealthCare Needs. "Negotiating complex communication in a clinical encounter is a more difficult task and might be associated with increased dissatisfaction with care". Similarly, in the study done by Davies, Larson, Contro and Cabrera[14] Mexican American families perceived poor quality of care and discrimination by their pediatric health care providers as a result of language barriers.

Public school nurses in Alabama reported on the communication challenges they faced with their growing English-as-a-Second-Language (ESL) student population.[15] A third of the nurse respondents reported difficulty communicating with the students while over half reported difficulty communicating with parents of the students. Nearly 50% of the nurses stated they used the students as interpreters when speaking to their parents, even though interpreter services were available. "This raises serious concern over the quality and accuracy of the communication between the school nurse and the parents".[15] The study related possible internal structural issues or lack of knowledge on the nurse's part related to the lack of use of interpreter services. The researchers saw this language barrier as a serious impediment in the nurses' efforts to care for ESL student and their parents. Furthermore, the authors stated that by providing school nurses with interpreter services barriers to access and health disparities can be significantly reduced

Each of the four articles recommended cultural competence training, education or both in order to increase the knowledge and skill of pediatric health care providers in the area of communication. Kerfeld et al.[13] and Whitman et al.[15] emphasized the importance of training pediatric nurses and health care providers in culturally and linguistically congruent communication techniques. Davies et al.[14] stated, "training and continuing education must include language proficiency and cultural competence". Additionally, education may be focused on available resources such as the use of interpreter services for school nurses or learning specific cultural facts and cultural norms of certain groups.[15,14] Kerfeld et al.[13] advised that health care providers educate themselves on what is important to the children and families they serve in relation to their health and illness.

Provider Openness and Awareness: In the study done by Davies et al.[14] the Mexican American parents that participated in the study perceived discrimination as a result of their race/ethnicity, limited English proficiency, socioeconomic status, or appearance. While these parents did not perceive that all healthcare providers discriminated against them, their specific encounters in the study were with individual pediatric nurses and physicians that had long-lasting and deep effects on them. When these parents were asked for suggestions on how to decrease these incidences of discrimination, one mother recommended hiring healthcare providers who are "more sensitive. Who can accept people from everywhere".[14]

Similarly, the Swedish parents that participated in the study by Tavallali et al.[12] reported that in order to have a successful encounter with children and their families from a different culture the nurses needed to be sensitive to the patient's needs. This involved having the knowledge about the family's particular culture. The parents felt that if the healthcare provider had knowledge about the patient's culture it would allow them to treat patients the way they wanted to be treated. The parents from this study stressed what comes with sensitivity towards patient's cultural needs is the ability of the healthcare provider to be open to cultural differences. To these parents it was simply a question of mutual respect and understanding. Johnson, et al.[16] supported this thought stating that maintaining openness to learning about cultural practices will allow healthcare providers to respond better to the needs of children and their families.

Being open to learning about cultural practices stems from the health care providers true motivation or desire to provide care that is culturally responsive.

Health care providers must possess the genuine desire and motivation to work with ethnically diverse clients. It includes a genuine passion to be open and flexible with others, to accept differences and build on similarities.[17] Davies et al.[14] stated that providing opportunities to change healthcare providers beliefs and behaviors is essential to developing cultural competence.

Learning around cultural practices and cultural competence has been done in a variety of ways including lectures, seminars, and in-services. Berlin, Nilsson and Tornkvist[18] recommend a combination of approaches since cultural competence involves value judgments. The authors recommend specific approaches such as case methodology, or seminars and activities. These approaches include participatory learning that will facilitate active and reflective learning to help develop critical thinking and problem solving.

Javier, Hendriksz, Chamberlain and Stuart[19] suggested an alternative strategy for training pediatric residents in cross-cultural education through the use of a patient-centered template approach. The authors projected this strategy will provide physicians with broadly applicable skills, knowledge, and attitudes so they can approach all patients individually by trying to understand their unique contexts in which they exist. "The core principle is that trainees are taught to treat all patient encounters as cross-cultural and to consider all patients' unique cultural beliefs and practices on an individual bases".[19] Kerfeld et al.[19] recommended the same practice when working with all families and their children. Family-centered culturally competent care shoud

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be provided to all families regardless of race, ethnicity, values or beliefs, which will help alleviate health disparities and dissatisfaction with care.

DISCUSSION

This scoping literature review was guided by the following two research questions: Are pediatric physicians and nurses delivering culturally competent care to their patients and families? What do pediatric physicians and nurses report are the issue related to providing culturally competent care to their patients and families? With the growing diversity of our society, being culturally competent is crucial yet studies have shown this is proving to be an extremely difficult task with slow progress to date. The theme of culturally competent communication is vitally important in the delivery of culturally sensitive pediatric health care. In the studies performed by Tavallali et al.[12] Davies et al.[14] and Kerfeld et al.[13] families reported decreased satisfaction with care as a result of communication that was not culturally competent. Culturally competent communication not only includes the ability of the health care provider to interact with the patient and family in their primary language (a basic right of the patient), but it also includes an awareness of their cultural practices and beliefs. All of which will lead to increased satisfaction of patient-provider care.

The study reporting an increase in cultural competence of Swedish pediatric nurses following training[18] is an indication that training has an effect on cultural competence, but other studies in this review revealed that discrimination and health disparities still exist.[14,13] Whitman et al.[15] stated that as a result of the increasing diversity in Alabama, school nurses are now in need of necessary cultural and linguistic training and resources to provide culturally sensitive care to their students and families. Cultural competence education and training for pediatric healthcare providers has not kept up with the growing diversity of our population.

While the literature revealed that cultural competence is progressing slowly and that pediatric physicians and nurses need to be culturally and linguistically trained, limited information was found in this review that discussed how pediatric health care providers can enhance and support their ability to provide culturally competent care. The following discussion explores two potential solutions to help in the delivery of culturally competent care with pediatric patients; cultural mediation and family-centered care.

Cultural mediation has been used in a variety of settings including business and law. European countries utilize cultural mediation more widely in health care to help immigrants from other countries access and use health care services.[20] Martin and Phelan[20] stated differences exist between medical interpreters and cultural mediators. Cultural mediators are essential when advocacy for the patient is needed, and not just for interpretation of a language. Martin and Phelan[20] stated, "Cultural mediation is required when lack of cultural awareness and understanding of the system is the main impediment for the migrant population to access and benefit from health services."

Cultural mediators help in the facilitation of a therapeutic relationship between the patient and the healthcare provider by assessing the situation and participating in the plan of action with both parties. Cultural mediators help healthcare providers understand the patient's cultural practices and beliefs that may have an impact on their health, illness and health services. Additionally, cultural mediators inform patients on the health care system and how to access services they are entitled to.

Even when healthcare providers and patients speak the same language this is not insurance that the patient's needs are being understood or met. An English speaking Hispanic person living in the United States may have limited knowledge of how the health care system works. Additionally, the patient may have different cultural beliefs of health and illness and practices than the health care provider. In situations such as this, conflicts may arise between the health care provider and the patient. Cultural mediators serve as negotiators, or cultural brokers bridging the differing views, beliefs and practices between the two parties.

Martin and Phelan[20] stress the important role that cultural mediators have as motivators for patients, and how they are a source for empowering patients to voice their needs and concerns. Cultural mediators also help healthcare professionals monitor the progress of the patient and ensure that there is follow-up. "Cultural mediators could become agents in bringing about change in the healthcare services by fostering equality and fairness. By steering healthcare users to use the proper services and healthcare providers to better understand needs, cultural mediators also help to increase effectiveness in healthcare." [20]

The study performed by Kerfeld et al.[13] examined the association between parents' reported delayed care and dissatisfaction with care for their child with special healthcare needs with the parent's perception of cultural competence of their child's healthcare provider. One of the findings of the study was that there was no consistent association between racial or ethnic groups and their perceptions of provider cultural competence. As a result of this finding, the authors recommended that focus of the healthcare provider should be on family centered care.[13] Family-centered care can be defined as "placing the needs of the child, in the context of their family and community, at the center of care and devising an individualized and dynamic model of care in collaboration with the child and family that will best meet these needs."[21] Health care providers who are family-centered practitioners understand and acknowledge the essential role that families play in ensuring the health and well-being of their children, or any aged family member.[21] Family-centered health care providers understand that emotional, psychosocial, and developmental supports are key factors in health care. It is

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a mutually beneficial partnership that promotes the health and well-being of individuals and families and in turn restores dignity and control to families.

The Institute for Family-Centered Care[22] states that family-centered care leads to better health outcomes, better allocation of resources and greater patient and family satisfaction. One of the core concepts of family-centered care is dignity and respect where health care providers listen to, value and honor the family's perspectives, choices and decisions. The family's knowledge, values, beliefs and cultural background are incorporated into the planning and delivery of care.[22] By following this core principle of family-centered healthcare providers focus on the individual family and their individual values, beliefs, and practices regardless of their race and ethnicity.

Future research in the areas of cultural mediation and family-centered care is needed to explore if these two strategies increase the level of culturally competent care provided by pediatric physicians and nurses.

CONCLUSION

There is evidence from this review that pediatric health care providers, specifically physicians and nurses are still coming up short in delivering culturally competent care and that significant progress still needs to be made in this area when caring for children and their families. Literature from this review showed that awareness of cultural competence issues are being brought forward for particular groups such as Mexican Americans, families of Children with Special HealthCare Needs and Alabama school nurses. However, culturally competent care needs occur with every child and family that pediatricians, pediatric nurse and pediatric healthcare providers interact with.

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