

Classification, clinical features, and genetics of neural tube defects

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ABSTRACT

تشكل عيوب الأنبوب العصبي (NTDs) عبئاً صحياً كبيراً (0.5-2/1000 حالة حمل في جميع أنحاء العالم) ويظل السبب قابلاً للوقاية في كلا من ولادة المواليد المتوفين، ووفيات حديثي الولادة والرضع، والإعاقات الشديدة على مدى الحياة. تنتج التشوهات من فشل الطيات العصبية لتلتحم في خط الوسط ويتكون الأنبوب العصبي بين الأسبوع الثالث والرابع من التطور الجنيني. تناقش هذه المراجعة تصنيفاتها، ومظاهرها السريرية، وعلم الوراثة. أكثر عيوب الأنبوب العصبي متفرقة وتشترك كلا من العوامل الوراثية والبيئية في حدوثها. اقترح أن زواج الأقارب يساهم في ارتفاع حالات الإصابة بعيوب الأنبوب العصبي في عدة دول بما في ذلك المملكة العربية السعودية. ترتبط المتلازمات في الغالب بالشذوذ الصبغي وتمثل <10% من جميع عيوب الأنبوب العصبي وقد تم توثيق نسبة عالية بلغت 20% في المملكة العربية السعودية. كما أن الاستعداد الوراثي يشكل عامل خطر مع إشارة قوية من الجينات التي تنظم استقلاب الفولات للكربون الأولي ومستوى قطبية الخلية.

Neural tube defects (NTDs) constitute a major health burden (0.5-2/1000 pregnancies worldwide), and remain a preventable cause of still birth, neonatal, and infant death, or significant lifelong handicaps. The malformations result from failure of the neural folds to fuse in the midline, and form the neural tube between the third and the fourth week of embryonic development. This review article discusses their classification, clinical features, and genetics. Most NTDs are sporadic and both genetic, and non-genetic environmental factors are involved in its etiology. Consanguinity was suggested to contribute to the high incidence of NTDs in several countries, including Saudi Arabia. Syndromes, often associated with chromosomal anomalies, account for <10% of all NTDs; but a higher proportion (20%) has been documented in Saudi Arabia. Genetic predisposition constitutes the major underlying risk factor, with a strong implication of genes that regulate folate one-carbon metabolism and planar cell polarity.

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Neural tube defects (NTDs) constitute one of the most common malformations of human structure with a major public health burden whose prevalence has fallen over recent decades in high-income countries.¹⁻³ They occur very early in pregnancy between 21 and 28 days after conception, and result from failure of the neural folds to fuse in the midline and form the neural tube.^{4,5} This leads to secondary abnormal development of the mesoderm responsible for forming the skeletal and muscular structures that cover the underlying neural structures. Affecting 0.5-2 per 1000 pregnancies worldwide, they constitute a major cause of still birth, neonatal, and infant death, or significant lifelong handicaps.^{6,7} This review article discusses their classification, clinical features, and genetics.

Terminology, classification, and phenotypes. The term dysraphism indicates persistent continuity between the posterior neural ectoderm and cutaneous

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ectoderm. Cranial dysraphism (failure of cranial neural tube closure) includes anencephaly and encephaloceles, whereas spinal dysraphism (due to failure of caudal neuropore closure) designates spina bifida cystica and occulta. Neural tube defects can be ventral, or dorsal midline defects. They can also be open (exposed to the environment through a congenital skin defect), or closed (covered by skin). A rare form of NTD is craniorachischisis, which results from failure of the neural tube closure over the entire body axis.

Cranial dysraphism. This includes anencephaly and several types of midline skull defects. Anencephaly results from failure of the cephalic folds to fuse into a neural tube.⁸ Secondary absence of the mesodermal tissue dorsal to the neural elements leads to failure of bony skull development (Figure 1A). The brainstem, cerebellum, and spinal cord are present, and part of the diencephalon may be preserved. The condition is lethal within a few hours to weeks, and is easily diagnosed antenatally.

The midline skull defects are classified under the term cranium bifida, and the most benign form of cranium bifidum occultum is the persistent wide fontanelle, or persistent parietal foramina, which often close over time. A more serious type of cranium

bifidum is encephalocele, which results from failure of the anterior neuropore to close during days 26-28 of gestation. They are 3-16 times less common than spina bifida cystica.^{9,10} In Western countries, 85% of encephaloceles are found on the dorsal surface of the skull, whereas in Asia (for example, the Philippines and other Pacific Rim countries) anterior encephaloceles are more common (Figures 1B, 1C, & 1D). Posterior encephaloceles (Figure 1E) may contain infratentorial, or supratentorial brain structures or both,^{10,11} and have poor prognosis. The overall prognosis of anterior encephaloceles is considerably better compared with the posterior anomalies.¹²

Encephaloceles are uncommonly found in defined syndromes, the most frequent of these is Meckel-Gruber syndrome (MKS, OMIM 249000).¹³⁻¹⁶ This syndrome, also known as Gruber syndrome or dysencephalia splanchnocystica, is an autosomal recessive ciliary dysfunction disorder characterized by an occipital encephalocele, and is associated with holoprosencephaly, polydactyly, polycystic kidneys, micrognathia, and cardiac anomalies (Figure 2A). Other associated malformations include microcephaly with a sloping forehead, cerebral and cerebellar hypoplasia, anencephaly, and hydrocephaly, with or without Chiari

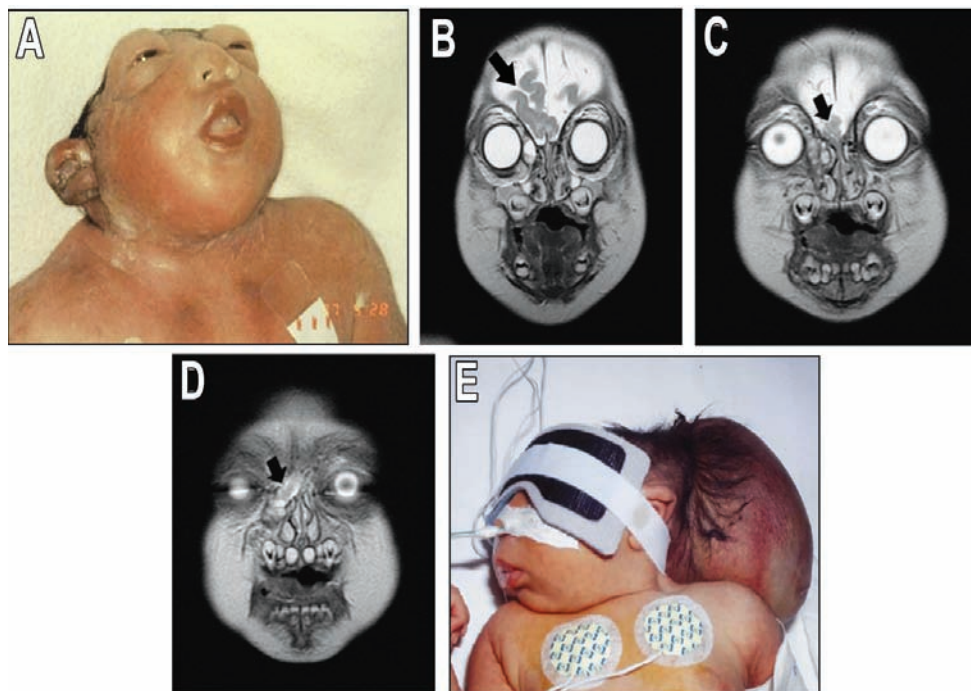


Figure 1 - Images showing cranial neural tube defects: A) a newborn with anencephaly. B, C & D) Anterior encephalocele. Sequential coronal MRI scan showing brain herniation through the right nasal bone (arrows in C & D); and E) large posterior encephalocele.

malformation.^{17,18} The worldwide incidence varies from one in 13,250 to one in 140,000 live births, but is high in the Finnish population (one in 9000).¹⁹ The incidence is also high among Belgians and Bedouins in Kuwait (1 in 3,500).²⁰ The highest incidence of one per 1,300 live births was reported in the Gujarati community, originating from the Gujarat State in Western India.²¹ A relatively high incidence of 1:17,134 was reported in Saudi Arabia, and was attributed to the high rate of consanguinity.¹⁶ At least 10 genes have been found to be responsible for MKS,²²⁻²⁵ including a novel pathogenic mutation: c.1506_2A>G in TCTN2 (NM_024809.3) in a Saudi patient.^{24,25}

Another malformation associated with encephalocele is Joubert syndrome, which is also an autosomal recessive ciliary dysfunction disorder.^{22,23,26-28} It is characterized by hypoplasia of the cerebellar vermis with the characteristic brainstem malformation and neuroradiologic “molar tooth sign” (Figures 2B, 2C & 2D).²⁹ Joubert syndrome has an incidence of one in 100,000 births, and can be

associated with posterior encephalocele, Dandy-Walker malformation, hypoplasia of the corpus callosum, renal polycystic disease, hepatic disease, polydactyly, and retinitis pigmentosa.^{27,30} It is genetically heterogeneous with more than 20 genes identified to date in several studies including a large comprehensive molecular series from Saudi Arabia.^{30,31}

Encephaloceles are frequently associated with other birth defects including cleft palate, microphthalmia, cerebellar defects, agenesis of the corpus callosum, and holoprosencephaly (Figures 2E & 2F).³²

Spinal dysraphisms. Spinal dysraphisms constitute a heterogeneous group of congenital disorders of the spine and spinal cord due to aberrant formation of the midline mesenchymal, bony, and neural structures. They are thought to affect 300,000 persons worldwide, are usually diagnosed at birth or in early infancy, but may sometimes be discovered in older children and adults.^{32,33} They originate from abnormalities occurring during one of 3 embryonic periods. The first of these is

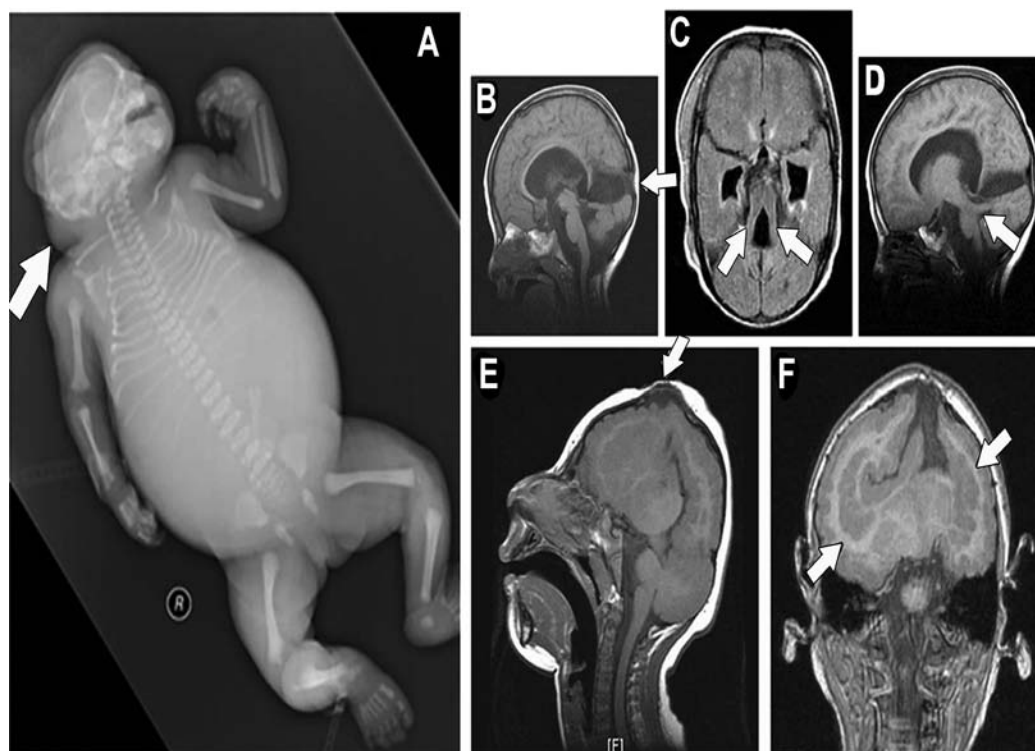


Figure 2 - Images showing: A) posterior encephalocele (arrow) seen in an x-ray carried out on a newborn who had Meckel-Gruber syndrome. The abdomen is distended due to associated polycystic kidneys. Polydactyly of the right foot is also shown; B, C, & D) MRI features of a child who had Joubert syndrome associated with posterior encephalocele. Note the osseous defect of the cranium (arrow, B); C) axial image at the level of midbrain shows the classic “molar tooth sign” with the roots of the tooth formed by the thick and horizontally oriented superior cerebellar peduncles (arrows); D) parasagittal image demonstrating a thick and horizontally oriented superior cerebellar peduncle (arrow); E & F) holoprosencephaly; E) sagittal MRI image showing an associated encephalocele (arrow); and F) coronal image revealed fusion of the cerebral hemispheres, associated with band heterotopias (arrows).

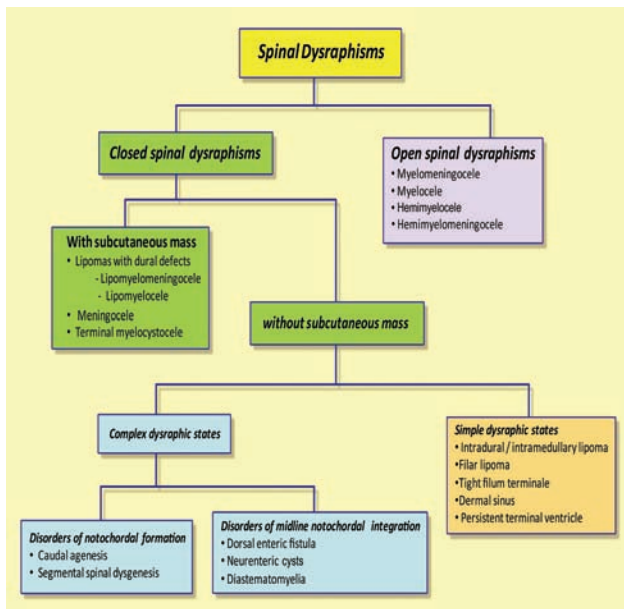


Figure 3 - Classification of spinal dysraphisms.

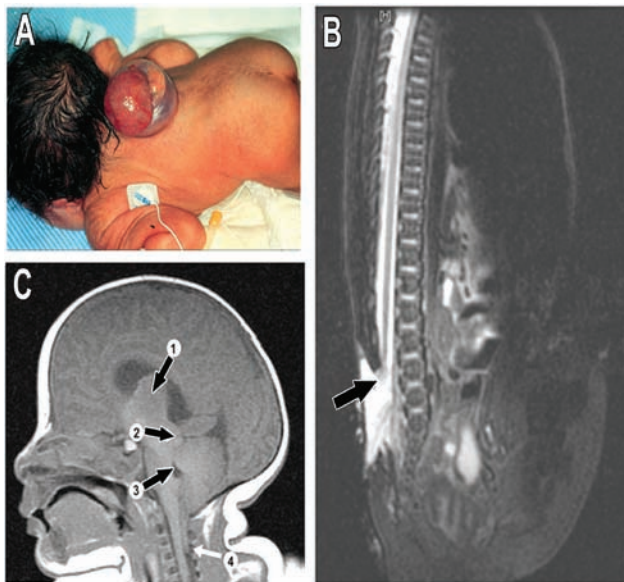


Figure 4 - Images showing: A) newborn with thoracic myelomeningocele. The diaphanous sac is filled with CSF and contains fragile vessels in its membrane. A placode-containing remnants of the nervous system can be seen in the lower half of the lesion; B) a one-day-old neonate with myelomeningocele at the lumbar region. A T2-weighted MRI image with fat saturation showing low-lying spinal cord tethered to the upper end of spina bifida (arrow); C) sagittal brain MRI image shows features of Chiari II malformation. There is small-sized posterior fossa, downward herniation of the cerebellar tonsils, through the foramen magnum (4), deformed shape of the fourth ventricle (3), tectal beaking (2); and prominent massa intermedia (1).

gastrulation (at weeks 2-3), which involves the function of the intervening mesoderm in the initially bilaminar embryonic disk. The second is primary neurulation (at weeks 3-4) during which the neural ectoderm bends, and folds along the midline to form the neural tube. The third is secondary neurulation (during weeks 5-6) when an additional part of the neural tube is produced caudal to the posterior neuropore resulting in the formation of the tip of the conus medullaris and the filum terminale.

Open spinal dysraphisms include myelomeningocele, myelocele, hemi myelocele, and hemi myelomeningocele (Figure 3). In each of these, the nervous structures are exposed without skin covering. Myelomeningocele and myelocele constitute approximately 95% of overt spinal dysraphism, and originate from defective closure of the primary neural tube, with persistence of a segment of incompletely fused plaque of neural tissue, referred to as the neural placode.³⁴ They are basically identical apart from the fact that myelomeningocele is bulging, whereas myelocele is flat (Figure 4A). Lumbar or thoracolumbar lesions include more than half of the cases of myeloceles, lumbosacral lesion occurs in over 25%, whereas cervical and thoracic locations together account for approximately 11% of cases.³⁵

At birth, the appearance of myelomeningocele is that of a sac-like structure covered by a thin membrane that is often ruptured, with cerebrospinal fluid (CSF) leak (Figures 4A & 4B). The arachnoid surrounding skin is often angiomatic. The spinal roots pass forward into the sac. The CNS anomalies associated with myelomeningocele include Chiari II malformation and hydrocephalus in 80-90% of cases.^{36,37} Hydrocephalus may already be present at birth, but usually appears within 2 to 3 days after surgical myelomeningocele repair.³³ Chiari II malformation is a congenital hindbrain anomaly characterized by a small posterior fossa associated with downward displacement of the cerebellar vermis, fourth ventricle, and brain stem below the foramen magnum (Figure 4C).^{38,39} The pathophysiology of Chiari II malformation was highlighted by McLone and Knepper⁴⁰ who attributed its causation due to CSF leak from the ventricles through the central canal into the amniotic fluid. This causes chronic CSF hypotension within the developing neural tube and failure of the ventricular system to increase in size, leading to lack of induction of the perineural mesenchyme of the posterior cranial fossa. Both the cerebellum and brain stem become destined to develop within a smaller than normal posterior fossa leading to both upward and downward herniation through the

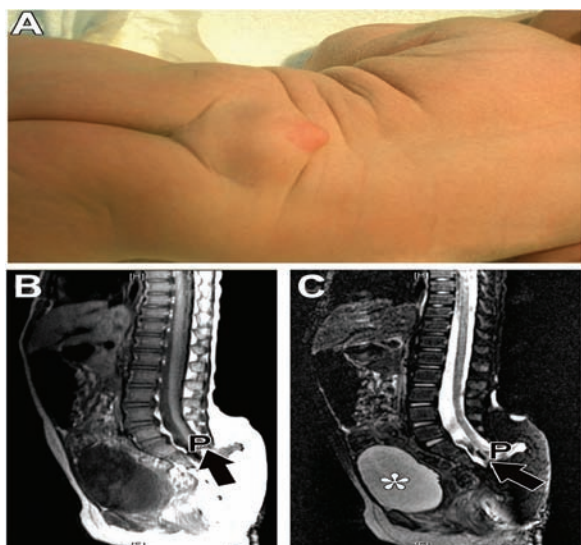


Figure 5 - An image showing lipomyelomeningocele: A) a newborn with subcutaneous mass above the gluteal crease; B) sagittal T1-weighted MRI image (taken at the age of 26 months) shows large subcutaneous lipoma with fatty tissue extending through a wide posterior spina bifida into the spinal canal (arrow) to connect with the placode (P); C) sagittal T2-weighted MRI image (with fat saturation) showing the lipoma attached (arrow) to the placode (P). Note the distended urinary bladder (asterisk) with irregularity of the posterior wall suggesting the presence of neurogenic bladder.

tentorial groove and the foramen magnum.⁴¹ Also, the neuroblasts do not migrate outward from the ventricles into the cortex at a normal rate. Other CNS anomalies associated with myelomeningocele include cerebral ventricle abnormalities in >90%, syringomyelia (88%), brainstem malformations (75%), cerebral heterotopias (40%), polymicrogyria (15-30%), and agenesis of the corpus callosum (12%).⁴²

The third category of open spinal dysraphism is hemi myelocele, which results from failure of one hemicord to neurulate. When there is meningeal expansion, the malformation is called hemi myelomeningocele.

Closed spinal dysraphisms associated with subcutaneous mass include lipomas with dural defect and meningocele (Figure 3). The former consists of lipomyelomeningocele and lipomyelocele, which are characterized by a subcutaneous fatty mass located above the gluteal crease.⁴¹ The lipomatous mass herniates through the bony defect and attaches to the spinal cord, tethering the cord, and often the associated nerve roots (Figure 5). Meningocele results from herniation of the meninges through the bony defect (spina bifida) without an associated herniation of the spinal cord or nerve roots into the dural sac. Terminal myelocystocele

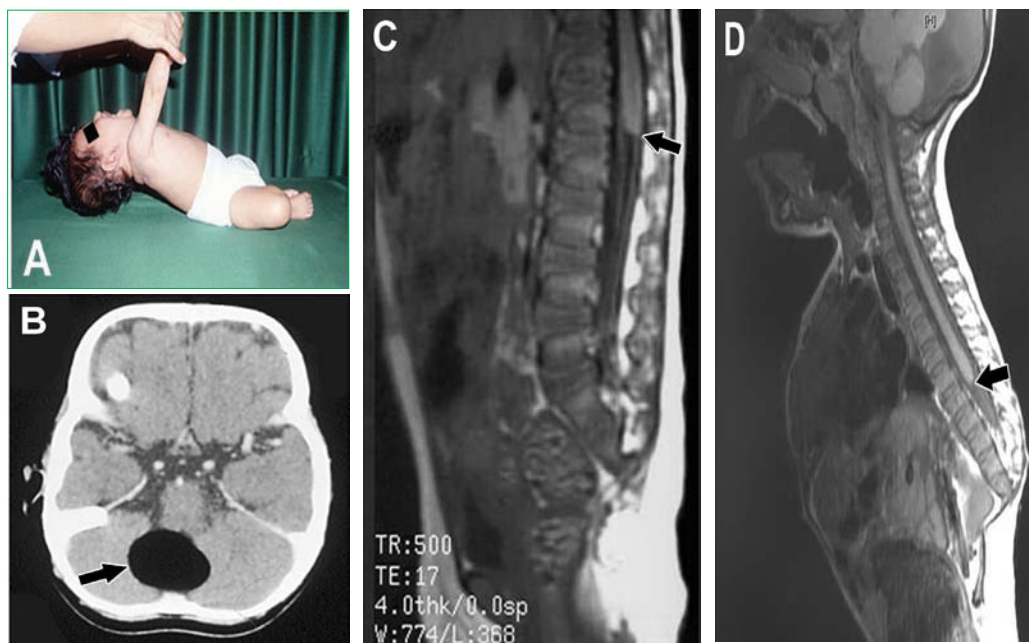


Figure 6 - Images showing: A & B) thoracic and cervicocephalic intramedullary lipoma: A) the affected 9-month-old presented as floppy infant syndrome. Spinal CT scans showed an expanded cervicothoracic spinal cord filled by a large low-density mass (image not shown); B) cranial CT revealed extension of the low-density mass (lipoma) in the posterior fossa (arrow); C & D) Caudal agenesis. C) sagittal T1-weighted (T1W) MRI image showing the less severe form, with blunted appearance of the distal cord (arrow) and dysplastic sacrum; and D) sagittal T1W MRI revealing severe caudal agenesis. There is also blunted appearance of the distal spinal cord (arrow).

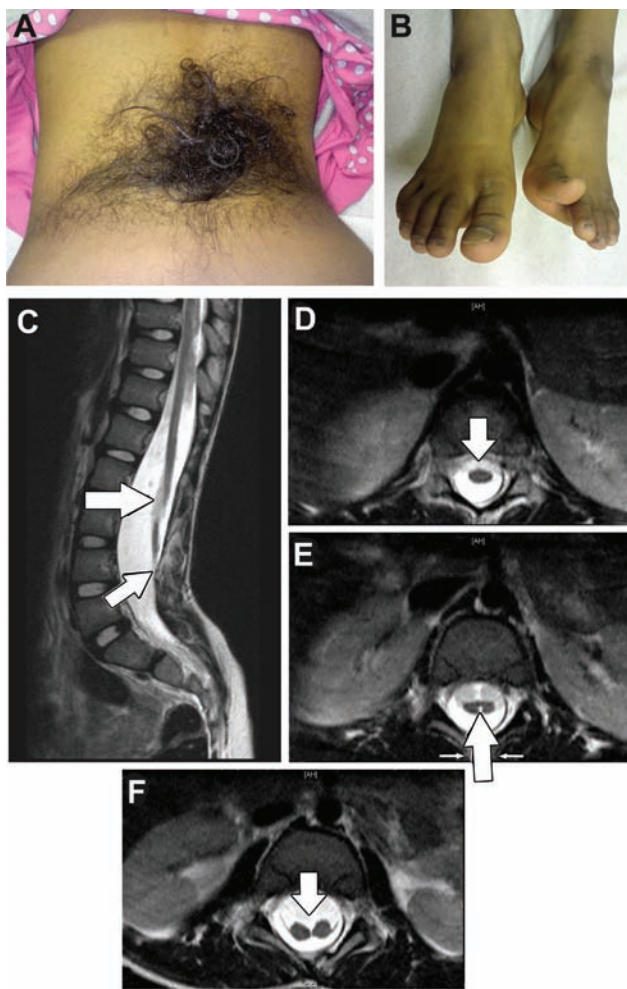


Figure 7 - Images showing: A) a 9-year-old girl presenting with a remarkable hair tuft at the back above the gluteal fold; B) the left foot was smaller, had equinus posture, and showed spontaneously upgoing big toe; C) sagittal T2-weighted MRI showed features of diastematomyelia with thinning of the spinal cord (large arrow) resulting from the intervening subarachnoid space between the 2 hemicords. There is also remarkable widening of the spinal canal with tethering of the cord (small arrow). D-F) serial axial T-2 weighted images revealed that the spinal cord started to divide at the level of L2 (E) into 2 halves (F).

constitutes the third entity of closed spinal dysraphisms with subcutaneous mass, and is characterized by a large terminal cystic dilatation of the spinal cord resulting from hydromyelia.

Closed spinal dysraphisms without subcutaneous mass encompass simple and complex dysraphic states (Figure 3). The subset of simple dysraphic states includes intradural and intramedullary lipomas, which are similar embryologically and pathologically to lipomas with dural defects. Intradural lipomas are commonly found at

the lumbosacral level, and usually present with tethered cord syndrome. On the other hand, cervicocephalic lipomas⁴³ generally produce insidious signs of spinal cord compression (Figures 6A & 6B). A fibrolipomatous thickening of the filum terminale due to an anomaly of the secondary neurulation constitutes filar lipoma. A short hypertrophic filum terminale, which produces tethering and impaired ascent of the conus medullaris produces the entity of tight filum terminale, which is usually associated with other malformations including diastematomyelia and dermal sinuses.^{33,44,45} A dermal sinus is formed by an epithelium-lined fistula that connects the skin surface to the CNS and its meningeal coating. Finally, a small ependymal-lined cavity within the conus medullaris constitutes a persistent terminal ventricle, which results from incomplete regression of the terminal ventricle during secondary neurulation.

Complex dysraphic states are disorders characterized by aberrant formation or integration of the notochord that constitutes the foundation of the axial skeleton and is the inductor of the neural ectoderm. These disorders of notochordal formation include caudal agenesis, which ranges from agenesis of the coccyx to absence of the sacral, lumbar, and lower thoracic vertebrae (Figures 6C & 6D).⁴⁶ They can be syndromic such as VACTERL syndrome (vertebral abnormality, anal imperforation, cardiac malformation, tracheoesophageal fistula, renal abnormalities, limb deformities, OMIM no. 192350) and Currarino syndrome (CS), which is a peculiar form of caudal regression syndrome (also known as autosomal dominant sacral agenesis [OMIM no. 176450]) characterized by partial absence of the sacrum with intact first sacral vertebra, a pre-sacral mass, and anorectal anomalies (Currarino triad).^{47,48} Nevertheless, approximately 15-25% of mothers of children with caudal dysgenesis have insulin-dependent diabetes mellitus.⁴⁸ Caudal agenesis is either high and abrupt, or low with less severe vertebral dysgenesis and up to S4 present as the last vertebra. The latter form typically presents with tethered cord syndrome. On the other hand, segmental spinal dysgenesis is characterized by segmental agenesis or dysgenesis of the lumbar or thoracolumbar spine, associated with segmental abnormality of the corresponding spinal cord and nerve roots.⁴⁹

Disorders of midline notochordal integration include dorsal enteric fistula, which is formed by an abnormal canal connecting the skin surface with the bowel (neurenteric canal) across the intervening space between a duplicated spine.³⁹ Localised forms of dorsal enteric fistulae constitute neuroenteric cysts, which are lined by

mucus-secreting cells resembling the alimentary tract.³⁹ Conversely, diastematomyelia refers to the separation of the spinal cord in 2 usually asymmetric halves, and a hairy tuft at the child's back above the gluteal fold is a reliable clinical marker of this condition (Figure 7).⁴⁵ Patients with diastematomyelia usually present with scoliosis and the neurological consequences of tethered cord syndrome.

Genetics and consanguinity. Most NTDs are sporadic, and both genetic and non-genetic environmental factors are involved in its etiology. However, recurrence risk for a second affected child is increased by 3-5 folds for couples with one affected infant, and by 10 fold for siblings of affected individuals, as compared with the general population.^{50,51} This recurrence fits a multifactorial polygenic or oligogenic pattern, rather than single dominant or recessive gene mode of inheritance; with reduced penetrance.⁵² Syndromes, often associated with chromosomal anomalies account for <10% of all NTDs cases.⁵³⁻⁵⁶ Nevertheless, a higher proportion (20%) has been documented in Saudi Arabia, reflecting the high prevalence of autosomal recessive diseases.¹⁶ These include, among others, Waardenburg syndrome, amniotic band sequence, Currarino syndrome, Joubert syndrome, and MKS.^{16,22,57,58} Chromosomal abnormalities associated with NTDs include trisomy 13, trisomy 18, triploidy, as well as partial aneuploidy.^{55,56} The paucity of large families with multiple affected members has hampered the strategy of genetic analysis based on positional cloning. Nevertheless, using smaller multiple families, genome-wide association studies (GWAS) implicated candidate NTDs loci in chromosomes 2, 7, and 10.⁵⁹⁻⁶¹ The recent genomic revolution will indeed give the opportunity to conduct large-scale NTDs-focused genomic discovery projects utilizing the power of GWAS and exome sequencing.^{1,2}

The reduction of 60-70% of NTDs following periconceptional folic acid administration initiated a series of clinical studies that showed an increased risk of NTDs in association with reduced maternal folate state and elevated homocysteine.^{62,63} This suggested that genes correlated with folate and methionine metabolism can be involved in the etiology of NTDs.⁶² Genes encoding 5,10 methylenetetrahydrofolate reductase (MTHFR), methionine synthase reductase (MTRR), cystathionine beta-synthase, and folate receptor genes might play a critical role in the formation of the neural tube.⁶⁴ However, most research centered on MTHFR following the observation of Frosst and associates⁶⁵ that persons with a thermolabile form of MTHFR have reduced

enzyme activity and increased plasma homocysteine levels, which can be lowered by supplemental folic acid. These individuals have a 677C>T polymorphism in the MTHFR gene. A year later, Ou et al⁶⁶ demonstrated that 677C>T homozygosity was associated with a 7.2-fold increased risk of NTD ($p=0.001$). To determine the contribution of polymorphic variation in genes involved in the folate-dependent homocysteine pathway, Relton et al⁶⁷ conducted a case-control association study in families affected by NTDs. Both gene-gene interaction and independent genetic effects were found in relation to NTDs risk. Meta-analysis studies^{68,69} strongly implicate the MTHFR 677TT genotype as a risk factor for NTDs in mothers (50-70% increase) and fetuses (80-90% increase). Maternal-fetal interaction was also observed when offspring carried the MTHFR 677C>T variant and mothers carried the MTRR 66A>G variant. The distribution of the 677C>T allele (T allele) of the MTHFR gene showed marked ethnic and geographic variation.⁷⁰ The homozygous TT genotype was particularly common in Mexico (32%), Southern Italy (26%), and Northern China (20%).⁷⁰ The TT genotype was low among newborns of African ancestry, intermediate among those of European origin, and high among newborns of American Hispanic ancestry.⁷⁰ The relative frequency of the TT genotype had geographical gradients in Europe (north to south increase) and China (north to south decrease).⁷⁰ On the other hand, a variant of MTRR gene (c.66A > G) is considered to be a risk factor, and a meta-analysis study implicates the maternal MTRR 66GG genotype as a risk factor for developing NTDs.^{71,72} Apart from MTHFR, very few other consistent findings have resulted from the candidate gene approach related to folate metabolism.⁷³ Zhang et al⁷⁴ surveyed the literature (1996-2011) and investigated the effects of 5 genetic variants pertaining to folate metabolism from 47 study populations. In this study,⁷⁴ meta-analysis strongly suggested a significant association of the variant MTHFR C677T and a suggestive association of reduced folate carrier (RFC-1 A80G) with increased risk of NTDs. Other variants involved in the folate pathway did not demonstrate any evidence for a significant marginal association on susceptibility to NTDs.

Liu et al⁷⁵ explored the interactions between single nucleotide polymorphisms (SNPs) in folate metabolism pathway genes and environmental risk factors to the etiology of NTDs in 602 Chinese families. The genotype MTHFR 677C>T was significantly associated with NTDs with synergistic effects when there was no folate supplementation and also in the presence

of gestational diabetes mellitus (GDM). On the other hand, 5-Methyltetrahydrofolate-homocysteine methyltransferase (MTHM) 501A>G genotype was significantly associated with NTDs in case of GDM, and betaine-homocysteine methyltransferase (BHMT) 716G>A in case of no folate supplementation. The 2 genotypes alone did not significantly associate with NTDs (both $p>0.05$).

Studies on the human homologue of mouse NTDs genes have contributed only limited positive findings, although recently, specific signaling pathways that are essential for neural tube closure could be identified.^{73,76} Nevertheless, the more recent advances in animal models have significantly contributed to unveil the interaction between genes and environmental factors in human NTDs.^{1,2} Recently, the possible role of the planar cell polarity (PCP) signaling pathway (which governs a wide array of polarized cell behaviors) in human NTDs was highlighted following the discovery that genes in the pathway underlie severe NTDs in several mouse mutants.^{1,2} This was followed by identifying mutations in several PCP genes in patients with NTDs.⁷⁷⁻⁷⁹

Familial cases and role of consanguinity.

Intrafamilial unions collectively account for 20 to >50% of all marriages in most communities of North Africa, the Middle East, and West Asia.⁸⁰ Families in which multiple members were affected with a broad spectrum of NTDs, suggesting the possibility of a common genetic etiology have been reported.⁸¹ An unusually high incidence (3.7 - 6.96/1000) of NTDs was observed among Egyptians, and has been attributed to the high coefficient of inbreeding.⁸² Nine percent of NTDs cases have a family history of a close relative with a similar condition, 16% had other associated abnormalities as part of a malformation pattern, or an identifiable syndrome. Most of the components of these syndromes were also present in other family members. Consanguinity was found to be remarkably high (69%) among 42 Palestinian Arab families with open NTDs.⁸³ This was significantly higher than the consanguinity rate of 44.3% observed in the general population. In Oman⁸⁴ much higher consanguinity rates were noted in families with NTDs and congenital hydrocephalus than in the general population, whereas in Algeria,⁸⁵ Iraq,⁸⁶ and Saudi Arabia,^{16,87} similar high prevalence of consanguinity was suggested to contribute to the high incidence of NTDs.

In conclusion, most NTDs are sporadic, and both genetic and non-genetic environmental factors are involved in its etiology. Consanguinity was suggested to contribute to the high incidence of NTDs in several

countries, including Saudi Arabia. Syndromes, often associated with chromosomal anomalies, account for a higher proportion of NTDs in Saudi Arabia. Genetic predisposition constitutes the major underlying risk factor, with a strong implication of genes that regulate folate one-carbon metabolism, and PCP.

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