COMMON PEDIATRIC DISEASES:
CURRENT CHALLENGES

Editors:
Nima Rezaei
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(*Volume 2*)

Common Pediatric Diseases: Current Challenges

Edited by

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Network of Interdisciplinarity in Neonates and Infants (NINI)
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PREFACE

Seeing the world through the eyes of a child/infant sounds inspirational. They are little, lovely and defenseless. Pediatrics is the science of taking care of these cute creations. Pediatrics is a branch of medicine that focuses on the diagnosis and treatment of infants, children and adolescents diseases. As medical sciences are getting more complex with the information explosion, interdisciplinarity is an essential tool to integrate different topics. Therefore, we established an interest group, titled "Network of Interdisciplinarity in Neonates and Infants (NINI)" in the Universal Scientific Education and Research Network (USERN), and invited pediatricians and scientists in the field of pediatrics from all over the world to join this multidisciplinary network: https://usern.tums.ac.ir/Group/Info/NINI

The "Updates on Pediatric Health and Disease" is a comprehensive series of books on infant and adolescent health and diseases. The series features volumes that update readers on the current understanding of basic information and advanced clinical practice in pediatric medicine. Neonatology, as well as different diseases in all subspecialties of pediatrics, including allergy and immunology, cardiology, endocrinology, gastroenterology, hematology, infectious diseases, nephrology, oncology, pulmonology, rheumatology, neurology, psychiatry and dermatology, are represented in each volume.

"Common Pediatric Diseases: Current Challenges" is the second volume of this book series. The first chapter of this book is a rapid introduction to challenges in the field of pediatrics and child health (Chapter 1). The second chapter discusses the positive and negative outcomes of sexting (Chapter 2). Chapter 3 takes a specific view of integrated care of children with neurodevelopmental disorders. The book contains chapters on the influence of non-genetic transgenerational inheritance on children and adolescents' development (Chapter 4) and the approach to pediatric genetic epilepsy (Chapter 5). The medical and social outcomes of cardiac diseases are also discussed (Chapter 6). In addition, the book provides updates on meconium-stained newborns (Chapter 7), transient tachypnea of newborns (Chapter 8) and fetal tumors (Chapter 9). Chapter 10 focuses on Autism Spectrum Disorder during infancy and its early symptoms. Last but not least, medical futility controversies and end-of-life care are discussed in Chapter 11.

The book "**Updates on Pediatric Health and Diseases**" is the result of the valuable contribution of scientists and clinicians from well-known universities/institutes worldwide. I would like to hereby acknowledge the expertise of all contributors, for generously devoting their time and considerable effort in preparing their respective chapters. I would also like to express my gratitude to the Bentham Science publication for providing me with the opportunity to publish the book.

Finally, I hope that this timely book will be comprehensible, cogent, and of special value for researchers and pediatricians who wish to extend their knowledge on pediatric challenges.

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I would like to express my gratitude to the Editorial Assistant of this book, Dr. Noosha Samieefar. With no doubt, the book would not have been completed without her contribution.

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DEDICATION

This book would not have been possible without the continuous encouragement of my family.

I wish to dedicate it to my daughters, Ariana and Arnika, with the hope that we learn enough from today to make a brighter future for the next generation.

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CHAPTER 1

Introduction of Challenges with Pediatric Diseases

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Abstract: Children and the knowledge of taking care of them, pediatrics, are faced with growing challenges. With the advancement of medical sciences, pediatrics is becoming a group of subspecialties. This could lead to improving the care and management of pediatric disorders, however, transdisciplinary management should not be ignored.

Although the health status of children has improved over the past years, still preventable child deaths are occurring, especially in low-income countries. The increased sexual abuse, discrimination, racism, increased intercountry adoption, malnutrition, environmental hazards like arsenic contamination, pornography, and surrogacy are among the most important current challenges to children's health. Worldwide vaccination coverage has declined from 86% in 2019 to 83% in 2020, and the number of completely unvaccinated children increased by 3.4 million. Approximately, 1 billion children are dealing with multidimensional poverty all around the world among which at least 356 million of them live in extreme poverty, and 100 million more children plunged into poverty as a result of COVID-19.

In this chapter, we will review the most important challenges of children's health and pediatrics with a focus on social and mental health problems.

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Keywords: Communicable disease, Disease, Epidemiology, Health, Health services, Infectious disease, Integrated medicine, Inter-disciplinary, Pediatrics, Pediatrician, Poverty, Medicine, Mental health, Multi-disciplinary, Non-Communicable disease, Social.

INTRODUCTION

Children and the knowledge of taking care of them, pediatrics, are faced with growing challenges. Pediatrics is a branch of clinical medicine that deals with the physical, mental, and social health and diseases of infants, children and adolescents.

This specialty of medicine is associated with many challenges. Pediatricians are faced with a child who cannot usually express her/his feelings, needs, and pain. On the other hand, the parents' anxiety and concerns make the situation more challenging [1]. With the advancement of medical sciences, pediatrics is becoming a group of subspecialties. This could lead to improving the care and management of pediatric disorders; however, transdisciplinary management should not be ignored. In fact, the health care team of children should consist of primary care pediatricians, pediatric subspecialists, pediatric surgical specialists, psychiatrists, psychologists, pediatric nurses and social workers.

Children's lives today are at risk of so many challenges. To name a few, increased sexual abuse, discrimination and racism, increased intercountry adoption, malnutrition, and environmental hazards like arsenic contamination, pornography, and surrogacy are among the most important current issues needing planning and investing [2].

Although the health status of children has improved over the past years, still preventable child deaths are occurring, especially in low-income countries. Identifying the cause and challenges could help in reducing the mortality rate, and improving the condition. The most important modifiable factors are as follows: a) delay in accessing health services due to distance, low health literacy or cost, b) social and environmental factors like sanitation or parents' substance abuse, c) primary care inefficiencies like incorrect recommendations by primary health care workers due to ignorance or the lack of a referral system to transport critically ill patients to high facility centers, and d) hospital inefficiencies like lack of triage, misdiagnosis and maltreatment, nosocomial infections, ineffective monitoring and malnutrition [3].

In this chapter, we will review the most important challenges of children's health and pediatrics.

ACCESS TO HEALTH SERVICES

Although immunization is one of the most important health achievements in the last century, global immunization rates remain below expectations. Worldwide coverage has declined from 86% in 2019 to 83% in 2020, and the number of completely unvaccinated children increased by 3.4 million. Approximately 23 million children under the age of one year have not received basic vaccines. More than 60% of these children live in Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Mexico, Nigeria, Pakistan and the Philippines [4].

Factors that decrease the rate of pediatric immunization can be classified into three groups: 1) system barriers including persistent and equivocal changes in the guidelines, the complexity of vaccine schedules and poverty or low socioeconomic status leading to missed immunization opportunities, 2) healthcare provider barriers such as their lack of information about contraindications and involvement of multiple healthcare providers in any child's immunization process and parent, and 3) patient barriers including misperception of uneducated parents about vaccination and possible side effects, having a child too ill to vaccinate and religious objections [5 - 7].

More than 50% of the world's population does not have access to essential health services. Efficient healthcare services in Sub-Saharan Africa and Southern Asia are harder to access, and even in more affluent regions such as Eastern Asia, Latin America and Europe, it is a challenge to spend a noticeable fraction of household budget on health expenses. National averages can conceal low levels of health service coverage in deprived population groups; for example, only 17 percent of mothers and children in the poorest fifth of households in low- and lower-middl--income countries obtained at least six of seven basic maternal and child health interventions, compared to 74 percent for the wealthiest fifth of households [2]. Every six-second, a child younger than 5 years old dies in the world, mostly by preventable causes, and 40% of them occur in countries involving humanitarian crises.

Despite all the endless challenges, United Nations International Children's Emergency Fund (UNICEF) tries to enhance the rate of maternal, newborn and child survival by establishing efficient healthcare services, immunization programs and preventive promotive curative systems for pediatric diseases such as pneumonia, diarrhea and malaria all around the world. UNICEF also focuses on child and adolescent health and well-being by supporting national health plans and helping countries combat non-communicable diseases. Moreover, UNICEF works on strengthening health systems focusing on health, nutrition, early

CHAPTER 2

Positive and Negative Outcomes of Sexting

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Abstract: Historically, the concept of "sexting" (the sending of nude pictures or videos between teenage youth) has been associated with extremely negative outcomes, including legal vulnerabilities, lost future opportunities, and depression and suicide. These negative outcomes have been widely promoted in the news media and in research on the phenomena. Yet despite diligent efforts by adults to warn youth of these negative outcomes, sexting persists and may even be more common than was first thought. Almost a decade ago, the first research began to emerge that suggested that these risks may be less common than first thought. More recent research has filled out our knowledge about sexting by outlining positive outcomes of sexting that may help explain why underage youth persist in these behaviors despite draconian warnings. This paper outlines some of these positive outcomes, such as improved feelings of self-confidence and attractiveness; strengthening of existing relationships; and the view that sexting is a safe way to explore emerging sexuality. Given this mix of both potential positive and negative feelings about sexting, I propose here that sexting education should follow the best practices long established for sex education, namely, ensuring that youth understand risks, consider relationships and feelings, and do not engage in sexting because of pressure or coercion.

Keywords: Cellphone, Computer, Cyberbullying, Digital Behaviors, Digital sexual harassment, Internet sex, Nude, Nudity, Online sex, Photos, Pictures, Sex, Sext, Sexting, Sexual content, Sexual harassment, Videos, Virtual, Virtual behavior, Virtual nudes.

INTRODUCTION

The concept of sexting was brought to the public's attention in 2005. That year, the Los Angeles Times published a news story about a phenomenon they referred

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to as "sext-messaging." Within a few years, the National Campaign to Prevent Teen and Unplanned Pregnancy, in partnership with Cosmogirl.com, released the results of a survey of 1,280 teens and young adults about that topic. In that survey, 22% of teenage girls and 18% of teenage boys reported that they had sent or posted a nude or semi-nude photo of themselves [1].

This was the emerging phase in knowledge and research about sexting. Sexting was, without a doubt, a shocking and disturbing phenomenon for most adults. In this first phase, adults understood that such pictures could be fascinating and stimulating for youth, but they also viewed sexting as an activity that could have dangerous and potentially life-changing consequences. Early cases of sexting reported in the media tended to reinforce this viewpoint. Young girls, in particular, were viewed as hapless victims who commonly found their pictures were widely distributed; one girl interviewed in the NCPTUP study described how a topless photo was sent around and, within hours, "the whole county had it" [2]. Tragic cases made headlines; all too often sexting and the chronic sexual harassment that seemed to inevitably follow led to tragic cases of suicide. Sexting seemed, at least at times, to be a life-or-death issue. Parental anxiety increased steadily, fed, no doubt, by discomfort with adolescent sexuality, combined with a sense that sexting was a new and scary digital behavior. National Public Radio's headline in 2009 reflected the public mood: "Sexting: A Disturbing New Teen Trend?" [3]. The article focused on a high school in Seattle, Washington, where adults discovered that football players were distributing nude photos of two female students. One parent told NPR that she feared the incident would permanently scar her daughter's life. Meanwhile, legal prosecutions of sexting cases began in earnest, and states often used felony child pornography laws. In all the cacophony, few attempted to understand why sexting was occurring, how risky it was in reality, and how sexting might be engaged in for different reasons.

SEXTING: POSITIVE AND NEGATIVE OUTCOMES

Around 2012, in what might be viewed as the second phase of this understanding of sexting behaviors, researchers began to introduce studies that explored the possibility that sexting was a more complicated and nuanced behavior. The first author of this article published just such a report in 2012, titled "Low Risk Associated with Most Teenage Sexting." In that report, I reported on a study of 617 18-year-olds that found that most sexting did not, in fact, lead to draconian consequences, such as peer harassment or detection and punishment by adults [4]. Other studies showed similar findings, pointing out that sexting was not strongly related to other high-risk variables such as high risk sexual behavior or poor self-image [5, 6]. Contrary to media depictions, it was not found to be reliably associated with sexual harassment [7]. Victimization online, such as through

cyberbullying, was related to suicidal ideation, but sexting didn't appear to follow the same pattern [8]. At the same time, professionals in law enforcement, such as District Attorneys, were beginning to seek out alternatives to using felony child pornography laws in sexting cases. Generally the sense was that such laws were inappropriate, especially when cases involved voluntary sexting between two minors [9].

On the other hand, researchers began to perceive that sexting was not always a fun and fully consensual activity, and that at times youth were pressured or coerced into sexting [10, 11]. The consequences of pressure or coercion were noted, in studies at MARC, to be an increase in negative outcomes [4]. Other researchers have framed coercive sexting as part of the larger issue of sexual coercion [10]. Increased partner aggression and physical coercion have also been associated with coerced sexting [7].

A recent survey of 742 youth aged 18 and 19 studied as part of research at the Social and Emotional Research Consortium (SERC) examined sexting behaviors. Youth were surveyed online between October 2019 and May 2020, at universities in Massachusetts and Colorado.

The results of this study reflect the most current knowledge about sexting. Currently, while research on sexting is significantly more advanced than even a few years ago, the state of knowledge has not always filtered down to the general public. For example, we know that sexting is not, as was first assumed, a deviant behavior engaged in by a small slice of youth. In reality, it often happens between dating couples, especially for females [11]. The current study found that more than half of the sample had engaged in sexting by age 18, and 64% of all sexting occurred within a romantic relationship.

Further, while early attempts at sexting education often emphasized the legal troubles that, were suggested, engulfed youth; in contrast, this study found that very few cases of sexting were ever actually detected by adults. That in turn suggests that legal consequences are almost certainly the exception, rather than the rule.

Perhaps most interestingly, the current study found that while sexting has often been depicted in the media as an overwhelmingly negative experience for youth, it leads to positive outcomes. As with adolescent in-person sexual behaviors, some experiences with sexting are negative but, importantly, not all. The positive outcomes that were most commonly reported were increased self-confidence, a more positive self-image, the strengthening of a romantic relationship, and viewing sexting as a positive way to explore sexuality. These positive outcomes were actually reported by subjects at higher rates, compared to negative outcomes

CHAPTER 3

The Role of Integrated Services in the Care of Children and Young People with Neurodevelopmental Disorders and Co-Morbid Mental Health Difficulties: An International Perspective

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Abstract: Children and Young People (CYP) affected by Neurodevelopmental, Emotional, Behavioural and Intellectual Disorders (NDEBIDs) such as Attention Deficit and Hyperactive Disorder (ADHD) and Autism Spectrum Disorder (ASD) are at increased risk of other Mental Health (MH) difficulties such as anxiety and depression. Therefore, they require comprehensive and holistic services to meet their complex needs. However, many countries still offer them disjointed services involving different healthcare providers and professionals each looking at only one aspect of the CYP's needs. To address this problem, the framework of "Integrated Care" is recommended as a template for providing comprehensive and joined-up care to meet the complex needs of these CYP with NDEBIDs and MH difficulties. This chapter aims to explore integrated care. It outlines the adverse impacts of disjointed care including: unnecessary multiple referrals, inefficient multiple assessments, delays in accessing required assessment and treatment, frustration and distress for affected CYP and their families and conflicts among professionals. Identified barriers to integrated care include problems with health planning, limited evidence-base, inter-professional difficulties related to different training and professional cultures and mental health stigma. The chapter highlights the benefits of integrated care including user satisfaction, the shortened path to point of care, systemic efficiencies and improved professional relationships. Finally, the chapter discusses the following desirable characteristics of integrated care: joint care commissioning, adequate ring-fenced funding, strategic leadership and planning, cross-training for professionals and good

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adherence to evidence-based protocols. Perspectives from Low and Middle-Income Countries (LMICs) were also discussed to acknowledge the international nature of the problem.

Keywords: Adolescent, Children, child-health services, Co-morbidities, Holistic services, Integrated care, Mental-health difficulties, mental-health services, Neurodevelopmental disorders, Paediatric services, young people.

INTRODUCTION

Millions of Children and Young People (CYP) worldwide are affected by Neurodevelopmental, Emotional, Behavioural and Intellectual Disorders (NDEBIDs) such as Attention Deficit and Hyperactive Disorder (ADHD), Autism Spectrum Disorder (ASD), tics and Tourette Syndrome (TS), motor coordination disorder, dyspraxia, sensory processing disorders, developmental delay and learning disabilities [1 - 7]. Prevalence rates of up to 15% have been reported for NDEBID in High-Income Countries (HIC), including up to 10% prevalence for developmental delay [8, 9]. The co-existence of a number of NDEBIDs within the same CYP and sharing of symptoms across other disorders (co-morbidity) is the rule rather than the exception [10, 11]. CYP with NDEBIDs are typically managed by a wide range of professionals including health visitors, nurses, social workers, education specialists, paediatricians, General Practitioners (GP), Speech and Language Therapists (SALT), child neurologists, child psychiatrists, psychologists, neurophysiologists, dentists, clinical geneticists, Occupational Therapists (OT) and Physiotherapists [10, 12].

Studies show that CYP with NDEBIDs are at increased risk of developing sleep disorders [13] and secondary Mental Health (MH) difficulties such as anxiety, depression, Obsessive Compulsive Disorder (OCD), self-harming, suicidal behaviours and conduct disorder in up to 50% of those affected [9, 14] (Table **1**). For example, CYP with ASD have elevated rates of anxiety and depression compared with typically developing children. A recent large scale comprehensive systematic review examining a total of 2755 records, revealed a high burden of co-morbid psychiatric disorders including anxiety disorders, depressive disorders, bipolar and mood disorders, schizophrenia spectrum, suicidal behaviour disorders, attention deficit/hyperactivity disorder, disruptive, impulse-control and conduct disorders amongst diverse age groups with ASD. These findings provide high-quality evidence for the integration of MH services for people with ASD at both clinical and policy-level decision-making from a global viewpoint [15, 16].

Co-morbidities such as conduct disorders (45%), emotional difficulties (14%), learning difficulties (17%), autism (7%), motor coordination difficulties (7%),

Tourette syndrome (3%) and specific scholastic difficulties (3%) were also found among young people with ADHD who recently transitioned to adult services [17]. Furthermore, CYP with ADHD are known to be at higher risk of suicidal behaviour compared to their peers [18]. Thus, many CYP with NDEBIDs experience additional MH difficulties which can lead to further personal suffering, extra functional and education impairment, and in some cases, elevated risk of death from suicide. There is also increasing evidence that these additional MH risks can be long-term and extend into adulthood [19].

Table 1. Prevalence of anxiety and depressive disorder among CYP with three common NNDs.

Neurodevelopmental Disorder	Prevalence of Anxiety Disorders (Source)	Prevalence of Depressive Disorder (Source)	Prevalence of Conduct Disorder (Source)
ADHD	23% [117]	9% [118]	25-50% [119]
ASD	55.3% [120]	12.5% [121]	12% [122]
Tourette Syndrome	36.1% [123]	29.8% [123]	29.7% (DBD) [123]
FASD	21% [124]	7% [124]	7% [125]
DCD	Emotional problems 70% [126]	-	43% [126]
Developmental delay	13.7% [127]	3.2% [127]	43.2% (ODD) [127]
Intellectual disabilities	8.7% [128]	1.5% [128]	25% [128]

The bio-psycho-social and ecological origins [20] of NDEBIDs and associated MH difficulties make it imperative that the assessment and treatment of affected CYP should be multimodal, comprehensive and holistic. Such comprehensive assessments are required to capture the full range of CYP's needs in order to produce a full formulation and profile to inform their care plans. Unfortunately, clinical practice in many countries does not reflect this self-evident rationale for holistic assessment and treatment for affected CYP [21]. Services that are designed to support these CYP often tend to be fragmented and disjointed such that the CYP have to attend multiple clinic appointments with different healthcare providers and professional groups each looking at only one aspect of their complex need often without any coordination [22, 23]. In some countries, one or more of the NDEBIDs would be assessed and treated by Paediatric and Child Health Services (PCHS) while others and any associated MH difficulties may be addressed by Child and Adolescent Mental Health Services (CAMHS) [22]. The split between these services can be even more complex such that for the same NDEBIDs such as ASD, some younger children may be seen by PCHS while older young people are seen by CAMHS [23]. The rationale for these service-splits is often opaque and seems arbitrary. Some of the splits may have arisen

CHAPTER 4

Epidemiological Evidence for Influences of Non-genetic Transgenerational Inheritance on Child and Adolescent Development

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Abstract: Our use of the term 'Non-genetic transgenerational inheritance' concerns the influence of environmental exposure to one generation on phenotypes in later generations in the absence of changes in the structure of the DNA. Although animal experiments have shown that the phenomenon exists in plants and animals, many scientists have expressed doubt as to whether this type of inheritance is detectable in humans. In this chapter, we describe the observational epidemiological data that has been published and evaluate the evidence for this type of inheritance. We mainly concentrate on the environmental exposures concerning famine, cigarette smoke and radiation, and chart the associations between pre-conception and prenatal exposures. We describe associations between these exposures and outcomes for the offspring and grandchildren. In general, we demonstrate frequent evidence of sex-specific differences in the likelihood of particular phenotypes, depending on whether it is the maternal or paternal ancestor who is exposed. We also show that the timing of the exposure is often important regarding specific outcomes, with particular emphasis on the 4-5 years before puberty for preconception exposures and the trimester of pregnancy for prenatal exposures. The evidence for non-genetic transgenerational inheritance is increasing. Interestingly, the consequences of exposures that are harmful to one generation often have a beneficial effect on a subsequent generation. It is important that future epidemiological studies are planned to collect information concerning previous and/or subsequent generations so that transgenerational consequences of exposures, such as medications or pesticides, can be charted.

Keywords: Asthma, Autism, Betel nut, Cognition, Diethylstilbestrol, DNA methylation, Endocrine disruptors, Environment, Epigenetic, Famine, Fat mass, Grandparental exposures, Hearing, Medications, Nutrition, Parental exposures, Radiation, Smoking, Taste, Transgenerational inheritance.

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INTRODUCTION

There is international recognition of the importance of environmental factors such as diet, smoking, social circumstances, air pollution and stressful events, in influencing outcomes such as child growth, behavior and neurocognitive development. Such influences may continue throughout individuals' lives [1]. In parallel, though, there is considerable evidence from twin, adoption, and family studies that many outcomes have a strong familial component [2]. However, Genome-Wide Association Studies (GWAS) of DNA variants are often shown to explain relatively small proportions of this heritability [3], so other aspects of inheritance need to be considered. Non-genetic transgenerational inheritance is a major candidate. The phenomenon is currently recognized more among plant and animal rather than human research. It comprises the study of how exposure to an individual in one generation has a demonstrable effect on one or more later generations. Such effects may be beneficial or detrimental.

NOMENCLATURE

Non-genetic inheritance has been known variously as intergenerational, multigenerational, or transgenerational, depending on whether the germline has been directly exposed or not (Fig. **1**). Intergenerational and multi-generational inheritance has been used synonymously, and it is assumed that the route of transmission is *via* a gonad. There are two possible scenarios for such a form of inheritance: (i) exposure of an individual boy/man or girl/woman (F0) prior to the conception of the next generation (F1); and (ii) the exposure of a pregnant woman (F0) with consequent (indirect) exposure of the embryo or fetus (F1) and thus of his/her developing gonads. These will be subsequently involved in the conception of the next generation (F2). Transgenerational inheritance has been defined as the consequence(s) of exposures to the initial generation (F0) on subsequent generations, excluding those covered by the definitions of inter- or multi-generational inheritance. Because these definitions can be confusing, the term epigenetic inheritance has started to be used to encompass any effect on a subsequent generation that does not involve a change in the DNA itself, such as a mutation.

EXPERIMENTAL EVIDENCE

Non-genetic inheritance is known to exist in plants and insects, with evidence of environmental exposure to a single generation resulting in a phenotypic change that may be inherited for many generations in the absence of the exposure. For mammals, most experiments that are of possible relevance to human observations involve rodents. Many show sex-specific effects, and examples of effects on the

fourth-generation or later have been published. Below are described two typical recent examples.

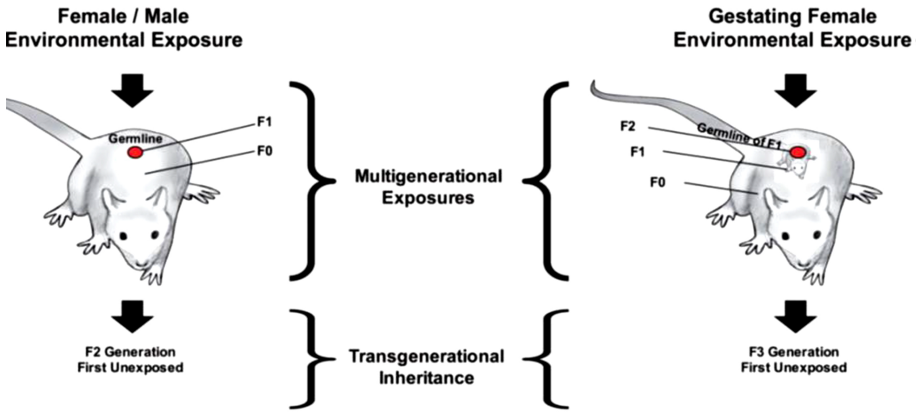

Fig. (1). Environmentally induced transgenerational epigenetic inheritance. Schematic of multigenerational versus transgenerational environmental exposures [4].

Toxic Metal Exposure

A study by Camsari and colleagues [5] demonstrated that exposure of female mice to cadmium and mercury around the time of conception had adverse effects on the male but not female offspring in regard to increased adiposity and impaired glucose metabolism. Subsequent experiments where they continued to breed from the offspring (but with no further exposures) showed that the adverse adiposity and glucose phenotypes persisted in males down the female, but not the male line, even as far as the fourth generation when compared to controls [5].

Endocrine Disruptors

There are many endocrine disruptors in the environment, but Bisphenol A (BPA) is one of the more ubiquitous. A recent study [6] has confirmed previous transgenerational studies and showed BPA administered in one pregnancy to be associated with patterns of social recognition in subsequent generations. The authors also showed that transmission was down the female line, and that the behavior was reflected in biomarkers in the brains of the third generation.

Many other animal experiments involving transgenerational associations are concerned with the impact of chemicals such as fungicides (*e.g.*, vinclozolin), pesticides and insecticides (*e.g.*, methoxychlor, DDT, and permethrin), and hazardous pollutants (*e.g.*, dioxin, phthalates, BPA, benzo(a)pyrene) on transgenerational outcomes such as disorders of the reproductive and renal systems, as well as on obesity and behavior changes (see Nilsson *et al.* [4] for a discussion).

CHAPTER 5

Clinical Approaches to Genetic Epilepsies in Children

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Abstract: A genetic etiology is determined in more than 30% of all diagnosed cases of epilepsy with onset at the pediatric age. About 210 single disease-causing genes and 400 chromosomal imbalances are associated with epilepsy, and a presumed pathogenic role has been suggested for about 7000 different genes.

Genetic epilepsies can be divided, according to the main correlated epileptogenic mechanisms, into the following groups: a) channelopathies, b) transportopathies, c) disorders of the intermediate metabolism, d) disorders of the neuronal cellular cycle and signaling, e) disorders of synaptic vesicles trafficking and release, f) disorders involving neuronal structural proteins, g) disorders of synaptic secreted proteins and h) chromosomopathies and pathogenic copy number variants.

A careful diagnostic work-up should be focused on the exclusion of acquired causes of seizures, the analysis of family history, the definition of seizure semiology and epileptic syndromes, and the characterization of associated neurological and non-neurological manifestations.

Traditional genetic techniques (karyotype, array CGH, and Sanger sequencing) remain useful for known epilepsy phenotypes (*e.g.* Dravet syndrome) and for various syndromes including neurodevelopmental impairment.

Next-generation sequencing (NGS) includes different techniques (targeted gene panels and whole genome sequencing) that allow a simultaneous sequencing of exons belonging to a selected group of genes organized in panels or to the whole exome or genome.

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Advantages of NGS include: a) the identification of new disease-causing genes associated with epilepsy, b) an expansion of the known phenotypes associated with previously discovered disease-causing genes, c) an improvement of genetic counseling, d) a reduction of the times for the diagnosis, and e) a reduction of economic costs.

Keywords: brain, bioinformatic tools, cortical excitability, children, developmental delay, developmental encephalopathies, Epilepsy, epileptic encephalopathies, epileptogenesis, genotype, gene, genetic counselling, intellectual disability, infants, neurogenetic disorders, neurometabolic disorders, next-generation sequencing, phenotype, newborns, seizures.

INTRODUCTION

Epilepsy is the most common neurologic disorder at the pediatric age with an incidence of about 70 per 100.000 cases in children under the age of 2 [1].

The complex landscape of genetic etiologies of epilepsies has largely expanded in the last decades. About 7000 genes with a presumed pathogenic role and more than 150 genes with a known associated clinical phenotype were reported in the literature (about 30% of the whole diagnosed epilepsies) [2]. Most of the genetic epilepsies were prominently studied in subjects in which an early or very early onset of seizures and a very severe developmental and neurological impairment occurred [3]. In this context, the OMIM database has currently reported 99 diseases that were classified as “developmental and epileptic encephalopathies” [4]. Other common associated clinical presentations include facial dysmorphisms, abnormalities of head circumference (microcephaly or macrocephaly), movement disorders, and malformations in other organs such as the heart, eye, skeleton, or kidney [5].

Most of the reported genes encode ion channel subunits, membrane receptors/transporters and proteins involved in the transduction of neuronal signaling or enzymes of the intermediate metabolism. Pathogenic variants of these genes result in dysfunctions of different stages of neuronal development and functioning, including synaptogenesis, pruning, neuronal migration and differentiation, and neurotransmitter synthesis and release.

Epilepsy phenotypes and severity, degree of developmental impairment, and concurrent neurological and non-neurological manifestations are extremely variable according to the functions of the different involved genes and their role in epileptogenic mechanisms. Several studies also evidenced a remarkable heterogeneity in terms of different clinical conditions resulting from variants of the same genes (*e.g. SCN2A* causes both familial benign neonatal infantile epilepsy and severe epileptic encephalopathy; *KCNQ2* was initially associated

with familial benign neonatal seizures and, subsequently, with an early onset epileptic encephalopathy) or similar clinical syndromes caused by different genes (*e.g.* Dravet syndrome can be caused by pathogenic variants of *SCN1A, PCDH 19, STXBP1 or GABRA1*).

About 400 different chromosomal imbalances associated with epilepsy have been reported, including several Copy Number Variants (CNVs) [3]. In this context, physicians should always consider the involvement of genes in the deleted or duplicated region that could have a known or presumed link with epileptogenic mechanisms [1, 2].

CLINICAL AND DIAGNOSTIC APPROACH

The suspect of a genetic etiology in a child with epilepsy should be primarily suggested by four main steps: the exclusion of acquired causes of seizures, the careful analysis of family history, the characterization of seizure semiology and epileptic syndromes and the evaluation of associated neurological and non-neurological signs and symptoms [6].

Acquired causes of epilepsy seizures include hypoxic-ischemic encephalopathy or other neonatal disorders, infectious or autoimmune encephalitis, traumatic brain injuries, stroke, neoplasm, vasculitis, drug withdrawal or toxicity, metabolic disturbances (including those conditions resulting in hypoglycemia, hyponatremia, or hypomagnesemia).

Family history should be investigated regarding recurrent epilepsy phenotypes in different family members and the mode of inheritance of specific disturbances. Family history of different seizures and EEG patterns might suggest either a genetic condition with variable phenotypes or the possibility of different causes of seizures among the involved family members [1].

Clinical presentation of genetic epilepsy can be differentiated into two main patterns, including seizures as prominent/ unique symptoms or seizures associated with a syndromic phenotype, even if the variability is high, and several diseases may present with both clinical patterns.

In patients presenting with the first pattern, seizures are the most evident and characterizing feature, and other neurological symptoms include a cognitive and developmental delay that could precede or follow the onset of epilepsy. Among newborns and infants belonging to this group and presenting with intractable seizures, a therapeutic trial for vitamin-dependent epilepsies (mainly through the administration of pyridoxine, pyridoxal phosphate or folinic acid) should always be considered, because it also has a diagnostic role for the characterization of

CHAPTER 6

Medical and Social Outcomes in the Management of Cardiac Diseases in Children

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Abstract: Children with cardiovascular diseases, especially congenital heart diseases are exposed to socioeconomic burdens ranging from poverty, economic difficulties, and emotional breakdown to parental schism.

There are various ways by which cardiac diseases affect children. These include the effect of the disease on the child, the family and the nation as a whole. Management of cardiovascular diseases in children comprises diagnosis, investigations, medical and surgical rehabilitation/ergonomics and follow-up. All these steps in management have both medical and social implications on the child.

The effects of cardiovascular diseases are not limited to health, but can seep into social life, as well. Affected individuals tend to forgo a lot of things, including restrictions in their life, depression and even family structure disintegration, decrease life expectancy and family disharmony in some cultures.

The socio-economic burden of pediatric cardiovascular diseases is quite huge both for the individual, household and society. The impact includes loss in financial resources, productivity, increased disability-adjusted life years, decreased quality of life, catastrophic expenditure and premature death. These burdens are more in the low and middle-income countries. This chapter aims at eliciting the various social and economic burdens that children with heart diseases encounter in the course of their illness.

Keywords: Cardiovascular, Catastrophic, Children, Congenital, Death, Disease, ergonomics, Family, Financial, Follow-up, Heart, Investigations, Management, Medical, Parental, Poverty, Rehabilitation, Schism, Socio-economic, Surgical.

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INTRODUCTION

Cardio-Vascular Diseases (CVDs) are the leading cause of mortality worldwide [1, 2]. Mortalities by CVDs could be acquired or congenital in origin. The acquired type occurs mainly due to Coronary Heart Disease (CHD), stroke, Rheumatic Heart Disease (RHD) and Myocardial Infarction (MI), while the congenital variety stems from cyanotic and acyanotic congenital heart defects. Cardiovascular disease (CVD) accounts for nearly half of noncommunicable diseases (NCDs) and is the leading global cause of death, accounting for 17.3 million deaths per year; this will double by 2030. In children, the bane of cardiac diseases is structural heart diseases, which are mostly congenital [3].

EPIDEMIOLOGY OF CARDIAC DISEASES IN CHILDREN

In Nigeria, a multi-center study on the variable prevalence of congenital heart disease exists. For instance, Sadoh *et al*, in their study in southeast Nigeria, among 605 children, noted Ventricular Septal Defect (VSD; 46.6%) as the commonest congenital heart defect. Other heart defects in order of frequency were Patent Ductus Arteriosus (PDA;12.1%), Atrial Septal Defect (ASD;8.7%), and Atrio-Ventricular Septal Defect (AVSD;8.2%). Tetralogy of Fallot (TOF;7.8%) was the commonest cyanotic congenital heart defect seen in their study [4].

In the study of Miyague *et al*. [5] in Brazil, among 4,538 children in a pediatric hospital over a three-year period, 44.4% of the children were diagnosed with congenital heart diseases, with 4.4% being acquired, and 1.2% presented with arrhythmias. Congenital heart diseases were noted in 71.5% of the cases. In their series, VSD was seen as the most frequent acyanotic anomaly, and TOF was the most frequent cyanotic anomaly.

In China, Liu *et al*. [6] in their study among 1,817 children with CHD noted the overall prevalence of 16.4 per 1,000 live births with boys being higher with the prevalence of 24.1 per 1,000 live births and females with 20.0 per 1,000 live births. Males presented with a higher prevalence of ASD with a prevalence of 10.6 per 1,000 live births. They noted that a variety of maternal antenatal correlates such as pregnancy infections, older age, pregnancy-induced hypertension, family history of CHD, gestational diabetes and lower education level are implicated as a causal effect of congenital heart disease [6].

Chinawa *et al*. [7], in Enugu, Nigeria, in their work among 31,795 children that attended children outpatient clinics of the hospital over 5 years, noted an overall prevalence of children with cardiac disease as 0.22%. The commonest congenital heart disease seen in their study was VSD, followed by TOF. They also noted some extra-cardiac anomalies that were associated with these defects, such as

Downs's syndrome and VACTERL (Vertebral defects, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Renal anomalies and Limb abnormalities).

In a meta-analysis of the world prevalence of congenital heart diseases, Denise *et al*. [8] noted that CHD accounts for almost a third of all major congenital anomalies. They opined a varying birth prevalence of CHD worldwide. In the systematic review of 114 papers involving 24,091,867 live births with CHD, they identified 164,396 children with congenital heart defect. They noted an increase in prevalence from 0.6 per 1,000 live births from 1930 to 1934 to 9.1 per 1,000 live births after 1995. They found very significant geographical differences in their study. For instance, in Asia, they found the highest CHD birth prevalence, at 9.3 per 1,000 live births, and pulmonary outflow obstructions as a predominant cardiac lesion. Their report from Europe was significantly higher than in North America with 8.2 per 1,000 live births and 6.9 per 1,000 live births, respectively [8 - 13].

Rheumatic heart disease is the commonest cause of acquired heart disease. Paar *et al*. [14], noted the high morbidity and mortality of children with heart disease which is disproportionate among children in developing countries when compared with their Western counterparts. In their study among 3,150 children aged 5 to 15 years and 489 adults aged 20 to 35 years from urban and rural areas, they noted an overall prevalence in children of 48 in 1,000 while the prevalence in urban children was 34 in 1,000, and in rural settings, this was 80 in 1,000. Poor socio-economic class, poverty, and very poor political will have been implicated as the causes of this rise in prevalence.

Saxena *et al*. [15], among children between the age of 5-15 years from randomly selected schools in four regions, noted that among 16,294 children, RHD was detected using echocardiography in 125 children giving a prevalence of 7.7/1000.

Finally, cardiomyopathy, another acquired cardiac disease in children afflicts about 100,000 children worldwide. One in every 100,000 children who are less than 18 years is affected in the United States. It is commoner in children less than one-year-old, with very high morbidity and mortality. It is documented that about 40% of children with cardiomyopathy undergo heart transplantation or die within 2 years [16].

Dilated Cardiomyopathy (DCM) is the commonest cardiomyopathy seen in children. It causes heart failure in both children. Other types of cardiomyopathy are Left Ventricular Non-Compaction cardiomyopathy (LVNC), Arrhythmogenic Right Ventricular Dysplasia (ARVD), Hypertrophic Cardiomyopathy (HCM) or Restrictive Cardiomyopathy (RCM), as well as a mixed phenotypic disease *e.g.* dilated-hypertrophic cardiomyopathy. Dilated Cardiomyopathy is usually

CHAPTER 7

Meconium Stained Newborn

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Abstract: Meconium Stained Amniotic Fluid (MSAF) and Meconium Aspiration Syndrome (MAS) in newborn are commonly encountered by obstetricians and neonatologists world over, and more so in developing countries. MAS is a serious condition as it causes severe respiratory morbidity and complications like air leak, pneumothorax, Persistent Pulmonary Hypertension (PPHN), surfactant inactivation and death in many cases. There have been several changes in the management of pregnant mothers and their neonates, as well as in the endotracheal suctioning guidelines for babies born with MSAF ever since the pathogenesis of intra-uterine passage of meconium and meconium aspiration syndrome, and evidence on intervention outcomes became known. This chapter shall review the mechanism of meconium stained amniotic fluid, the pathophysiology of meconium aspiration syndrome and management of the newborn infant in the labor room, NICU and beyond, as per the present consensus. Potential newer therapies and drugs shall also be briefly addressed.

Keywords: Amniotic fluid, Chemical pneumonitis, ECMO, Endotracheal suction, Fetal distress, High-frequency ventilation, Inhaled nitric oxide, Meconium stained amniotic fluid, Meconium staining, Meconium aspiration, Meconium aspiration syndrome, Mecometer, Meconiumcrit, Neonatal pneumothorax, Non-vigorous infant, NRP, Persistent pulmonary hypertension, Respiratory distress, Surfactant, Vigorous infant.

INTRODUCTION

The earliest stool of the newborn is meconium, which may occasionally be passed before birth, in-utero or during the process of being delivered, thereby causing staining of the amniotic fluid. This condition is called Meconium-Stained Amniotic Fluid (MSAF). The MSAF has always been a cause of concern to obstetricians and neonatologists, pertaining to its management and perinatal outcome after Schwartz (1857) first time opined that intra-uterine passage of meconium as a marker of perinatal hypoxia. Right from Aristotle's time, when he

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associated MSAF with a state of sleepiness and depression in a neonate, to date the subject has been a topic of research and inquisition. The Meconium Aspiration Syndrome (MAS) is perhaps the diffusion of meconium into the fetal airways that poses serious neonatal morbidity and mortality. Debates and controversies have continued to surround the management of MSAF and MAS.

Meconium, derived from the Greek word *mekoni* meaning poppy juice or opium, was believed to keep the baby calm and quiet in the womb. Meconium is the fetal feces that accumulate in the colon throughout gestation. It is thick, blackish-green in color, odorless in smell, and consists of desquamated cells from the intestine and skin, lanugo hair, mucin from the gastrointestinal tract, vernix fat and secretions from the amniotic fluid. It is comprised of: 75% water and 25% solids viz, lipids, cholesterol, mucopolysaccharides, protein, enzymes including pancreatic phospholipase A2, bile acids and salts and some drug metabolites if the mother is taking medicines. Amniotic fluid is clear and colorless and essentially sterile, except for a few vernix particles and some microbiome DNA; the significance of the latter is not known as of now [1, 2]. However, the in-utero passage of meconium imparts color to the amniotic fluid and is alarmingly a telltale sign of fetal hypoxia and acidosis until proven otherwise.

Meconium appears in the fetal intestine around the 10th week of gestation, and gradually increases in amount to about 200 grams at term. Low motilin levels, a hormone that initiates intestinal peristalsis, and the presence of a terminal cap of viscous meconium and a tonic anal sphincter prevent gut peristalsis and passage of meconium during fetal life. The gastrointestinal system matures as gestation progresses. Increasing cholinergic innervations near term gestation and transient parasympathetic stimulation of the gut; transient umbilical cord or fetal head compression after rupturing of membranes and rising motilin levels may account for MSAF in the term and post-term newborn infants in the absence of perinatal asphyxia. The incidence of MSAF is about 10%–15% of all pregnancies worldwide, being higher in the blacks and South Asian ethnicity, and associated with 20% of non-vigorous infants [3]. MAS develops in approximately 10% of babies [4, 5], and contributes to one neonatal death in 2000 infants [6]. The incidence of MSAF rises with advancing gestational age, ranging from 13% for infants 36–39 weeks to 31.5% for infants born after 42 weeks gestation [7]. However, changes in clinical practice to avoid gestation beyond 41 weeks have consequently shown a decline in the prevalence of MSAF and MAS [8]. Poor integrity and maturation of the parasympathetic system and low levels of the hormone in early gestation make MSAF an uncommon event in preterm infants. The reported incidence of MSAF is only 3–6.7% in the preterm population [9].

ETIOLOGY

Apart from fetal maturation a hypoxic insult to the fetus in the form of fetoplacental insufficiency, nuchal cord, cord compression, abruptio placentae or metabolic acidosis and intra-uterine infection by E. Coli, Group B streptococci and Listeria, can also cause increased intestinal peristalsis and relaxation of anal sphincter leading to passage of meconium in-utero (Table **1**).

Table 1. Etiology of meconium-stained amniotic fluid.

Antenatal Period	Intra Natal Period
Placenta and umbilical cord structure and function abnormalities.	Physiological gut maturation and peristalsis.
Placental low glycogen stores.	Sudden pressure on the forehead and umbilical cord on the spontaneous rupture of membranes.
Placental senescence: full-term gestation, gestational diabetes, smoking and drug abuse.	Cephalo-pelvic disproportion.
Intra-uterine growth retardation	Prolong labor.
Abruptio placentae.	Fetal heart arrhythmia, Fetal heart decelerations on Cardiotocography CTG.
Nuchal cord, hyper-coiled cord and low umbilical coiling index.	Uterine atony or tetany.
Pre–eclampsia and chorioamnionitis.	Umbilical cord avulsion.
Intra-uterine infection: Listeria, E. coli and Group B Streptococci.	Perinatal asphyxia with acidosis.

Note: the underlying pathology for MASF remains perinatal asphyxia until proven otherwise.

Meconium Staining is a state when the umbilical cord, skin, and nails of a newborn infant are stained yellow at birth. Meconium Aspiration (MA) is a condition when meconium is present below the vocal cords. When a neonate aspirates meconium during intrauterine gasping or initial breaths at birth, it is described as primary meconium aspiration. The infant also ingests MSAF during delivery which may cause gastritis. Secondary meconium aspiration results after birth when the infant may vomit MSAF and aspirate. Meconium aspiration can be diagnosed by direct visualization of the meconium below the vocal cords by laryngoscope, by aspiration of meconium through an endotracheal tube, or after taking a chest skiagram. Meconium may be present in the fore –waters or hind-waters; the former has more pathological significance. The presence of meconium in the forewaters has similar significance in breech delivery as in vertex presentation.

CHAPTER 8

Transient Tachypnea of the Newborn

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Abstract: Transient Tachypnea of the Newborn (TTN) is the most common respiratory morbidity in term infants. In fetal life, the lungs are filled with fetal alveolar fluid, which is secreted by the alveolar epithelium through chloride channels. In late gestation and by the onset of labor, chloride-secreting channels switch to sodium-absorbing channels, and alveolar fluid is cleared away, leaving space for air after birth. Disorders that compromise the absorption of fetal lung fluid would end up in respiratory distress, tachypnea and hypoxemia. Elective cesarean section is the major risk factor for TTN, as well as other risk factors. Clinical features and chest radiograms are sufficient for the diagnosis. The disease is usually benign and self-limiting, but in some cases, respiratory support may be needed along with supportive treatment. The prognosis is usually good but with an increased risk of asthma in childhood.

Keywords: Alveolar epithelium, Amiloride, Asthma, Aquaporin, Beta-adrenergics, Cesarean section, Chloride channels, Cyanosis, Fetal alveolar fluid, Glucocorticoid, late preterm, Lung ultrasound, Mechanical ventilation, Oxygen, Preterm, Respiratory distress, Sodium channels, Surfactant, Tachypnea, Transient tachypnea, Vascular markings.

INTRODUCTION

Transient Tachypnea of the Newborn (TTN) was first described by Avery *et al.* in 1966, and has been one of the most common causes of neonatal respiratory distress. Synonymous names include wet lung, respiratory distress type 2, and benign respiratory distress. Since most of the infants recover uneventfully, pathological findings are difficult to describe. Due to the same reason, the true incidence of the disease is not known, but it is estimated that the incidence is about 3.6 to 5.7 per 1000 term infants [1, 2], and almost 4% in late preterm infants [3]. In infants delivered by cesarean section before the onset of labor, respiratory

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symptoms occur in 35.5 infants per 1000, whereas in infants delivered by cesarean section with labor, the rate is 12.2 per 1000. This rate is 5.3 per 1000 births in infants delivered through the vaginal route [4]. Some mild cases of respiratory distress syndrome as well as infants with pulmonary maladaptation may actually be TTN. On the other hand, some persistent cases may actually be respiratory distress syndrome or may be called "malignant" tachypnea of the newborn.

Dynamics of Fetal Lung Fluid

During fetal life, lungs are filled with Fetal Lung Fluid (FLF), which maintains alveolar distention and development. Although lungs receive only 10% of total cardiac output, this is sufficient for the production of FLF. Fetal lung fluid is produced by type I alveolar cells, fills in the alveolar space, and moves towards the trachea by fetal chest movements. Some of FLF is swallowed through the esophagus, while some of it joins the amniotic fluid. Since intratracheal pressure is almost 2 mm Hg higher than the amniotic fluid pressure, flow is maintained by the pressure gradient. Research in fetal lambs have revealed that FLF is produced 50 ml/kg per day in mid-trimester, increasing to 120 ml/kg per day in late-gestation [4]. The amount of fluid increases from 4-6 ml/kg body weight at mid-gestation to about 30-50 ml/kg near term in fetal lambs [5]. This increase is associated with increased pulmonary vasculature and increased epithelial surface [6]. A few days before vaginal delivery, the fluid begins to decrease to approximately 15-18 ml/kg [7]. Fetal lung fluid contains 157 meq/L chloride, and since fetal alveolar eptihelium is inpermeable to proteins, its protein and bicarbonate content are very low.

The activity of ions and water through the lung epithelium is analyzed in 3 phases:

1. Fetal phase: Although the protein content of the fetal lung interstitium and the osmotic gradient is high, alveolar epithelium actively secretes chloride to the airways, followed by obligatory water secretion. In spite of chloride secretion, sodium channels are inactive, and sodium absorption is very low. Chloride enters the epithelial cell through the basement membrane with sodium and potassium. Thereafter, with the help of the Na-K-ATPase enzyme at the basolateral membrane, sodium is exchanged with potassium, and it moves to the extracellular space. (3 sodium ions are exchanged for 2 potassium ions), increasing the chloride content of intracellular space. This reaction uses energy. Increased chloride within the cell crosses the apical membrane through Cystic Fibrosis Transmembrane Regulator (CTFR) and other chloride channels passively into the alveoli. Sodium is transferred into the alveoli through

paracellular routes. Water moves through the epithelial cells, and couples with chloride through water channels such as Aquaporin 5. Aquaporin 5 is expressed heavily on type 1 cell surfaces, and the majority of water transport occurs through these channels [8]. Type I cells are permeable to water, and secretes chloride to the alveoli also [9] (Fig. **1**). Low pH activates chloride channels, and increases FLF [10].

2. Transition phase: This stage involves the reversal in the direction of ions and water movement. It is expected that immediately before birth, the epithelium absorbs water from the alveoli and alveoli becomes ready to be filled with air after birth. This two-step process is completed in 2-6 hours by an interplay of change in sodium, potassium and chloride absorption, and secretion by Na-K-ATPase through amiloride-sensitive Epithelial Sodium Channels (ENaC) on the epithelial cell surface. The number of these channels is very low in preterm compared to term infants [11]. The first step is passive movement of sodium from lumen across the apical membrane into the cell through Na channels. The second step is active extrusion of sodium from the cell across the basolateral membrane into the serosal space. In the first step, by the intracellular transport of sodium, membrane potential begins to change, and chloride starts to move into the cell through chloride channels. A concomitant increase in Na-K-ATPase facilitates sodium absorption, followed by intracellular movement of water. Secretion of this fluid may be inhibited by bumetanide, which implies Na-K-2Cl co-transport [5]. In cases of oligohydramnios, the movement of FLF to the amniotic fluid is increased due to the increased pressure gradient, which results in decreased intraalveolar pressure and lung hypoplasia.

Amiloride blocks sodium transport on the luminal surface of the epithelium, whereas ouabain blocks Na-K-ATPase activity on the basolateral surface. The stress associated with preterm delivery does not affect sodium absorption; therefore, lung edema is frequently observed in preterm infants [9]. Glucocorticoids increase the expression of Na-K-ATPase, epithelial sodium channels and aquaporins as well as alpha, beta and gamma subunits of ENaC, which results in increased number and decreased breakdown of membrane channels [12].

Cation channels on the apical surface are the rate-limiting step, responsible for more than 90% of the resistance to the transcellular sodium transport [13]. In vaginally delivered infants, ENaC levels fall dramatically within 30 hours after birth. In preterm infants and in infants delivered through cesarean section, this fall is much slower. In other words, slow rates of epithelium sodium transport due to ENaC levels contribute to the development of TTN. The expression of sodium channels is regulated by the “microenvironment” which includes glucocorticoids, oxygen, beta-adrenergics and surfactant [14 - 17].

CHAPTER 9

Fetal Tumors: Diagnosis and Management

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Abstract: Tumors can be formed in any organ throughout life. The fetal period is no exception to this fact, and it is important to diagnose these tumors as soon as possible to provide timely care to patients. If management is halted, tumors can cause complications in delivery, child development and even death. In this chapter, we discuss the diagnosis and management of several common fetal tumors. We also overview possible future directions in the management of tumors found during the fetal period.

Keywords: Broncho-Pulmonary Sequestration, Cancer, Congenital Cystic Adenomatoid Malformation, Diagnostic imaging, Fetal development, Fetal tumors, Glioma, Gynecology, Heart rhabdomyoma, Intracranial tumors, Interstitial Lung Tumors, Kidney tumors, Liver tumors, Management, Obstetrics, Ovarian masses, Pelvic tumors, Perinatal care, Pleuro-Pulmonary Blastoma, Pregnancy, Teratoma.

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INTRODUCTION

Cancers occur at any age and can involve any tissue in the body. Even though the risk of cancers increases with aging as a result of the accumulation of carcinogenic mutations and decreased host immune response to cancer cells, some cancers have a predilection for young individuals [1, 2], such as Leukemia, Neuroblastoma and Wilm's tumor [3]. Rarely, cancers occur before birth, during the fetal period, and their prevalence is estimated to be around 2 to 14 in 100,000 live births [4 - 6]. However, the exact prevalence of fetal cancers cannot be determined as they can remain undiagnosed or be misdiagnosed during pregnancy. These tumors can remain asymptomatic, or can manifest as polyhydramnios or even intrauterine fetal demise, which in many cases are not further investigated. Most fetal masses are benign, however, about 40% of them are malignant based on postnatal investigations [4]. As is the case for other malignancies, timely diagnosis of fetal cancers is important in that decisions regarding prenatal treatment and route of delivery, as well as postnatal care must be made as soon as possible.

Fetal cancers are challenging in many respects. Firstly, their diagnosis is mostly incidental, and usually, an accurate diagnosis is not possible until after delivery, when a histopathologic examination can be performed [7]. Another challenge is the lack of precise guidelines for the management of fetal cancers. Our knowledge regarding the management of fetal cancers is confined to a few case reports. On the other hand, many of the diagnostic tools for the detection of cancers are prohibited during pregnancy [8]. Furthermore, there is no consensus on the management of fetal malignancies.

In this chapter, we describe the most common malignancies of the prenatal period and diagnostic tools for their detection. Current management and possible future directions in the treatment of these cancers are also discussed.

THE MOST COMMON PRENATAL TUMORS

Many of the tumors that are common in the prenatal period are not malignant. However, we mention all common fetal tumors, regardless of being malignant. Table **1** summarizes some of the most common fetal tumors and malignancies.

Table 1. Common tumors found during fetal period.

Tumor	Incidence	Presentation/ complications.
Sacrococcygeal Teratoma	~1 in 40000 live births [9]	Dystocia, fetal hydrops and arrest of delivery.
Heart tumors	~1 in 1000 pregnancies [10]	Arrhythmias and reduced contractility.

(Table 1) cont.....

Tumor	Incidence	Presentation/ complications.
Brain tumors	~1 in 500000 live births [11]	Polyhydramnios and decreased fetal movement.
Neuroblastoma	~1 in 100000 live births [12]	Mass (mostly adrenal).
Wilm's tumor	~1 in 63000 live births [13]	Polyhydramnios and fetal hydrops.

To date, there is no consensus regarding the classification of prenatal tumors. However, an acceptable classification based on the location of these tumors was proposed by Meinzer [14]. He classified locations in which the tumors arise into four major categories, including 1) head and brain, 2) face and neck, 3) thorax and 4) abdomen and retroperitoneum, as well as four minor locations being 1) extremities, 2) genitalia, 3) sacrococcygeal region and 4) skin. We follow a similar classification for the tumors reviewed.

Intracranial Tumors

The prevalence of intracranial tumors varies between 0.34 to 3.4 per one million live births, due to different temporal classifications [11, 15]. However, their incidence has increased in the past two decades [16]. These tumors either remain asymptomatic, or present with non-specific manifestations such as hydrocephalus, macrocephaly or intracranial mass. Ultrasound (US) is the first-line diagnostic tool in the detection of intracranial lesions. Further imaging investigation using Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) can unveil more details regarding the lesion. Intracranial lesions other than tumors, such as vascular malformations or hemorrhage must be considered as well [17]. A definite diagnosis is mostly halted until after birth following a histopathologic study. Unlike many other fetal cancers, tumors of the Central Nervous System (CNS) are sporadic, and not associated with other abnormalities such as aneuploidy [18]. These tumors are associated with poor prognosis and mostly lead to death either prenatally or shortly after birth [18]. The survival rate for tumors of the CNS is reported to be approximately 28% [19].

Teratoma

Teratomas are the most common tumors of the CNS diagnosed perinatally [20], and account for 27%-62% of prenatal CNS tumors in different series [11, 18, 19, 21]. Even though they are benign in nature, they have the worst outcome of intracranial tumors and have an overall survival of as low as 10% [20, 22]. Their prognosis is greatly affected by tumor size, and gestational age at diagnosis and larger tumors, and those diagnosed at an earlier gestational age have worse prognoses. On imaging, teratomas present as heterogeneous masses mostly due to cysts resulting from necrotic lesions, and to a lesser extent due to hemorrhage within the mass. Cystic lesions can help differentiate teratomas from other

CHAPTER 10

Autism Spectrum Disorder during Infancy: Implications for Diagnosis, Prognosis, and Therapeutic Approaches

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Abstract: Autism spectrum disorder (ASD) is a complex psychiatric and neurodevelopmental issue related to delays in the acquisition of behavioral and social skills. The main symptoms of ASD are impairments in communication, limited interest and skills in social interactions, and repetitive behavior. In the present chapter about ASD during infancy, we reviewed the behavioral indicators of ASD, different ways of diagnosis, and the significance of an early and correct diagnosis. While children with ASD are usually diagnosed between ages 2-4, many pediatricians and psychiatrists are interested in understanding the developmental course of ASD in early infancy and infancy. Such an understanding would help both infants with ASD and their family members to identify useful interventions to cope more favorably with difficulties related to the infants' symptoms of ASD. We highlighted that ASD traits unfavorably impact a child's and their family's social, behavioral, and the family's economic status and conditions. Given this, an early diagnosis and timely and appropriate interventions should mitigate ASD-related issues in everyday life. To this end, assessing a child's behavior is the gold standard for ASD diagnosis. Most of the symptoms appear in the second year of life; often language acquisition is impaired. Considering the signs of ASD in infancy, promising perspectives on ASD diagnosis will be introduced in the future.

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Keywords: ASD, Autism spectrum disorder, Behavioral skills, Brain development, Childhood, Children, Clinical approach, Communicational skill, Diagnosis, DSM-5, Early diagnosis, Early intervention, ICD-11, Infancy, Infant, Intervention, Neurodevelopmental disorder, Quality of life, Signs, Symptoms, Treatment.

INTRODUCTION

Autism spectrum disorder (ASD) is a complex and lifelong neurodevelopmental disorder. The main etiology is unknown yet, but both environmental and genetic risk factors are associated with the onset of this disorder [1]. The prevalence of ASD significantly increased in early decades [2]: A comprehensive systematic review and meta-analysis including a total of 74 studies comprising 30,212,757 participants reported a worldwide prevalence rate of 0.6%. Importantly, prevalence rates varied among continents: Asia: 0.4%, Europe: 0.5%; America: 1%; Australia: 1.7%, and Africa 1% [3].

Children with ASD suffer from impairments in communication, limited interest and skills in social interactions, and repetitive behavior. Symptom severity may individually vary. Generally, in younger children with ASD, the following signs are observed: 1) avoiding eye contact with others, 2) repetitive movements, 3) not smiling when others are smiling at them, and 4) not talking as much as other same-aged children. In older children with ASD, the following additional behaviors are observed: 1) problems in making friends or preferring to stay alone, 2) showing great and increased interest in certain objects or very specific topics, 3) taking the content of a sentence completely literally (for example they may not perceive idioms, irony, sarcasm, verbal hints, word games, word ambiguities), 4) problems in understanding other people's feeling (*i.e.*, lack of empathy), 5) problems in expressing how they feel (*i.e.*, lack of emotional competencies), and 6) usually following a strict daily routine [4].

ASD imposes challenges on children with ASD and their parents. However, early detection and intervention can reduce this burden and lead to better developmental and cognitive improvement in the future. While ASD is usually diagnosed between the ages of 2 to 4 years, it is required to identify ASD in early infancy and infancy, thus, among infants and toddlers age up to 36 months. Typical behavioral signs are: Motor delays, lack of response to name, lack of proper eye contact, or a decreased variety of gesture types; further signs which will be elucidated in this chapter in more details are discussed below [5 - 7].

The aims of the present chapter are three-fold: a) To thoroughly show typical behavioral indicators of ASD, along with their impact on everyday life; b) To showcase the importance of the early diagnosis and detection of ASD to improve

a favorable outcome of children with ASD; c) To streamline future directions of early diagnosis based on most recent publications in the field.

WHAT IS AUTISM SPECTRUM DISORDER?

In 1943, Leo Kanner, an Austrian-American child psychiatrist, described three girls and eight boys, including a five-year-old boy called Donald. Unlike the general behavior of five-years-old children, Donald was the happiest when he was alone; he didn't cry to stay with his mother; he was indifferent to his father's homecoming and uninterested in visiting his relatives; in a room, he ignored people and was solely interested in objects; words' meanings were strict and unchangeable to him. He also didn't understand the meaning of facial expressions such as smiling. In 1944, Hans Asperger, an Austrian pediatrician, described four boys. A 6-year-old boy called Fritz was one of them who had some considerable behaviors such as: Quickly learned to talk and express himself in words, couldn't get involved in a group of playing kids, was indifferent to the respect to adults, talked to strangers without shyness, and also stereotypic habits and movements were observed. Both Kanner and Asperger portrayed a set of behavior not matching behaviors of typically developing children and of the general child population; their descriptions paved the ground for the today's autism spectrum disorder [8]. ASD is a psychiatric and neurological disorder characterized by significant delays in social and behavioral skills, communication, and language development. The etiology is unclear, but different immunological, biological, psychological [9], and genetic [10] models may explain the occurrence and development of ASD. In other words, ASD is a complex disorder with a relatively homogeneous pattern of symptoms and different possible etiologies. Further, pharmacological treatments target on mitigating symptoms and ASD-behavioral issues such as aggression, self-mutilation, sleep disorders, and repetitive behaviors [11].

Further, psychiatric, medical, or developmental co-occurring conditions are observed in almost 70% of individuals with ASD. Co-occurring conditions in childhood might cross into adolescence, while some of these conditions may develop in adulthood for the first time *(e.g.*, depression and epilepsy). A higher amount of co-occurring conditions is associated with more disabilities [8].

MAIN TYPES OF AUTISM SPECTRUM DISORDER

Asperger syndrome is commonly used informally in ASD communities, but it has been used as the first level of autism spectrum disorder through medical professions. A child with Asperger syndrome may have problems with social communication but will have strong verbal skills and above-average intelligence. Other signs and symptoms are inflexibility in behavior, problems in executive

CHAPTER 11

Medical Futility in Pediatrics: Challenges, Hopes, and New Perspectives

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Abstract: The concept of medical futility is explored, particularly in relation to the challenge of defining futile treatments, and the difficulties in identifying patient subgroups that strictly match the criteria for treatment futility. The issue of categorizing perinatal disorders as fatal is an important topic, with a focus on the moral and legal repercussions of identifying lethal malformation. The identification of a lethal malformation often has moral and legal repercussions, and the phrase "lethal" should be avoided unless it is precisely defined, used consistently, and covered in transparency in perinatal counseling following prenatal diagnosis.

We argue that a nuanced and carefully considered approach is required, one that takes into account the complex medical and ethical issues involved, and that focuses on the best interests of the patient and their family.

Overall, we highlight the importance of ethical considerations and effective communication in the provision of perinatal palliative care for fetuses with genetic disorders and congenital defects. Also, while there is much that remains uncertain and

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controversial in this field, continued research and discussions are necessary to ensure that the best possible care is provided for all patients and their families.

Keywords: Futility, Medical Futility, Medicine, Pediatrics.

INTRODUCTION

Medical futility has always remained a controversial issue in all fields of medicine, and pediatrics is no exception. Medical futility is defined as treatment or interventions that patients might not benefit from them. Some argue that patients should be autonomous regarding choosing whether they want to be over-treated or to be left untreated. To put it another way, withdrawing or withholding medical treatment must be optional for patients. However, the matter is far more complicated. The dilemma is even much more complex when you are facing an infant or a child [1, 2].

In recent decades, patients' autonomy has claimed considerable credit due to the emphasis on it as a major patient right, at least partly by social forces and philosophical contributions [3]. As a result, the patient-physician relationship has transformed from a paternalistic model to a partnership model [4]. The principle of autonomy states that the patient has the capacity to choose and the right to decide what is done with her body.

Pediatric ethics is challenging, as the pediatrician might behave according to the child's best interest and put a high priority on the child's rather than the parents' preferences. These facts might result in conflict among the child, parents, and pediatrician. Cultural, social, and religious differences might add complexity. Therefore, the physician must balance respecting the parents' responsibility and following the child's autonomy [5].

Far-reaching advances in medical technology have led to many realistic and unrealistic expectations, and doctors are sometimes faced with demands that are professionally futile, with no effect or benefit [4]. This study aims to review nuanced aspects of medical futility in pediatrics and shed light on the most controversial issues by highlighting future perspectives.

A BRIEF INTRODUCTION TO THE HISTORY AND DEFINITION OF MEDICAL FUTILITY IN PEDIATRICS

It is difficult to define medical futility, but as a working definition, one may call a preventive, diagnostic, or therapeutic medical intervention futile on the condition that it has no benefit for the patient [6]. Although the idea has surfaced since the 1960s, there's an aeonic background [7]. Hippocrates advises his students that

whenever the extent of a patient's illness is far beyond available treatments, they should not expect to overcome it [8]. At that time, physicians were free to decide, and patients' preferences had a minute role in medical decision-making [9].

The word futilis is from Greek mythology, in which trying to draw water in leaky sieves is condemned to failure [10]. Webster's definition of futility is “a useless act or gesture” [4].

There is not an all-inclusive definition of futility in medicine, but one of the best-known conceptions is due to Schneiderman. According to him, a futile medical intervention is one with an unacceptable probability of achieving a therapeutic benefit for the patient. For Schneiderman, medical futility has both quantitative and qualitative aspects. Quantitative futility is established when a treatment doesn't result in the desired outcome in recent 100 cases. He considers this aspect of medical futility as an adaptation of famous Hippocrates' instruction to his pupils that providing futile treatments in such conditions is evidence of co-occurring ignorance and insanity [11].

Qualitative futility is a treatment that falls short of supplying a satisfactory quality of life for the patient [12], or a treatment that preserves the patient in the unconscious state or is incapable of freeing her from intensive medical care [3]. This concept is adapted from Plato's dialogue The Republic, in which Asclepius, the deity of medicine, is mentioned as not treating and prolonging the miserable life of people with very severe diseases. Furthermore, some experts place qualitative futility into two categories: first, when the disadvantages of treatment outweigh its benefits, and second, when the treatment is of little value for the patient's quality of life, so remaining alive doesn't worth it [13]. It must be noted here that providing care and relief for a patient's pain and suffering is never futile and should continue at all costs.

Besides these common conceptions, other definitions of medical futility have also been proposed. For instance, Youngner, in 1988, distinguished between two other types of medical futility:

Physiologic futility: a treatment that is unable to meet the physiological goals of the physician. Here, the physician and the patient are in mutual agreement about the goal of treatment, but they argue about whether treatment can achieve that goal.

Normative futility: a treatment that can fulfill the goals of the patient or her surrogates, but these goals are worthless from the physician's point of view. Here, the dispute is on the value of the goals of the patient or her surrogates. Many com-

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