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Review

Neural Tube Defects: Etiology, Epidemiology, Risk Factors, and Advances in Prevention and Treatment

R. Manimekalai*[1], A. Rahana[2], Shruti Srinivasan[3]

[1]Professor, Sree Abirami College of Nursing, L&T Bypass Road, Eachanari (P.O), Coimbatore, Tamil nadu – 641 021, India

[2,3]Assistant Professor, Sree Abirami College of Allied Health Sciences, Sree Abirami Hospital (P) Ltd., 33, Madukkarai Road, Sundarapuram, Coimbatore, Tamil Nadu - 641024, India

*Author for Correspondence: Prof. R. Manimekalai
Email: balamanihari@gmail.com

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Abstract

Neural tube defects (NTDs) are severe congenital malformations resulting from incomplete closure of the neural tube during embryogenesis. These defects, including spina bifida, anencephaly, and encephalocele, contribute significantly to infant mortality and long-term disability. Despite advancements in prenatal screening and folic acid supplementation, NTDs remain a critical public health issue. This review provides a comprehensive analysis of the etiology, epidemiology, risk factors, genetic and environmental influences, diagnostic approaches, preventive strategies, and current therapeutic interventions for NTDs. Emphasis is placed on the role of folic acid in prevention, the impact of genetic predispositions, and the latest research on molecular pathways involved in neural tube closure. Current trends in prenatal diagnosis and the potential for future therapeutic approaches, including gene editing and regenerative medicine, are also discussed. Understanding the complex interplay of factors leading to NTDs is crucial for developing effective prevention and treatment strategies.

Keywords: Neural tube defects, spina bifida, anencephaly, folic acid, congenital malformations.

INTRODUCTION

Neural tube defects (NTDs) are congenital anomalies of the central nervous system that occur due to the failure of the neural tube to close completely during embryonic development. These defects can lead to severe neurological impairments or death, making them a significant concern in prenatal and neonatal healthcare. The primary types of NTDs include spina bifida, anencephaly, and encephalocele. This review aims to provide a comprehensive overview of NTDs, encompassing their etiology, epidemiology, risk factors, genetic and environmental influences, diagnostic approaches, preventive strategies, and current therapeutic interventions.

Etiology of Neural Tube Defects

NTDs arise from the failure of the neural tube to close during the early stages of embryogenesis, typically between the third and fourth weeks of pregnancy. This closure process is critical for the proper development of the brain and spinal cord. The etiology of NTDs is multifactorial, involving a complex interplay of genetic, environmental, and nutritional factors.

Genetic Factors

Genetic predisposition plays a crucial role in the occurrence of NTDs. Several genes have been implicated in neural tube closure, including those involved in folate metabolism, such as MTHFR (methylenetetrahydrofolate reductase). Mutations in these genes can disrupt folate metabolism, leading to an increased risk of NTDs. Additionally, defects in genes regulating cell signalling pathways and transcription factors essential for neural tube development can contribute to NTDs [1].

Environmental Factors

Environmental influences, including maternal hyperthermia, exposure to teratogenic substances, and certain medications, can increase the risk of NTDs. For instance, maternal exposure to antiepileptic drugs, such as valproic acid, has been associated with a higher incidence of NTDs. Similarly, exposure to agricultural pesticides and certain industrial chemicals has been linked to an increased risk of these defects [2].

Nutritional Factors

Adequate maternal nutrition, particularly folate intake, is critical for neural tube closure. Folic acid, a synthetic form of folate, has been shown to significantly reduce the risk of NTDs when taken before conception and during early pregnancy. Folate is essential for DNA synthesis, repair, and methylation, processes vital for cell division and differentiation during embryogenesis [3].

Epidemiology of Neural Tube Defects

The global incidence of NTDs varies widely, with higher rates observed in regions with inadequate folate intake and limited access to prenatal care. In the United States, the prevalence of NTDs has decreased significantly since the mandatory fortification of cereal grains with folic acid was implemented in 1998. However, NTDs remain a significant public health concern in many low- and middle-income countries where folate deficiency is more prevalent.

Incidence and Prevalence

The incidence of NTDs is estimated to be approximately 1 per 1,000 live births globally. However, the prevalence can range from 0.5 to 2 per 1,000 live births depending on geographical location, maternal nutrition, and genetic factors. In regions with mandatory folic acid fortification, such as North America and parts of Europe, the prevalence of NTDs has declined by 20-50% [4].

Geographical Variations

The incidence of NTDs exhibits significant geographical variation, with higher rates observed in areas with lower socioeconomic status and limited access to healthcare. For example, regions in South Asia and Sub-Saharan Africa report higher prevalence rates compared to North America and Europe. These variations can be attributed to differences in folate intake, genetic predisposition, and environmental exposures [5].

Temporal Trends

Over the past few decades, the incidence of NTDs has shown a declining trend in many high-income countries due to improved maternal nutrition and the implementation of folic acid fortification programs. However, in some low- and middle-income countries, the rates of NTDs have remained relatively stable or even increased due to persistent nutritional deficiencies and lack of access to prenatal care [6].

Risk Factors for Neural Tube Defects

Understanding the risk factors associated with NTDs is crucial for developing effective prevention strategies. These risk factors can be broadly categorized into genetic, environmental, and nutritional factors.

Genetic Risk Factors

A family history of NTDs significantly increases the risk of recurrence in subsequent pregnancies. The risk of having a child with an NTD is approximately 3-5% if one parent or sibling is affected. Specific genetic mutations, such as those in the MTHFR gene, also elevate the risk of NTDs [7].

Environmental Risk Factors

Several environmental exposures have been linked to an increased risk of NTDs. Maternal hyperthermia during early pregnancy, resulting from febrile illnesses or the use of hot tubs and saunas, has been associated with a higher incidence of NTDs. Additionally, maternal exposure to certain medications, such as antiepileptic drugs, and environmental toxins, including pesticides and industrial chemicals, can increase the risk of these defects [8].

Nutritional Risk Factors

Maternal folate deficiency is a well-established risk factor for NTDs. Women with low dietary folate intake or impaired folate metabolisms due to genetic mutations are at higher risk. Other nutritional deficiencies, such as low levels of vitamin B12 and zinc, have also been implicated in the development of NTDs [9].

Genetic and Environmental Influences on Neural Tube Defects

The interplay between genetic and environmental factors plays a pivotal role in the development of NTDs. Genetic predispositions can influence the body's response to environmental exposures and nutritional deficiencies, thereby modulating the risk of NTDs.

Gene-Environment Interactions

The interaction between genetic mutations and environmental factors, such as maternal nutrition and exposure to teratogens, can significantly impact neural tube closure. For example, women with mutations in the MTHFR gene who also have low folate intake are at a markedly increased risk of having a child with an NTD. Understanding these interactions is crucial for identifying high-risk populations and developing targeted prevention strategies [10].

Epigenetic Mechanisms

Epigenetic modifications, such as DNA methylation and histone acetylation, play a critical role in regulating gene expression during embryonic development. Disruptions in these epigenetic processes due to genetic mutations or environmental exposures can impair neural tube closure, leading to NTDs. Research into epigenetic mechanisms offers potential avenues for therapeutic interventions aimed at modulating gene expression to prevent NTDs [11].

Diagnostic Approaches for Neural Tube Defects

Early diagnosis of NTDs is essential for optimal prenatal care and timely interventions. Several diagnostic approaches, including maternal serum screening, ultrasonography, and amniocentesis, are employed to detect NTDs during pregnancy.

Maternal Serum Screening

Maternal serum alpha-fetoprotein (MSAFP) screening is a widely used method for detecting NTDs. Elevated levels of MSAFP in maternal blood are indicative of a potential NTD in the fetus. This screening is typically performed between the 15th and 20th weeks of gestation and is often combined with other biomarkers to improve diagnostic accuracy [12].

Ultrasonography

Examination is a crucial tool for the prenatal diagnosis of NTDs. High-resolution ultrasonography can visualize the fetal spine and brain, allowing for the detection of structural abnormalities associated with NTDs. Ultrasonography is usually performed between the 18th and 22nd weeks of gestation as part of routine prenatal care [13].

Amniocentesis

Amniocentesis involves the extraction of a small amount of amniotic fluid from the amniotic sac surrounding the fetus. This fluid contains fetal cells and biochemical substances that can be analyzed for genetic and chromosomal abnormalities, including NTDs. Elevated levels of alpha-fetoprotein (AFP) and acetylcholinesterase (AChE) in the amniotic fluid are indicative of an open NTD [14].

Preventive Strategies for Neural Tube Defects

Preventing NTDs involves a multifaceted approach that includes nutritional supplementation, public health initiatives, and genetic counselling.

Folic Acid Supplementation

Folic acid supplementation is the cornerstone of NTD prevention. Women of childbearing age are advised to take 400-800 micrograms of folic acid daily, starting at least one month before conception and

continuing through the first trimester of pregnancy. This supplementation has been shown to reduce the incidence of NTDs by up to 70% [15].

Dietary Interventions

In addition to folic acid supplementation, promoting a diet rich in natural sources of folate, such as leafy green vegetables, legumes, and fortified cereals, is essential for preventing NTDs. Public health campaigns aimed at increasing awareness of the importance of folate intake can help improve maternal nutrition and reduce the risk of NTDs [16].

Genetic Counselling

Genetic counselling can provide valuable information to couples with a family history of NTDs or known genetic mutations associated with these defects. Counselling can help identify high-risk individuals and offer guidance on preventive measures, including folic acid supplementation and prenatal screening [17].

Current Therapeutic Interventions for Neural Tube Defects

While prevention remains the primary strategy for reducing the incidence of NTDs, therapeutic interventions are essential for managing affected individuals. Advances in medical and surgical treatments have improved the quality of life for individuals with NTDs.

Prenatal Surgery

Prenatal surgery, also known as fetal surgery, is an emerging approach for treating certain NTDs, such as spina bifida, before birth. This intervention involves surgically repairing the spinal defect in utero, thereby preventing further damage to the spinal cord and improving neurological outcomes. Prenatal surgery has shown promising results in reducing the severity of disabilities associated with spina bifida [18].

Postnatal Care

Postnatal care for individuals with NTDs involves a multidisciplinary approach that includes medical, surgical, and rehabilitative interventions. Management of spina bifida, for example, may require surgical repair of the spinal defect, treatment of hydrocephalus with shunt placement, and ongoing physical therapy to address mobility issues. Early intervention programs and specialized education plans are crucial for maximizing developmental outcomes and quality of life [19].

Medicine

Regenerative medicine, including stem cell therapy and tissue engineering, holds potential for future therapeutic approaches to NTDs. Research into the use of stem cells to repair damaged neural tissue and promote neural regeneration offers hope for developing novel treatments for NTDs. While still in experimental stages, these approaches represent promising avenues for future clinical applications [20].

CONCLUSION

Neural tube defects are complex congenital anomalies with significant implications for affected individuals and their families. Understanding the multifactorial etiology, including genetic, environmental, and nutritional factors, is essential for developing effective prevention and treatment strategies. Advances in prenatal screening, folic acid supplementation, and surgical interventions have improved outcomes for individuals with NTDs. Ongoing research into the molecular mechanisms underlying neural tube closure and the development of innovative therapeutic approaches, such as regenerative medicine, holds promise for further reducing the burden of NTDs. Continued efforts in public health education, nutritional interventions, and genetic counseling are crucial for preventing these debilitating defects and improving the quality of life for those affected.

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