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NEURAL TUBE DEFECTS: ETIOLOGY, RISK FACTORS, AND THE IMPACT OF FOOD FORTIFICATION PROGRAM

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ABSTRACT

Neural tube defects (NTDs) are a group of congenital malformations that result from incomplete closure of the neural tube during embryonic development. Neural tube forms the brain and spinal cord, while its failure to close properly can result in severe defects, such as spina bifida and anencephaly. This review article provides a logical classification of various defects as well as an overview of the causes, regional incidences, disease severity and outcomes. It further discusses risk factors such as family history, genetic disorders and maternal factors including folic acid deficiency, obesity and exposure to certain drugs during pregnancy. Initial research on NTDs generated 3,397 publications but following our inclusion criteria, we selected 186 papers to review. Our findings indicate that the incidences vary by ethonogeographic perspective, but on average, global prevalence is 1 in 1,000 live births. The effects of NTD range from mild to severe, while some individuals requiring life-long medical care and others having limited mobility or intellectual disability. The major cause of NTD is mineral deficiency of various vitamins particularly diatery folate. Over 123 countries as participants of the food fortification programs (FFP), under the world foodprogram (WFP) have aimed to reduce mineral deficiencies but many vulnerable populations still remain beyond reach. We explain how NTDs continue to affect vulnerable populations and thus build a case for further strengthening the FFP.

Keywords: *Neural tube defect (NTD), folic acid, 1-C folate pathway, spina bifida, anenecephaly, open and closed spinal dysraphisms.*

INTRODUCTION

Neural tube defects (NTDs) are serious brain abnormalities caused by the failure of rostral neuropore to completely close during the fourth week of development. Spina bifida and anencephaly are the most frequent NTDs, and anencephaly is the only one that is thought to be lethal [1-3]. Neural tube defects are the second most common type of serious birth defects. They lead to physical and/or mental disabilities paving an economic burden on the healthcare system of any country [4]. In higher vertebrates, theneural tube is formed

by mechanisms that form, bend or potentiate fusion of the neural plate while dorsal midline fusion seals the neural tube as it forms. Until the completion of neural tube closure in embryo, the neural tissue remains uncovered in brain or spinal cord [5]. This causes neurodegeneration *in-utero* with significant functional cognitive loss leading to anencephaly if anterior neural tube fails to close by day 28 [6].

Anencephaly always results in a fatality, either in the form of a stillbirth, a neonatal death, or on rare occasions a post-neonatal death. Encephalocele and spina bifida have been known to cause newborn or infant mortality and frequently causing severe disabilities in the absence of a palliative surgery, such as lower-limb paralysis,incontinence, convulsions, and recurrent central nervous system (CNS) infections [7]. The pathogenesis of this morphogenic defect has not yet been fully elucidated,however, many genetic and environmental risk factors have been widely reported [8]. This article highlights the importance of preventing NTDs through proper prenatal care and manintaining proper nutrition of the mother, like maintaining a proper intake offolic acid has been shown to be an effective preventative measures [9], which is involved in the one-carbon folate metabolism during pregnancy shown in (**Figure 1**). It further emphasizes the underlying importance of ongoing research and focuses on NTDs in order to improve outcomes for affectees and to reduce the burden onhealthcare system caused by this preventable disorder.

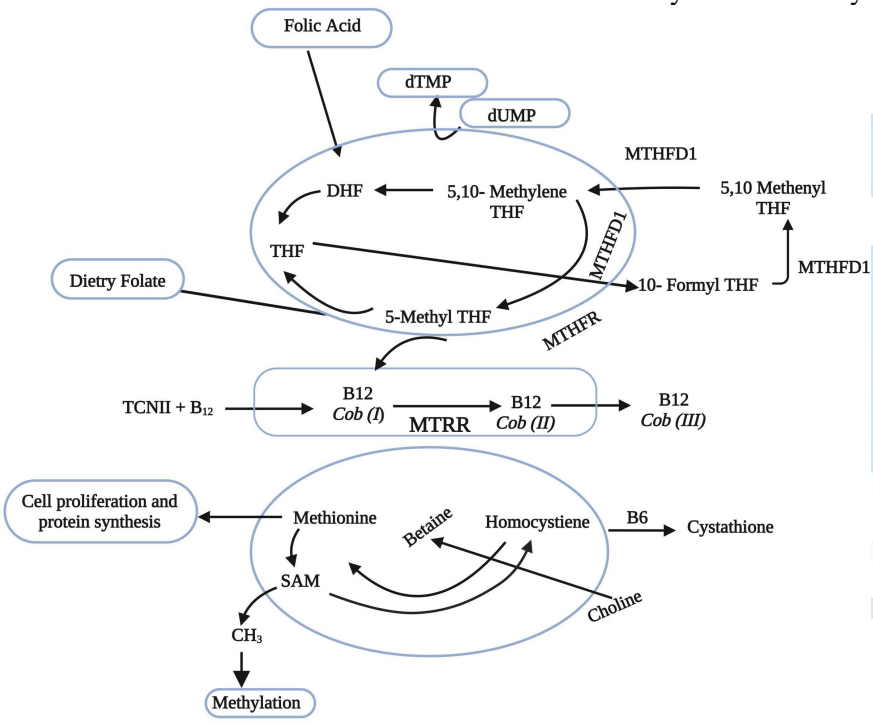


Figure 1: Maternal folate-one carbon metabolism during pregnancy [10]. The one- carbon metabolic pathway. Folate, as 5-methyl-THF, serves as the substrate for metabolic transformation of homocysteine to methionine via MTR. Methionine isconverted to *S*-adenosylmethionine (SAM), which serves as the principal methyl donor for methylation. Vitamin B12 acts as an intermediate methyl carrier during the MTR- catalysed re-methylation of homocysteine (Hcy) to methionine, cycling between two states, cobalamin (I) and methylcobalamin (III) via TCN II. Cobalamin (I) is a strong reductant that can be oxidised to produce inactive cobalamin (II), which undergoes reductive methylation to methylcobalamin (III) via the methionine synthase (MTRR) enzyme using SAM as the methyl donor. Choline derived betaine can also serve as a methyl donor for the conversion of homocysteine to methionine. Thymidylate synthaseenzyme uses methylene tetrahyrofolate (methylene THF) as carbon source and asreducing agent to form dTMP (an essential DNA precursor) from dUMP. **Abbreviations used: B6**, vitamin B6; **B12**, vitamin B12 (cobalamin, in various oxidative forms); **CH3**, methyl group; **DHF**, Dihydrofolate; **Hcy**, homocysteine; **MTHFR**, methylenetetrahydrofolate reductase; MTHFD1, methylene tetrahydrofolate dehydrogenase 1; **MTR**, methionine synthase; **MTRR**, methionine synthase reductase; **SAM**, S-Adenosylmethionine; **SAH**, S- adenosylhomocysteine; **TCN II**, Transcobalamin II; **THF**, tetrahydrofolate; dUMP, Deoxyuridine monophosphate; dTMP thymidylate monophosphate. Modified after Jankovic-Karasoulos et al. (2008)

Epidemiology

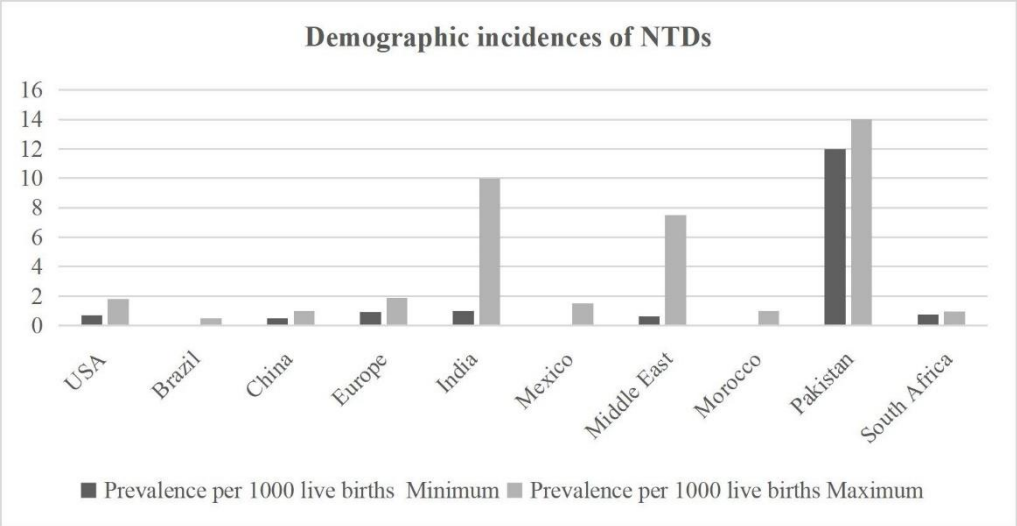
It is estimated that annualt around 300,000 babies, with neural tube defects, are born worldwide. Based on geographic location, literacy rate, nutrition status, consanguinity and gender etc., the rate of occurrence varies. Accordint to Center for Disease Controland Prevention (CDC),anencephaly affects about 3 out of 10,000 births in the U.S annulay [1, 10]. Neural tube defects (NTDs) affect on an average 1 in 1000 recognized pregnancies worldwide, yet variations in NTDs prevalence between 0.2 and 10 per 1000 have been observed in various parts of the world [8].

This disease set is more prevalent in low- and middle-income countries, where there is a lack of access to effective prenatal care and nutritional supplements including folic acid [9, 10, 11]. In the United States, the incidence of NTDs was estimated to be on average 0.7 per 1,000 live births between 2004-2006 [1, 12], however, certain populations, such as Hispanic Americans, exhibit a higher than the National average incidence. In Mexico, the incidence of NTDs is estimated to be around 1.5 per 1,000 live births [13] as shown in **table 1 and figure 2**. The incidence of NTDs, in India,was estimated to be between 1 and 10 per 1,000 live births [1] but one randomized study estimated it to be 4.5/1000 births [14], while another study from the northern parts of India estimated it to be 7.48/1000 [15]. Similarly, in China, the incidence of NTDs was estimated to be around 0.5 to 1 per 1,000 live births [16], while northern China reported a rate higher than the national average, reaching about 5 in 1000 births,but for southern China the incidence was aligned with other developed countries [17]. In Brazil, the incidence of NTDs fell from 0.79 to 0. 55 per 1000 live births from 2001-2014 due to flour fortification [18]. In Morocco it was 1 in 1000 [19] while in South Africa, the incidence of NTDs was between 0.76 to 0.94 per 1000 live births [20]. In Pakistan, although no formal data was available but one particular hospital reported the occurrence of NTDs to be between 12 to 14 per 1000 live births [21], making it the highest rate in the world. A data of more than 11000 cases in Europe was used from 23 population based registries in 18 countries, covering over 12.5 million births. The study concluded that during the 20 years period (1991-2011) the prevalence remained almost unchanged i.e., ~9/10,000 (or 0.9/1000) live births [22] but data from Germany recorded almost twice the European estimate at 18.72/10000 (or 1.872/1000) [23]. In Middle East (data from about 13 countries) the prevalence of NTDs varies from 0.62/1000 in United Arab Emirates to 7.5/1000 in Algeria [24], while intrafamilial marriages account for 20-50% of all marriages [25], however, the prevalence of congenital anomalies in consanguineous marriages was estimated to be 1.7-2.8% higher than the background population risk attributable to autosomal recessive disorders [26]. A Separate study calculated consanguinity in Qatar and found the risk of autosomal recessive genetic disorders aggravated to 45.5% compared with 22.4% of non-cansanguineous marriages [27].

Table 1: Neural tube defect incidence estimates from various regions and countries

Serialno.	Country	Prevalence per 1000 live births		References
		Minimum	Maximum	
1	USA	0.7	1.8	[1, 12]
2	Brazil	0	0.5	[18]
3	China	0.5	1	[16, 17]
4	Europe	0.9	1.87	[22]
5	India	1	10	[1,14,15]
6	Mexico	0	1.5	[13]
7	Middle East	0.62	7.5	[24]
8	Morocco	0	1	[19]
9	Pakistan	12	14	[21]
10	South Africa	0.76	0.94	[20]

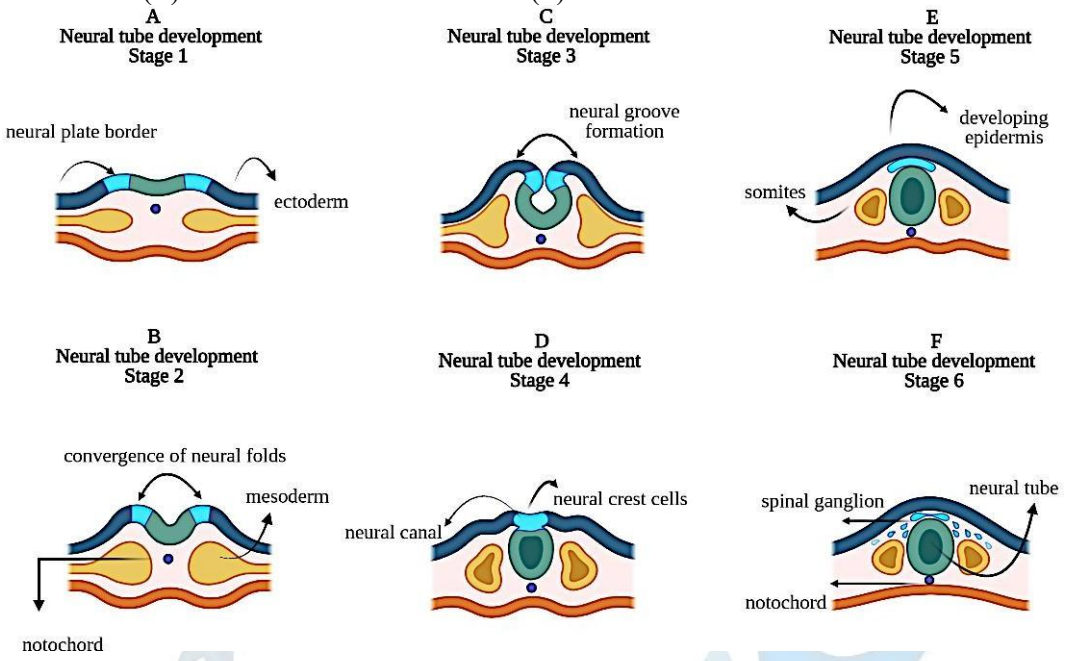
Figure 2: Graphical representation of incidence of NTDs in some countries and regions



Neural tube development

Immediately following fertilization of the oocyte, gastrulation ensures and ectoderm is formed, which thickens in response to a series of molecular signals released by the notochord, thus giving rise to the neural plate. The ectoderm cells form the neural tube by bending or potentiating fusion of the neural plate while dorsal midline fusion (primary neurulation) seals the neural tube (**Figure 3**). The initial embryonic development of the central nervous system in vertebrates takes place within 17-28 days,post-fertilization, in a process referred to as neurulation. Secondary neurulation, in the caudal region, involves cellular condensation and progressive differentiation (mesenchymal-to-epithelial transition) to close the neural tube [28]. In mammals, primary neurulation is a multi-site process and recent evidences suggest that there are two closure sites in humans (the prospective cervical region and the mesencephalon- rombencephalic boundary) [29]. Mammalian neurulation is a highly regulated and energy dependent process which involves the formation of an anterior neuropore (ANP)and posterior neuropore (PNP). These neuropores are openings that progressively reduce in size until fusion occurs to complete the process of neural tube closure (NTC) [30].

Figure 3: Stages of neural tube development in the embryo. Formation of neural plate (A), convergence of neural border (B), formation of neural grove (C), neural canal formation (D), epidermis formation emerging from the ectoderm (E) and formation of neural tube (F).

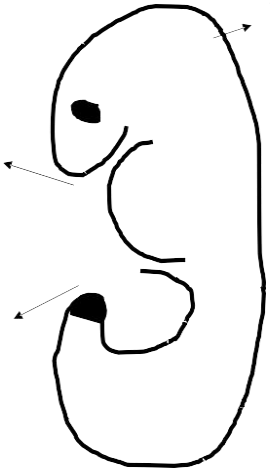


Classification of NTDs

The classification of NTDs varies which leads to a confusion of proper diagnosis of these conditions. These classifications follow different criteria, while a unifying criterion is a remiss.

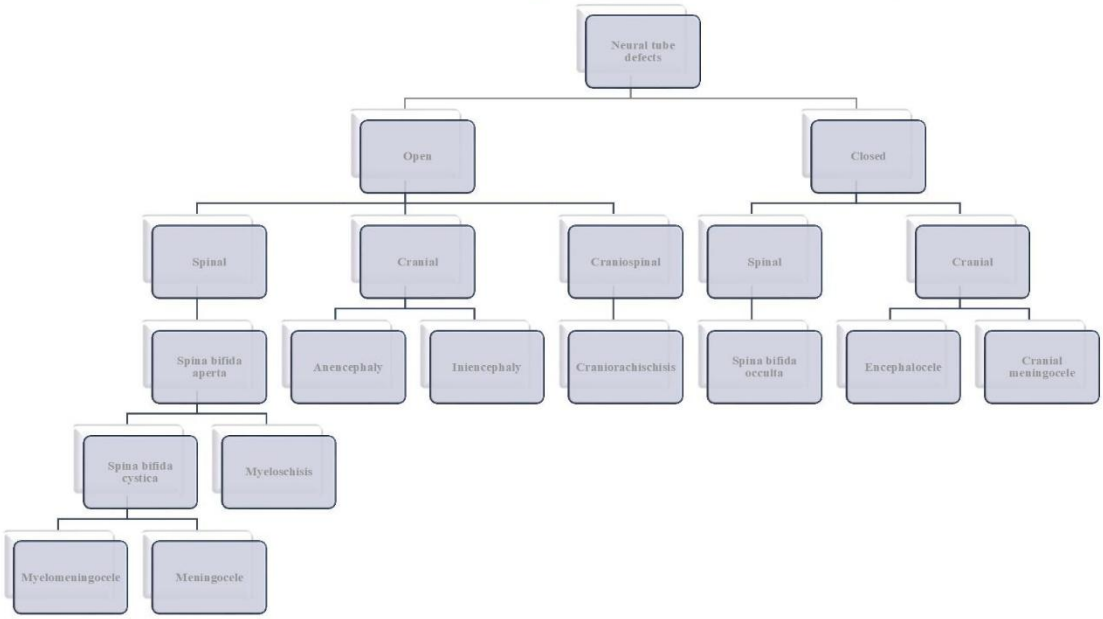
Classically the NTDs have been sub-divided into two main groups (open and closed), while the extremely stochastic pathology largely depends on the exact site of the lesion[31]. This very stochastic nature of lesions often leads to the confusion and thus varied classifications. However it is important to understand that classification should not be based on one parameter (location of lesion) only, rather it should be based on at least four confounding parameters, i.e., open or closed pathology, location, tissue or organ affected, and neurulation. Neural tube defects (NTDs) are broadly classified as open (when neural tissue is exposed) or closed (when covered by skin). Open defects arise during neurulation followed by closed defects thereafter.

NTDs may include such varied defects (**Figure 4**) that could arise from improper folding and fusion of the neural tube (called craniorachischisis), or failure of closure of the anterior neuropore (anencephaly) and failure of closure of posterior neuropore(spina bifida) [32].



SECOND closure event.
Failure causes Anencephaly.
Anterior neuropore
THIRD closure event.
Failure causes Spina bifida occulta.
Posterior neuropore
Hindbrain neuropore
FIRST closure event.
Failure causes Craniorachischisis.
Figure 4: Neurulation events in the mamammalian embryo. Neural tube closure begins with the hindbrain neuropore at 6-7 somite stage (*). The second closure event is initiated at the fore/midbrain boundary (**), while the third event occurs at the rostral extremity of forebrain (***). Failure of these closure events could lead to respective NTDs as shown in the figure.
Interestingly, many classification systems exist today but since Lemire (1988), a uniform system has not been proposed. We consider the classification (**table 2**) proposed by Badhiwala et al. (2020) to be most effective for clinical evaluations [33].

Table 2: Classification of NTDs, adapted from Badhiwala et al. (2020) [33]



Open NTDs
Open neural tube defects (NTDs) are disorders that arise when the neural tube, whichis the embryonic progenitor for the development of brain and spinal cord, fails to close properly during early embryogenesis **(Figure 3)**. Therefore, NTDs are considered serious congenital abnormalities of the central nervous system (CNS) that are causedby a failure of the embryonal morphogenetic process [34]. The neural tube is formed inhigher vertebrates by processes that shape, bend and fuse the neural plate, followed by fusion in the dorsal midline that increasingly seals the neural tube as it forms. If the neuroepithelium is not completely closed, it remains exposed to the environment and hence susceptible to degeneration and neuronal deficiency. The kind and severity of these open NTDs vary according to the body axis that is affected.

Open spinal dysraphisms

Any NTD that originates from the incompletely closed posterior neuropore **(Figure 4)** and not being cevered by skin is referred to as an open spinal dysraphism. The term spina bifida (SB) is variously classified but in reality it is an all-inclusive term for any condition characterized by a non-closure of the vertebral arches. Neuropathological conditions, associated with SB are also often reported with imprecise and confusing terminology [35]. The loosely classified condition SB can be differentiated into its sub-types by considering whether only the spine is affected or meninges along with the spinal cord is also affected [29, 36-38].

Spina bifida aperta (SBA):

This condition refers to a defect in which the neural tissues are exposed to the extrenal environment. The condition causes a varied spectrum of neurological problems according to the degree of neurulation. Motor and sensory deficits occur in areas innervated by the spinal cord segments at and around the site of the lesion. Bladder and bowel dysfunction, along with associated orthopedic abnormalities such as clubfeet, scoliosis, kyphosis etc., are also commonly reported [39]. As regards the nomenclature of SBA subtypes, one overarching term "myelomeningocele" is used to describe all of them in literature, which is highly misleading and confusing [31, 40]. The condition called SBA can be rationally sub-divided into spina bifida csytica (SBC) and myeloschisis [33]. This uniformity in classification is essential not only for the clinicians, basic scientists and surgeons but also for diagnostics experts who rely heavily on mutation analysis through next generation sequencing.

Spina bifida cystica (SBC)

This is a sub-type of SBA, which is characterized by a lesion being contained within the meningeal lining that forms a cerebrospinal fluid filled sac or cyst. If there is only aherniation of meninges, associated with spinal defect then it is called meningocele, but if there is herniation of both meninges and neural elements then it is called myelomeningocele. The defect can be further sub-divided into the following types.

Spinal meningocele

Meningocele is a type of open neural tube defect (NTD) in which the protective membranes surrounding the spinal cord protrude through an opening in the spinal column, forming a sac that is visible on the outside of the body, but this defect is not associated with an accompanying neurologic deficit. A simple form of the condition basically consists of the meninges and cerebrospinal fluid protruding into the sub-cutaneous tissue forming a sac. Meningocele is asymptomatic with no associated neurolgic deformities [40]. Membrane lesions occur rostrally, while skin lesions can occur anywhere along the spine. Membranous meningocele in the cervical region could be sometime associated with aqueductal stenosis, hydromyelia or Chiari malformation. In rare cases meningocele could appear anteriorly as an intra-abdominal or a pelvic mass [41]. An MRI (magnetic resonance imaging) scan is essential to determine the contents of the mass, along with the spine. According to Gupta et al. (2017), upon careful examination of pateints, sometimes significant abnormality may be observed which might include equinovarus deformity, gait imbalance and bladder dysfunction, suggesting trapped nerve roots within the defect [42, 43].

However, according to most authors, the spinal cord in meningocele is not affected, so individuals with this condition may have fewer neurological problems and a better prognosis, as surgical repair of the mininges can significantly improve a patient's health. Post-operative patients may still experience some level of physical and functional problems, such as back pain or difficulty with movement, depending on the location and size of the meningocele. Meninges that have emerged via a spinal defect into the subcutaneous tissue constitute a simple meningocele. There are further spinal defects connected to a complicated meningocele. Acute neurologic problems are not linked to meningocele, thus it is an asymptomatic spinal abnormality [40]. A rare co- morbidity called "Tourniquet syndrome" is sometimes observed alongside meningocele. This is a rare condition which involves obstructed blood flow and subsequent ischemic injury [44].

Spinal myelomeningocele

Myelomeningocele (also known as open spina bifida) is an open NTD in which the spinal cord and its protective membranes (meninges) protrude through an opening in the spinal column **(Figure 5).** It eventually results in exposed meninges and neural tissue at the level of the damaged vertebra, along with a fluid-filled sac that bulges outwards [44]. So the characrteristic difference between meningocele and myelomeningocele is that the former condition shows up as a cerebrospinal fluid-filled sac that contains meninges but no neural tissue, while in the latter case the sac containsboth meninges as well as some part of the spinal tissue.

Being mostly lumbosacral, the anatomical location of myelomeningocele varies, and there is a range of associated anomalies. It is estimated that only 10% of neonates have hydrocephalus (fluid buld-up in the ventricles of brain) at birth, while the occurrence increases to 85% of neonates within the first week after birth. Almost all cases show Arnold Chiari 2 as a co-morbidity [45]. This defect frequently results in physical and cognitive problems such as paralysis, bladder and bowel incontinence, and hydrocephalus [46].

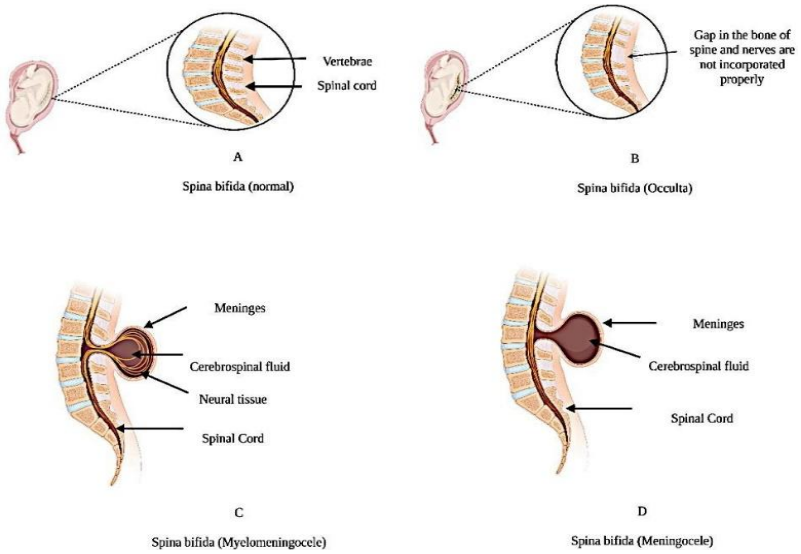
Myelomeningocele results in a fluid-filled sac that protrudes from the baby's back that contains part of the spinal cord, nerves and cerebrospinal fluid. The cause of myelomeningocele remains elusive but it is considered to be the cumulative effect of a range of gentic and environmental factors (discussed later in the article). However the most common underlying factor remains to be low level of nutritional folic acid at prenatal and neonatal stages. The three commonly used methods of diagnosis include blood test for alpha-fetoprotein at 16^{th} to 18^{th} week, prenatal ultrasound during the first (11-14 weeks) and second trimesters (18-22 weeks) and amniocentesis [47].

Myeloschisis

This is an open NTD in which the neural tissue is exposed at the surface without any accompanying meninges or sac. Prenatal diagnosis is the usual practice but surgery is possible after birth. The objective of a surgery is to cover the exposed neural tissue with skin to avoid infections [48].

A clear distinction between myelomeningocele (MMC) and myeloschisis (MSC) can be made based on the presence or absence of a CSF filled sac, respectively, however MSC is the more severe form. According to a study that was based on ultrasound and MRI scans of 111 *in utero* patients conducted over a period of 11 years (2011-2022) [49], MSC typically had more severe baseline tonsillar herniation compared withMMC. By definition MSC is a failure of the neural tube to close and often involves several adjacent spinal cord segments. The skin ectoderm remains attached to the borders of the neural plate, which prevents any vertebral arches from developing and thus leads to a rachischisis (a complete or severe defect in the spine) [50]. Before birth the neural tissue is exposed to amniotic fluid but immediately after birth and upon exposure to air, it becomes desiccated and results in haemorrhage along the surface of the neural plate [51].

Figure 5: Normal spine with vertebrae(A), spina bifida occulta nerves are into incorporated(B), spina bifida myelomeningocele a bulge formation in which neural tissue is exposed with cerebrospinal fluid(C), spina bifida meningocele meninges with cerebrospinal fluid are exposed outside the body except neural tissue(D).



Open cranial dysraphisms

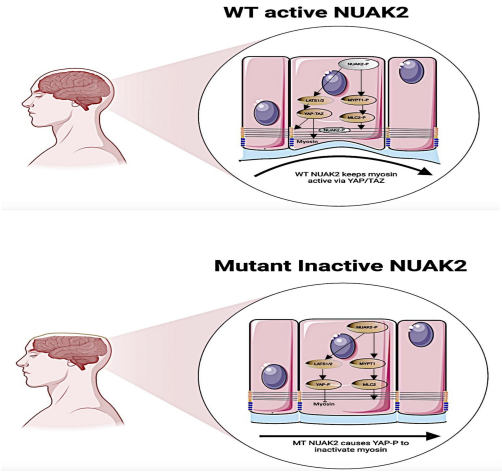
Exencephaly-Anencephaly

Anencephaly is a type of open neural tube defect (NTD) in which the brain fails to develop properly, resulting in a significant absence of the cranial vault and brain matter.Babies with anencephaly are usually stillborn or die shortly after birth, the structures generated from the forebrain and skull are absent [10]. The calvarium (cranial vault) is typically missing, and the parietal, frontal, and squama of the temporal and occipital bones are presented as primitive rudimentary structures; however the base of the skull is almost normal. The defect is either classified as **holoencephaly** (total absence of the brain) which is more common; or **meroanencephaly** (partial absence of brain), while in both conditions there is a lack of skin that covers the brain and cranial vault [52]. Anencephaly is the most common NTD [53], with an average global prevalence of 3/10,000 births [54].

During foetal development, a relatively normal brain forms, that lacks a covering for the skull/calvarium and meninges, in which case it is called exencephaly. However, if chemical and mechanical influences of the amniotic fluid on the exposed brain cause it to disintegrate, which subsequently leads to a failure of the development of skull and cerebral hemispheres, then it is termed as anencephaly [55]. Thus, exencephaly may beconsidered a less severe form of anencephaly.

Both exencephaly and anencephaly are considered multifactorial congenital disorders which could be linked to environmental as well as genetic factors [10]. One case of anencephaly (in a 20-week-old fetus, conceived of consanguineous Indian parents) has been linked to a homozygous missense mutation in the *TRIM36* gene on chromosome 5q22 [56]. While Bonnard et al. (2020) identified homozygosity for an insertion deletion mutation in the *NUAK2 (syn. ARK5)* gene located on 1q32.1, as a cause of anencephaly. Exome sequencing revealed a recessive germline 21-bp in-frame deletion in *NUAK2* gene, which subsequently causes impaired Hippo-YAP signaling (**Figure 6**)[57]. Additionally *do novo* mutations in the genes *VANGL2, SHROOM3, U2SURP* and *ANKRD32* have been linked to anencephaly [58, 59]. Given the stochastic nature of mutations and rare association with the disorder, mutation sequence analysis could not be used either as a diagnostic or prognostic marker [60]. In an investigation led by Bijok et al. (2022), genetic factors were linked to acrania/exencephaly/anencephaly in only 7/74 (9.5%) cases, while trisomy 18 was reported as the most common cause [61].

Figure 6. Impaired Hippo-YAP signaling in mutant NUAK2 phenotype leads to anencephaly.



Despite being hypoplastic and lacking the intermediate and posterior lobes, the pituitary is still present. Anencephaly is invariably accompanied by acrania, and without the calvaria, the brain is not protected thus it gradually deteriorates while the brainstem remains unharmed. More so, the aberrant brain structure and vas()cularization, which is characterized by the development of new blood vessels, arealso factors that contribute to overall damage. It is considered one of the severest forms of NTD and is usually fatal [62]. While Szkodziak et al. (2020) have proposed "beret" sign (resembling a soft, round, flat-crowned cap), in the differentiation of acrania from exencephaly and anencephaly, as a good diagnostic marker during ultrasound analysis. This sign can be observed as a thin anechoic space between an inertially rippled membrane and the brain structures, corresponding to cerebrospinal fluid during the first trimester (in sagittal and frontal cross-sectional ultrasound views) [63]. Human anencephaly may be divided into two types: meroacrania (if only the rostral brain is affected) and holoacrania (if posterior brain and skull are both affected) [64].

Iniencephaly

This open cranial dysraphism can be defined as an abnormality in the cervical vertebrae which causes severe cervico-thoracic spinal retroflexion**.** Developmental malformations of neural tube occur quite early in embryogenesis (day 26-30). Several theories have been presented to explain the cause of this pathology but nothing conclusive has been accepted [65]. However, radiologic perinatal lab pathological studies have revealed that at 26 weeks of pregnancy there was a multitude of congenital abnormalities detected, including cervical meningocele, neck hyperextension, short and deformed spine, congenital heart defect, coarctation (bore size narrower than usual) of aortic arch, accompanied by transposition of vessels. The meningocele of the aborted fetus (at 38th week) is covered from inside with dura mater, extending from the cranial cavity [66]. Some investigators have implicated teratogen exposure [67] or maternal age [68] as two of the risk factors of NTDs that could lead tovarying levels of lesion and severity. Some investigators have implicated extreme dorsal flexion as the cause of failure of neural tube closure, or rupture of a previously closed neural tube [69]. Iniencephaly may also be a primary defect in the neural tube formation or it may be a more severe form of Klippel-Feil syndrome or may belong to the spectrum of Dandy-Walker syndrome [70].

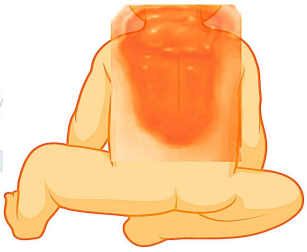
Figure 6. Clinical features of Iniencephaly which is an abnormality in the cervicalvertebrae which causes severe cervico-thoracic spinal retroflexion

Craniospinal dysraphism

Craniorachischisis

Craniorachischisis totalis is a rare and severe type of open neural tube defect (NTD) in which the brain and spinal cord are completely exposed and not protected by any bone or tissue, as observed in anencephaly with total open spina bifida, which results in gradual degeneration of tissue [71]. In one case report a craniorachischisis was diagnosed during the first trimester ultrasound at 11 weeks of gestation, which highlights the importance of an ultrasound being conducted during the first trimester to diagnose severe foetal malformation [72]. There is an absence of brain and cranial vault, which is a consequence of lack of skin covering, while the condition is aggravated by a bone defect of the cervical spine (which is devoid of a meninges, covering the neural tissue). Craniorachischisis is a lethal and non-syndromic anomaly. Eyes are normally formed, but bulging could be attributed to the absence of frontal portion of the cranial vault. Neck is shortened, while the cerebellum and brain stem are intact (**Figure 7**).

Figure 7. Craniorachischisis is characterized by anenecephaly and accompanied by a bony defect of the spine and exposure of the neural tissue.



Craniosrachischisis is therefore characterized by being an open lesion accompanied by anencephaly which is accompanied by a widespread spinal lesion. Sometimes there might be co-anomalies such as cleft lip and palate, omphalocele (congenital disorder characterized by infant's intestines, liver, or other organs sticking out through the bellybutton), limb defects or cyclopia (congenital disorder characterized by facial abnormalities). In terms of chromosomal aberrations, there have been some case reports of trisomy of chromosome 18 associated with craniorachischisis [72]. The neck may be short or non-existent, and facial dysmorphisms such as a big nose, exophthalmos, and low-set, folded ears may be present. Infants with craniorachischischisis seldom, if ever, live long after birth. The anomaly is considered one of the most severe forms of NTD and often leads to fetal death or severe developmental disabilities [73, 74].

Closed NTDs

Closed NTDs occur when the neural tube does not completely close, leading to a partial or complete failure of the neural folds to fuse, which therefore leaves an opening in the spinal cord or brain [75]. However, closed spinal dysraphisms are characterized by the neural and meningeal tissue being covered by skin or a subcutaneous tissue, thus the neural placode (non-neurulated neural tissue) is not exposed [76].

As per the classification mentioned above, closed NTDs can be further classified on the basis of having a spinal (closed spinal dysraphism) or cranial origin (closed cranial dysraphism).

Closed spinal dysraphisms

Spina bifida occulta (SBO)

This is the mildest form of closed spinal dysraphism, and involves a minimal neural involvement with hidden vertebral defect [77, 78]. There is no associated visible deformity, but sometimes it may be accompanied by a lump, red or purple patch (hemangiome) or a dark hairy skin patch (birthmark) at the site of the spinal defect. Most patients do not require a surgical correction [79, 80], but some associated symptoms of the defect include:

- bowel and bladder problems
- backache
- muscle weakness (especially in the legs)
- scoliosis (abnormal lateral curvature of the spoine)

The word "occulta" means hidden, thus the defect is often referred to as the "hidden spina bifida." Only 1 in 1000 people diagnosed with SBO experience any symptoms, which normally appear during adolescence as the spinal cord begins to stretch. Cause of SBO has been associated with either the lack of folic acid (vit B9) during pregnancyor a genetic family history of the defect. It has also been linked to diabetes or obesity or exposure to anti-seizure (anti-convulsant) drugs such as valproate and carbamazepine [81].

Closed cranial dysraphisms

Encephalocele

Encephalocele is often a closed and congenital neural tube defect (NTD), in which asac containing the brain, meninges, and cerebrospinal fluid bulges outside the skull due to a bone abnormality. Trauma, tumors, or iatrogenic damage (an illness caused by medical examination or treatment) can occasionally cause acquired encephaloceles. The sac is accurately referred to as a meningocele if the meninges and cerebrospinal fluid (CSF) filled sac protrudes from it, but it is known as an encephalocele when neural tissue is present [82]. The prevalence of encephalocele in population is estimated to be about 1 in every 4,000 live births. It is more common in developing countries, where it is often associated with poverty and lack of proper prenatal care [83].

Cranial meningocele

Cranial meningocele (CM) is a closed NTD and thus different from spinal meningocelewhich is an open NTD. It is a rare malformation of the central nervous system and characterized by herniation of meninges through a permanent defect in the skull. It is lined by arachnoid (an avascular membrane between the pia and the dura) and contains the CSF, but no brain tissue. The skin overlying meningocele is usually intact. The severity of this defect is linked with the size of lesion and the mass it contains, skull deformity and leakage of CSF [84].

Etiology of this defect remains elusive but some genetic syndromes have been associated with meningocele, such as HARD (hydrocephalus, agyria, retinal dysplasia),Meckel-Gruber syndrome, trisomy 13 or 18. Maternal factors such as young maternal age, alcohol use during pregnancy, low socioeconomic status, smoking, caffeine use, obesity, high glycemic index or gestational diabetes, have all been linked to the defect [85].

Public health and NTDs

Since NTDs are a common type of congenital birth defect, they are a leading cause of infant mortality and disability [34]. These defects can accumulate in the populace and become an economic burden for a country. Some factors contributing towards NTDs asa public health concern are as follows:

Economic burden

Children with NTDs can experience serious physical, intellectual, and emotional disabilities, which can have an impact on their quality of life and future prospects [86].

These defects can place a significant financial burden on families and society, as children with NTDs often require specialized medical care and support services throughout their lives [87]. A total of 14 cost of illness studies and 10 economic evaluations on prevention of NTDs with folic acid have been reported [88]. The latest such study was conducted in 2010 [89], according to which each enrolee on Medicaid insurance in the USA had to pay about $494/year, while a previous study estimated that cost to be between $51,574-65,177 in the year 2003 [90]. Each year over 400,000 infants are born globally with spina bifida and anencephaly [91]. Studies suggest that 50-70% of cases could be prevented by fortification of food with folic acid, especially during pregnancy [92]. Public health services recommend that all women of childbearing age should consume 0.4mg (400µg) of folic acid daily to reduce the risk of fetus being affected by NTDs [93]. However, folic acid supplementation advised during pregnancy is 4mg (4000µg) [155, 156].

Lack of awareness

Despite the high incidence and serious consequences of NTDs, there is often a lack of awareness and understanding about the severity of condition among the general publicand healthcare providers [94]. This risk factor can also be linked to the overall literacy rate and socio-economic background of the expecting mother.

Lack of proper prenatal care

NTDs are largely preventable through proper prenatal care, including folic acid supplementation and healthy lifestyle choices, making it a public health issue that is both preventable and impactful. The folate and vitamin C levels in red and white bloodcells, respectively, of mothers who gave birth to infants with NTDs were significantly lower than in controls [95]. This is an important and significant indication that proper antenatal nutritional guidance is of utmost importance.

Causes of neural tube defects

The development of NTDs is influenced by gene-environment interactions. Certain genetic abnormalities might enhance a person's susceptibility to NTDs, especiallywhen combined with environmental variables such as nutritionally poor food, exposure to environmental toxins, and certain medical disorders [96]. Understanding the role of gene-environment interactions can help in the development of preventative strategies and minimize the risk of NTDs [97]. It is important to understand the role of gene- environment interfaces in the development of NTDs, as this knowledge can help inform the development of preventative strategies [98]. A recent publication identified various possible causes of NTDs and separated them into genetic and environmental factors [99].

Genetic factors associated with NTDs

Inherited mutations

In neural tube defects (NTDs), certain inherited mutations have been linked to an increased risk of NTDs [100]. One of the most well-known genetic factors is the methylenetetrahydrofolate reductase (*MTHFR*) gene (rs1801133), which plays a crucial role in the metabolism of folic acid. A common genetic variation in the *MTHFR* gene can reduce the body's ability to process folic acid, which is a critical nutrient for neural tube closure [101]. Another genetic factor that has been implicated in NTDs is the *VANGL1* gene. The Vang-like protein 1 (*VANGL1*) gene, which is a planar cell polarity gene, has a role in the regulation of the neural crest cells, which are important for proper neural tube closure. Mutations in *VANGL1* have been identified in individuals with NTDs [102]. Another gene called the bone morphogenetic protein 2 (*BMP2*) is involved in the regulation of neural crest cells and the formation of the nervous system. Mutations in the *BMP2* gene have been related to an increased risk of NTDs [96]. As already mentioned NUAK family kinase 2 (*NUAK2*) located on 1q32.1, has also been implicated in the pathology of

anencephaly. Besides the Hippo pathway (a serine threonine kinase module that phosphorylates its effector protein Yes- associated protein called YAP), has also been linked to the *NUAK2* gene function in the neural plate folding. A mutated *NUAK2* causes the YAP to be retained in the cytoplasm, rather than being involved in the Hippo pathway, thus rendering the cofilin inactive for neural plate folding [57]. Another gene called *SHROOM3* transcribes an actin binding protein, which is a key regulator of apical constriction, and regulates the process by which cells convert their shape from cuboidal to wedge-like [103], overexpression of *SHROOM3* has been linked to altered cell morphology along with apical constriction that leads to altered apical cell-cell alignment [104]. Similarly U2 SnRNP Associated SURP Domain Containing (*U2SURP*) is a gene located in the nucleoplasm and enables RNA binding activity, thus involved in RNA processing [105-107]. It is further established that RBM17, U2SURP and CHERP regulate reciprocal protein stability and together they regulate the specific set of transcripts [108].

Family history

A family history of NTDs is a significant risk factor for the defect. This furthersuggests that there is a definite genetic constituent for the development of NTDs. If someone in a family has a history of NTDs, it increases the likelihood that descendents in the family would also develop NTDs [109, 110]. Women who have had two or more abnormal pregnancies are at a higher risk of recurrence by as much as 10%. The incidence is higher in like-sex twins (assumed to encompass all monozygotic instances)than in unlike-sex pairings, further indicating a genetic component. However, NTDs rarely manifest as several cases within families, thus a rather stochastic pattern is typically observed [111].

Polygenic inheritance

In some cases, NTDs may be attributed to the combined effect of interaction ofmultiple genes, which collectively increase the risk of NTDs. This is known as polygenic inheritance [111]. This kind of inheritance is complex and difficult to study, as it involves the interaction of multiple genes which is further complicated due to being influenced by both hereditary and environmental factors. NTDs can be influenced by multiple genes, each with a small individually contributing effect [112]. Polygenic nature also makes it difficult to identify the genes associated with a specific pathology and any recurring interactions thereof. Further research is needed to develop assays aimed at recognizing the role of polygenic inheritance in the development of NTDs and to identify potential targets for prevention and treatment [113].

Chromosomal abnormalities

Chromosomal abnormalities often refer to structural changes or alterations in an individual's chromosomes. Chromosomal abnormalities can have a wide range of effects, such as increasing the risk of certain diseases or disorders. In neural tube defects (NTDs), certain chromosomal abnormalities have been associated with increased risk of NTDs, for example, chromosomal abnormalities such as trisomy 18 and trisomy 13 [61, 72, 85], which result in an extra copy of these chromosomes. These chromosomal abnormalities can alter the development of the neural tube, leading to NTDs [113-115]. A detailed investigation to trace chromosomal aberrations associated with NTDs was conducted in 2008 by Chen et al., [116] and their findings are listed in **table 3** below.

Table 3: Chromosomal aberrations linked to NTDs

Mutation	Chromosomal aberration	Extent of deletion or duplication	Type of NTDs
Del (3p)	der(3)t(3;11)(p26;q21)mat	3p26->pter	Lumbosacral
		11q21->qter	Meningomyelocele
Dup (3q), del (3p)	rec(3)dup(3)(q21qter)del(3)(p25)	3q21->qter	Spina bifida
		3p25->pter	Sacral dimple
Dup (3q)	der(13)t(3;13)(q21;q34)mat	3q21->qter, 13q34->qter	Lumbar menigomyelocele

	dup(3)(q21qter), del(5)(p15.2)	3q21->qter, 5p15.2->pter	Lumbar menigomyelocele
	dup(3)(q21qter), del(5)(p15.2)	3q21->qter, 5p15.2->pter	posterior encephalocele
Dup (3p), del(3p)	der(3)del(3)(p26)dup(3)(p26p21.3)	3p21.3->p26,	Lumbosacral
		3p26->pter	meningomyelocele, holoprosencephaly
Dup (3p)	der(11)t(3;11)(p21;q25)mat	3p21->pter, 11q25->qter	Lumbosacral spina bifida
Del (3q)	del(3)(q12.2q13.2)	3q12.2->q13.2	Spina bifida, OEIS complex
	del(3)(q27)	3q27->qter	Parietal menigocele

Environmental factors associated with NTDs

Environmental factors refer to non-genetic elements in the environment that can influence the development of a particular condition or trait. Environmental variables can significantly influence the development of neural tube defects (NTDs) [117]. Someof the well-established environmental factors are discussed below.

Maternal health

Besides the direct role of genetic mutations accredited to NTDs, there are also indirect genetics involved. A woman's genetic makeup can influence her risk of developing certain medical conditions, for instance, the genetic propensity for diseases such as diabetes or hypertension can greatly raise the risk for developing NTDs. Gestational hyperglycemia, which increases the incidence of NTDs in children, has been linked to maternal diabetes. Awareness of maternal health and the risk of NTDs requires awareness of these indirect genetic impacts, which will help us in developing better preventative measures and individualised care plans for women at risk. Healthcare professionals can provide targeted therapies and genetic counselling to improve maternal health and lower the risk of NTDs in children by identifying genetic markers linked to NTDs and diseases such as diabetes or hypertension. Continued study in this area will help us comprehend the intricate connection between maternal genetics, polygenic interactions, overall health, and NTDs, ultimately leading to better prognoses for mothers and their offspring [98].

Folate metabolism and Maternal nutrition

Maternal malnutrition, particularly low levels of folate (a B-vitamin) and vitamin B12, have been linked with an increased risk of NTDs. Folate is important for the proper neural tube development in the embryonic phase, as already mentioned in the folate- one carbon metabolism (**figure 1**). Inherited mutations that affect the metabolism of folate can increase the risk of NTDs by reducing the amount of available folate in the developing embryo. Certain genetic mutations, such as those affecting folate metabolism, have been linked to a higher risk of NTDs. These mutations can be passeddown from parent to child and increase the likelihood of NTDs in offspring [118]. Some genetic variants may affect the way the body metabolises folate. If pregnant mothers do not consume sufficient amounts of folate (400µg/day) in their diets, while already carrying a mutated copy of the *MTHFR* gene, may have a significantly higher risk of developing NTDs. A single nucleotide polymorphism (SNP) in the methylenetetrahydrofolate reductase (MTHFR) gene is one particular genetic variation that may have an influence on folate metabolism and the risk of NTDs. Severalvariants of *MTHFR* gene, including C677T and A1298C, have been investigated in connection with folate metabolism and NTDs. The MTHFR enzyme's capacity to convert homocysteine to methionine is impaired by the C677T variation, which also affects the availability of folate for neural tube development. Additionally, the A1298C variation may affect the metabolism of folate and enzyme function. To effectively implement initiatives to avoid NTDs and enhance the health of both mother and the offspring, it is essential to comprehend the link between folate metabolism, maternal nutrition, and genetic variables. The prevalence of NTDs can be decreased, and healthier pregnancies can

be encouraged through good maternal nutrition and offering tailored therapies based on genetic differences vis-à-vis the *MTHFR* gene variants. [113]

Maternal Age

Age of the mother increases the chances of a child developing congenital neural tube abnormalities. Existing research supports the hypothesis that a higher probability of having a child with NTDs exists for women aged 40 or older. Old-age pregnancies are significantly at a higher risk of NTDs than younger ones. This might be attributable toa number of endogenous factors, including modifications in DNA repair pathways, reduced folate metabolism, and changes in egg quality brought on by ageing. It is crucial to remember that even among older maternal age groups, the absolute risk of NTDs is still rather low. This risk is more pronounced in spina bifida than in anencephaly. There is additional evidence that women below the age of 19 are also at an increased risk of bearing a child with spina bifida. It is interesting to note that new research suggests that a young maternal age may potentially raise the incidence of several NTDs. Younger age pregnancies may be impacted by factors including lack of required nutritional awareness, socioeconomic level, dietary inadequacies, and subpar prenatal care. These results emphasise the complicated interplay between maternal age and neural tube abnormalities, underscoring the necessity of thorough prenatal care andtherapies that are age- and group-specific. Healthcare practitioners should give women of all ages the correct advice and encouragement regarding the value of supplemental folate, healthy eating, and early prenatal care. It is feasible to enhance healthier outcomes for mothers and their newborns by addressing these factors and reducing the hazards related to maternal age. [119].

Exposure to toxins

Exposure to certain toxins during pregnancy has been associated with an increased riskof NTDs. Exposure to toxins refers to the presence of harmful substances in the environment that can have a negative impact on human health [5, 120]. Exposure to toxins can come from various sources, including the air breathed or water or food or perhaps absorption of pesticides through skin, in case of farm workers [121].

Infections

Certain infections, such as cytomegalovirus (CMV) and rubella, during pregnancyhave been linked with an increased risk of NTDs [122]. Other infectious linked with increasing thye risk for NTDs include viruses such as herpes simplex-2 (HSV-2), lymphocytic choriomeningitis virus (LCMV], parvovirus B19, rubella, varicella, Venezuelan equine encephalitis virus and Zika virus [123, 124]. Similarly bacterial infections that increase the risk for NTDs include *Treponema pallidum*, *Listeria monocytogenes*, and other parasites such as *Toxoplasma gondii*. There have been some infectious pathogens associated with the risk of pregnancy loss (e.g., *Listeria monocytogenes* and parvovirus B19), while others can cause birth defects (e.g., rubella and Zika viruses) [125, 126]. Several infectious pathogens increase the risk for defectsof the brain and eye, including CMV, LCMV, *Toxoplasma gondii*, and Zika virus. Some infections during pregnancy (e.g., CMV) are associated with auditory loss [127, 128]. Whereas cold and flu viruses, during early pregnancy, could also increase therisk of birth defects [129].

Medications

Use of certain medications, such as anti-convulsants, during pregnancy, have been linked with an occurrence of NTDs [121]. Additionally evidence shows that women who take certain antiseizure medications, such as phenytoin (Dilantin), carbamazepine (Tegretol) and valproic acid (Depakote) or antifolate (such as aminopterin) [120] are at a greater risk of having an infant with spina bifida and anencephaly than women with no exposure to such drugs [130, 131].

Alcohol

Alcohol consumption during pregnancy has not been associated with an increased risk of NTDs. In one cohort study with 73,595 subjects, 6 major congenital malformations were evaluated which included congenital heart defects (CHDs], male genital abnormalities, limb defects, cleft lip and/or cleft palate, severe brain abnormalities, and gastrointestinal obstructions. The investigators reported no significant increase in the risk of brain abnormalities [132]. Whereas, a similar study conducted in 2013 also could not find any significant increase in the risk of NTDs and alcohol consumption [133].

Maternal hyperthermia

Increased body temperature has also been linked to a greater likelihood of neural tube abnormalities (NTDs) in embryos [134]. Maternal hyperthermia was positively linked with the risk of NTDs. Studies have shown that even short-term exposure to hyperthermia, such as fevers or hot tub use, can impact fetal development and increase the risk of NTDs. Illness (associated with fever) during the first month of pregnancy was associated with an increased risk of NTDs [129, 130].

Obesity

According to research, Obesity increases the chance of neural tube abnormalities(NTDs) in the developing fetus. Obese women (BMI > 30) have a higher risk of developing NTD in the embryo rather than women with a normal BMI [131]. The exact mechanism by which obesity increases the risk of NTDs is not fully understood, but it is thought to be linked to the secondary effects of obesity (such as diabetes and hypertension) on the metabolism of the mother and the developing fetus [135]. Obesitycan cause changes in the level of hormones in the mother's body (such as insulin), which could affect the development process of the fetus's brain and spinal cord [136]. Obesity can also increase the risk of other serious health problems for the mother and baby, such as gestational diabetes, pre-eclampsia, and cesarean delivery [97].

Paternal smoking

Paternal smoking has also been linked with an increased risk of NTDs in the fetus [137]. Fathers who smoked at least ten cigarettes a day, before conception increased the risk of NTDs in their offspring. The research also established that this risk was further heightened when both the mother and father smoked before and during conception [138]. The specific mechanism through which smoking raises the risk of NTDs is unknown, however it is thought to be linked to the effect of compounds in tobacco smoke on the developing embryo [137]. It is believed that passive exposure to smoke from the father may have a negative effect on the health of the developing fetus. Paternal smoking may also raise the risk of fetal NTDs through altering the quality of sperm, such as spontaneous DNA mutations in sperm [139]. Nicotine, the narcotic compounds found in tobacco smoke, are known to constrict blood vessels and reduce blood flow to the developing fetus. This reduced blood flow can lead to a lack of oxygen and nutrients, which can be harmful to the developing brain and spinal cord. Carbon monoxide, another hazardous gaseous compound found in tobacco smoke, can also reduce the amount of oxygen available to the developing fetus [140]. Exposure to certain environmental pollutants and toxins such as lead and mercury, can also significantly raise the risk of NTD development [141].

DIAGNOSTIC TECHNIQUES

There are several methods that can be used to diagnose neural tube defects (NTDs) in the developing fetus. Some of the most common methods include the following [142]:

Pre-natal sonographic diagnosis

Ultrasound is a non-invasive technique that creates images of the fetus using high- frequency sound waves. An ultrasound can detect many types of NTDs, includingspina bifida, anencephaly, and encephalocele [143]. This is not meant to be a comprehensive and confirmatory test, and should be used only to assess potential dioagnostic and treatment strategies, because it does not include a comprehensive information

about the existing conditions. The test aims to investgate the position of conus medullaris in closed dysraphisms [144]. A complete list of sonographic diagnostic features was explained by Coleman et al, (2015) [145].

Alpha-fetoprotein (AFP) test

The test is routinely offered between 15th and 20th week of pregnancy. The test is not a confirmation of NTDs because it is advised to detect cancers, diabtes, Down's syndrome, any genetic disorders or NTDs [146]. This test sampled from the mother's blood, evaluates the level of alpha-fetoprotein (AFP), which is a protein produced by the fetus. Increased AFP levels (higher than the cutoff value) may suggest the presenceof a neurological disorder such as anencephaly or spina bifida. Open NTD raises the level of AFP in both amniotic fluid and maternal blood [147]. The level of AFP at certain gestation age is determined against standard AFP levels to determine if a NTD is indicative. It increases from the non-pregnancy level of 0.2 ng/mL to about 250ng/mL at 32 weeks of getstaion. If NTD exists, the AFP (secreted by the fetal liver) leaks directly into the amniotic fluid, therby giving elevated readings. An AFP multiple of median (MoM) of >2.5 is considered as indicative of NTDs [148].

Amniocentesis

A little amount of amniotic fluid is extracted from the chorionic layers of the developing embryo using a needle during this procedure. Chromosomal abnormalities and neural tube anomalies can be detected through the sampled amniotic fluid [149]. This is an invasive procedure, thus requires special attention and therefore performed under clinical supervision.

Chorionic villus sampling (CVS)

This is a procedure in which a small sample of the placenta is removed from the uterus using a needle. The placenta can be assessed for chromosomal abnormalities and neural tube defects [150]. Chorionic villus sampling is performed to biopsy placental tissue between 10-14 weeks of getstaion for prenatal gentic testing. The advatange of CVS over amniocentesis is that the results are available earlier in pregnancy, making it a safer option for pregnancy termination, if required [151].

Magnetic Resonance Imaging (MRI)

It is a non-invasive imaging technique that uses a magnetic field and radio waves to provide comprehensive images of internal organs such as the brain and spine, allowing for the detection of NTDs such as encephalocele, spina bifida, and anencephaly [152]. In a prospective study of 56 suspected fetuses with NTD, the prenatal diagnosis of spina bifida was 71.4% with ultrasound but only 39.2% with MRI. This specificity is a statistically significant difference as it shows that MRI has a clear advantage over prenatal ultrasound diagnosis. Since MRI provides a very good soft tissue resolution, itis often used as an effective test of detecting several CNS malformations [153]. Since genetic confirmatory tests are expensive and take a long time, therefore clinicians and radiologists are continually trying to define and fine-tune the fetal and neonatal imaging techniques.

Preventive and therapeutic strategies

Preconception folic acid supplementation

Taking a regular folic acid (a B vitamin) supplement prior to conception and during the first trimester of pregnancy can significantly lower the incidence of NTDs [154]. Most public health services and American Academy of Family Physicians (AAFP) as well as American Academy of Neurology (AAN) all agree on a daily supplement of 0.43 to 0.8 mg (400-800µg) of folic acid intake for women planning a pregnancy [155, 156]. However, according to the American Academy of Pediatrics, this dietary intake limit is 4mg (4000µg) for hish-risk populations, such as, women with a previous case history of NTD affected pregnancy, or having a close relative with an NTD or diabetes [157].

Prenatal screening
Prenatal screening tests, such as the alpha-fetoprotein (AFP) test, can detect NTDs in the developing fetus [146-148]. If an NTD is detected, further diagnostic tests such as ultrasound, amniocentesis, chorionic villus sampling (CVS) or MRI can be done to confirm the diagnosis [149-153, 158].

Surgery
Surgery is the most common treatment for NTDs [159]. Surgery is typically performedto repair the defect and prevent further damage to the developing brain and spinal cord during pregnancy [160].

Shunt
Hydrocephalus is common in spina bifida, which is caused by an accumulation of CSF in the brain. A shunt, which is a tube to drain the excess fluid, is often placed during surgery to reduce the pressure on the brain. This shunt is usually placed in the peritoneal region and thus referred to as the ventriculoperitoneal shunt. A criterion for shunting, as a remdial strategy, has been provided by Sinha et al, (2012). The timing ofrepair of NTDs remains controversial, but immediate repair is generally recommended. Shunting at 2-3 weeks of gestation with selection crietria of lateral ventricle >15mm and V:H ratio>0.4 was advised [161].

Physical therapy
Physical therapy is often used to help individuals with NTDs improve their mobility and strength, and to prevent complications such as contractures and scoliosis [160]. Results os several studies hoswed that patients of spina bifida had an inactive lifestyle, lower aerobic capacity, decreased level of dailyphysical activity, higher incidence of obesity, and lower than expected health-related quality of life, compared with the reference groups. It is therefore highly recommended to incorporate therapeutic interventions such as physical activity that help with reduced pain, increased biomechanical efficiency during wheelchair propulsion, and improved gait and balance[162].

Occupational therapy
Occupational therapy for surviving affected offsprings is often used to help individuals learn to perform activities that facilitate daily tasks and chores by developing fine motor skills [163]. Mobility guidelines for occupational therapy of patients with spina bifida have been discussed in detail by Wilson et al, (2020) [164]. Occupational therapy may sometimes require neuropsychological care and therapy, guidelines for which are also available [165].

Special education
Special education services may be needed for children with NTDs to ensure that they receive an appropriate education [166].

Family support
Family support is important for individuals with NTDs and their families to help them cope with the emotional and social challenges associated with the condition. [167]

Food fortification initiative (FFI)
Fortification is an important strategy for preventing neural tube defects (NTDs). Periconceptional folate supplementation boosts maternal folate status and prevents a substantial number of neural tube defect-associated births [168-171]. Folate supplementation is uncommon, particularly during unexpected pregnancies. For this reason, 70 countries worldwide have introduced compulsory folic acid supplementation for women of childbearing age [172, 173]. Several countries, including the United States, Canada, Costa Rica, Chile, and South Africa, have reported successful folic acid fortification programs that have reduced NTD prevalenceby 31 to 50%, depending on folic acid dosage and intake, and baseline

prevalence [174-179]. The FFI monitors the levels of food fortification in almost every country. About 186 countries out of 195, had data on both the occurrence of NTDs and the levelof folic acid fortification. The United States and Costa Rica are two nations that fortify their wheat, maize, and rice crops. There are fourteen countries that fortify wheat and maize, but not rice, whereas there are six countries that fortify wheat and rice, but not maize [180].

Almost all countries that fortify maize also fortify wheat, with the exception of Rwanda, and almost all countries that fortify rice also fortify wheat, with the exceptionof Bangladesh [181]. On the basis of fifty-nine countries achieving the criterion for required folic acid fortification of at least 1.0 ppm, it is projected that 50,270 out of a possible 288,500 cases of spina bifida and anencephaly were averted. In several nations, food fortification programs were implemented to increase folate consumption. This technique has increased blood folate levels and has been linked to a decrease in NTD incidence [9, 181]. A greater reduction in NTD prevalence was observed in females after folic acid fortification, particularly anencephaly and cervico-thoracic spina bifida, supporting the notion that NTDs may be etiologically heterogeneous [182].Fortification refers to the process of adding specific vitamins and minerals to food products in order to improve their nutritional value. One of the key nutrients that is added to food through fortification is folic acid, which is a B-vitamin that plays a critical role in the development of the neural tube. However, fortification alone is not enough to prevent all NTDs [183]. Other preventative measures such as dietary supplements, genetic counseling and prenatal care should also be considered . Additionally, fortification is an efficient and cost-effective way to provide folic acid to a large number of people [184].

Clinical trials

Multiple clinical trials and observational research have demonstrated that periconceptional folic acid consumption lowers the incidence of NTD-affected pregnancies [169,170, 185], according to a clinical research study (**NCT0158405)**, L- 5-MTHF may be a viable alternative to folic acid for usage in dietary supplements due to its efficacy in increasing folate status and decreasing plasma total homocysteine concentrations [186].

Conclusion

In conclusion, Neural Tube Defects (NTDs) are a serious public health issue that can cause lifelong physical and neurological impairments. While fortification of staple foods with folic acid has proven to be an effective preventive measure, it is importantto continue exploring new strategies for the prevention, diagnosis and treatment of NTDs. This may include developing more targeted fortification programs for specific at-risk populations, expanding access to quality healthcare, and investing in innovative research to better understand the underlying genetic causes of NTDs. A multi-faceted approach involving education, proper prenatal care, and access to appropriate medical treatment is crucial to ensure the health of mothers and their offsprings. In order to fully understand the complex interplay between genetic, environmental, and lifestyle factors that contribute to NTDs, further research is required. A comprehensive approach that combines fortification, education, and access to quality healthcare is necessary to effectively prevent and treat NTDs, and to improve the health outcomes ofmothers and their children.

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Data Availability Statement:

For most data included in this article, we referred to the online, publicly available reports on neural tube defects, its classification, prevalence and diagnosis. We also consulted peer-reviewed articles (a list is provided under the references section) that provide links and insights into the phenomena we discussed.

Conflicts of Interest:
The authors report no competing interest to declare.

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