REVIEW ARTICLE

Oral Biosciences

Neural tube defects and their significance in clinical dentistry: a mini review

Anuradha Garg[1], Ashok Utreja[1], Satinder P. Singh[1] & Suresh K. Angurana[2]

1 Unit of Orthodontics, Oral Health Sciences Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India
2 Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Keywords
anencephaly, encephalocele, myelomeningocele, neural tube defect, spina bifida.

Correspondence
Dr Anuradha Garg, Department of Orthodontics and Dentofacial Orthopedics, School of Dental Sciences, Sharda University, Plot no. 32, 34, Knowledge Park III, Greater Noida, Uttar Pradesh 201306, India.
Tel: +91-96549-88887
Email: garg.anuradha@yahoo.co.in

Received 9 February 2012; accepted 7 April 2012.

doi: 10.1111/j.2041-1626.2012.00141.x

Abstract

Neural tube defects are common congenital malformations that could be apparent at birth or manifested in later stages of life. Morbidity is high in anencephaly, whereas in spina bifida, there are neurological and motor disorders. These defects deserve paramount importance in clinical dentistry. Latex allergy, dental caries, difficulty in mouth opening, and sitting in a dental chair are common problems. There is a high risk of anaphylactic response during anaesthesia. There could be associated craniosynostosis causing maxillary deficiency, and malformed sella turcica might be seen. An association of the defects has been linked with orofacial clefts and Down syndrome.

Introduction

Neural tube defects (NTD) are malformations secondary to abnormal neural tube closure. They manifest between the third and fourth weeks of gestational age, resulting in structural defects that occur anywhere along the neural axis from the developing brain to the sacrum.[1]

Methodology

A literature search using the Medline database, PubMed, and Google was conducted for articles published between 1975 and 2011. Searches of systematic reviews using the Cochrane database and websites of international dental organizations were also conducted.

Etiology and pathogenesis

Genes interact with environmental factors and play a joint role in the causation of NTD.[2] Genes, such as Sonic Hedgehog,[3] the dishevelled and thermolabile variant of methylenetetrahydrofolate reductase (MTHFR), have been held to be responsible for NTD occurrence.[4,5] Infants with mutations in the folate receptor-α gene are at increased risk of NTD due to reduced binding affinity to 5-MTHF, which is the physiological form of folic acid. NTD can also result from hyperhomocysteinemia that arises as a result of deficiency of vitamins B_6, B_{11} and B_{12}, which are involved in the methylation cycle.[6] Low socioeconomic status, smoking, excess vitamin A, zinc deficiency, and high levels of organic matter have been cited as the risk factors for NTD occurrence. Maternal obesity, diabetes, the common cold in the first trimester, hyperthyroidism, stress, hyperthermia, and infections have been found to be associated with NTD.[7] The use of antiepileptic drugs during pregnancy is associated with an increased risk of NTD, due to free-radical induced damage.[8]

Theories of neural tube closure

Neural tube defects can be classified by closure sites where failure of closure occurs.[5]

Five sites of initiation of neural fold fusion

Consistent with the Van Allen model, closure 1 occurs at the rhombencephalon–spinal cord junction and extends rostrally and caudally. Closure 2 starts at prosencephalon–mesencephalon junction and progresses bidirectionally. Closure 3 begins at the rostral tip of the neural plate adjacent to the stomodeum, and progresses caudally to meet closure 2. Closure 4 starts between closures 1 and 2 over the rhombencephalon, and completes closure of the cranial portion of the neural tube from which the brain develops. Closure 5 starts at the caudal end of the neural groove and extends cranially to meet closure 1, completing closure of the spinal portion of the neural tube.

Three sites of initiation of neural fold fusion

Sites 1 and 3 are similar to the Van Allen model. Site 2 varies in position along the rostrocaudal axis.

Two sites of initiation of neural fold fusion

Site α is in the region of the rhombencephalon, and site β is in region of the rostral tip of the prosencephalon.

Classification of NTD

Neural tube defects have been classified into open and closed types, based on embryological considerations and the presence or absence of exposed neural tissue.[9] Open NTD are the most common type, and occur due to failure of primary neurulation. They occur when the brain and/or spinal cord are exposed at birth through a defect in the skull or vertebrae with associated cerebrospinal fluid leakage (e.g. spina bifida, anencephaly, and encephalocele). Closed NTD result from a defect in secondary neurulation, and are confined to the spine. Neural tissue is not exposed, and the defect is fully epithelialized (e.g. lipomyelomeningocele and tethered cord). Based on gross anatomic findings, these have been categorized into defects affecting cranial structures, such as anencephaly and encephalocele, and those involving spinal structures, such as spina bifida.[1]

Epidemiology

The incidence of NTD is 6.57–8.21 per 1000 live births in the Balrampur district of Uttar Pradesh, India, a region ranked as the least developed in the subcontinent.[10] The incidence of NTD in this region is among the highest worldwide. In the USA, the incidence of NTD declined by 50% between 1970 (1.3/1000 live births) and 1989 (0.6/1000 live births). In the UK and Ireland, the annual prevalence of NTD declined from 4.5 per 1000 live births in 1980 to 1.0–1.5 per 1000 live births in the 1990s.[11] In northern China, there was a 79% reduction NTD after the addition of folic acid supplements to women's diets (6.5/1000–1.3/1000 pregnancies).[12] In Australia, the prevalence of NTD (births + termination of pregnancies) was two per 1000 births for the period 1990–1994, but decreased to 1.2 per 1000 births in 2009. In 2009, very few infants (0.3/1000) were liveborn with a NTD.[13] Anencephaly has a female predominance, with a female-to-male ratio of 3:1. Risk tends to be higher in older or very young mothers. After the first NTD-affected pregnancy, the risk of a subsequent NTD-affected pregnancy is almost tripled. However, 95% of the affected infants are born to parents with no family history of NTD.[1,14]

Clinical presentation

Anencephaly, encephalocele, and craniorachischisis totalis are cranial presentations. Spinal presentations include spina bifida, myelomeningocele, congenital dermal sinus, lipomatous malformations, split-cord malformations, and caudal agenesis. Anencephaly is a serious developmental defect of the central nervous system in which the cerebrum, cerebellum, and cranial vault are either reduced in size or absent. It is classified anatomically as meroacrania if the defect does not involve foramen magnum, as holoacrania if it extends through the foramen magnum, and as holoacrania with rachischisis if anencephaly is accompanied by spina bifida. The majority of anencephalic fetuses are stillborn or aborted spontaneously.[15]

Spina bifida is a birth defect affecting the spinal column. Spina bifida occulta, meningocele, and spina bifida cystica (myelomeningocele) are the three types of spina bifida (Figure 1). Patients with spina bifida can have disabling conditions, such as cognitive deficit, pulmonary function abnormalities; scoliosis; hip, foot, and leg deformities; bladder dysfunction; and short stature. Myelomeningocele patients have a 90% chance of having hydrocephalus, which causes cognitive deficits.[16,17]

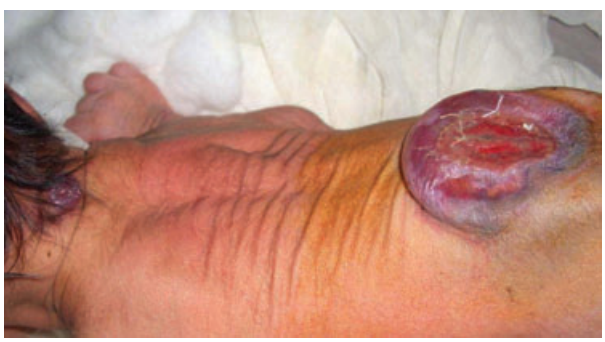

Figure 1. Lumbar myelomeningocele.

Cephalocele is the herniation of the brain or meninges through a defect in the skull. It has been classified as occipital, parietal, or anterior. Associated abnormalities include hydrocephalus, spastic quadriplegia, microcephaly, vision problems, mental and growth retardation, and seizures.

Significance in clinical dentistry

Anencephaly

Craniofacial malformations include hypoplastic or low-set ears or both; ocular proptosis; microphthalmia; subcutaneous nasal cleft; absent or incompletely-defined philtrum, cleft lip, cleft palate, bifid uvula, microstomia; and prominent maxillary alveolar ridges. Cephalometrically, the mandible is prognathic in every case. The thyroid gland might be normal, small, or larger in size. The neurohypophysis is hypoplastic and frequently found in the craniopharyngeal canal, which usually remains open in anencephaly. The hypothalamus is absent. The anterior and middle cranial fossae are constricted laterally, and the posterior cranial fossa is increased in lateral extension, but constricted anteroposteriorly.[15] The lesser wings of the sphenoid bone are rudimentary and extend parallel to the midline. The squamae of the frontal bone are reduced in size and form most of the orbital roofs. The posterior height of the vomer is increased, and the nasopharynx is enlarged. Zygomatic bones are rhomboid shaped in lateral view. The cranial base angle is reduced to a mean of 112.6 ± 16.9, with a more vertically-oriented clivus.[18]

Spina bifida

Hydrocephalus is a common residual problem in patients with myelomeningocele and is usually treated by shunt placement (Figure 2). Penicillin is commonly prescribed for shunt prophylaxis to prevent infective endocarditis in patients undergoing invasive dental procedures. Extractions and scaling/root planing are perceived to be high-risk procedures in patients with spina bifida.[19] The child is unable to open his mouth for a prolonged duration. Adaptive dental aids, such as a bite block, tongue retractor, and rubber dam, need to be used to control tongue movements and prevent swallowing of foreign materials.

The patient usually encounters difficulty sitting in the dental chair. Body position needs to be changed frequently to avoid pressure sores and uneasiness. Most patients with spina bifida have lower limb deformities and might need to be treated in their wheelchair, or an assistant might be needed to help the child move to the dental chair.[20]

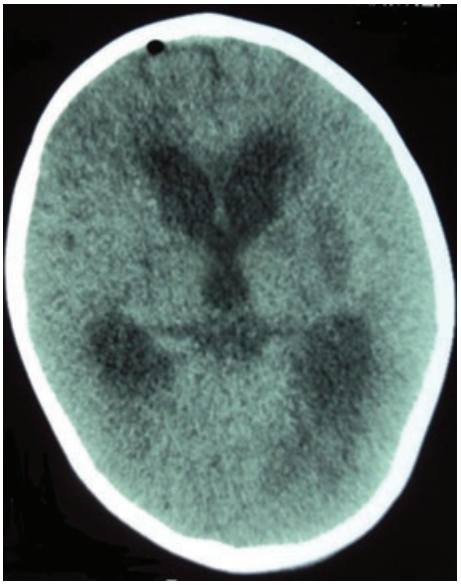

Figure 2. Non-contrast computed tomography image of head with dilated lateral and third ventricles, suggestive of obstructive hydrocephalus.

Patients with spina bifida usually have pulmonary function abnormalities and apnoeic episodes as a result of brain stem dysfunction due to Chiari malformation.[21] Thorough preoperative preparation should be done to decrease the risk of anaphylaxis during anaesthesia.

Children with these defects are more prone to childhood dental caries, because their neurological impairment can make dental care difficult, resulting in poor oral hygiene. These children also have poor nutrition, have to take medications containing sugar, and due to their physical problems, less attention is paid to their oral health. Therefore, these patients require periodic dental checkups and proper dental care.[22]

Children with spina bifida have a latex allergy prevalence of 28–67%. Thus, proper latex precautions should be taken in all patients during dental appointments. Dental products containing latex include gloves, rubber dams, mouth props, orthodontic elastics, toothbrush handles, polishing points, suction tips, and impression materials.[23]

Craniosynostosis in NTD

Patients with NTD can have diminished intrauterine movements, which in turn could help maintain the head in a fixed position against the pelvic bones. Facial bones are fused, resulting in a flat mid-face and protruding eyes. The patient exhibits a contracted upper jaw, resulting in a cross-bite and severely crowded teeth. Orthodontics and

mid-face advancement might be done early in life or after growth completion, depending on the particular needs of the child.[24]

Sella turcica in myelomeningocele

The anterior wall of the sella is found to be obliquely oriented in an antero-posterior direction instead of following a normal cranio-caudal direction, giving an impression of a wide sella turcica with less depth than normal (Figure 3). Because orthodontists regularly analyze a considerable number of lateral cephalograms, they will in many cases be the first to know the minor malformations of sella turcica. Appraisal of the morphology of sella turcica can be valuable in assessing any pathology in the pituitary gland.[25,26]

NTD and orofacial clefting

Neural tube defects and cleft lip, alveolus, and palate (CLAP) are the most common malformations in humans. NTD occurs at a rate of 1:1000, and CLAP between 1:500 and 1:1500. Both NTD and CLAP are known to be caused by a deficiency of folic acid and vitamin B_6 during pregnancy, but do not occur in combination. Both occur during the embryonal period, and are based on the closure failure of respective structures. The combination of the two malformations is virtually never observed clinically, except in genetic syndromes, such as anophthalmia clefting NTD and Wildervanck syndrome.[27]

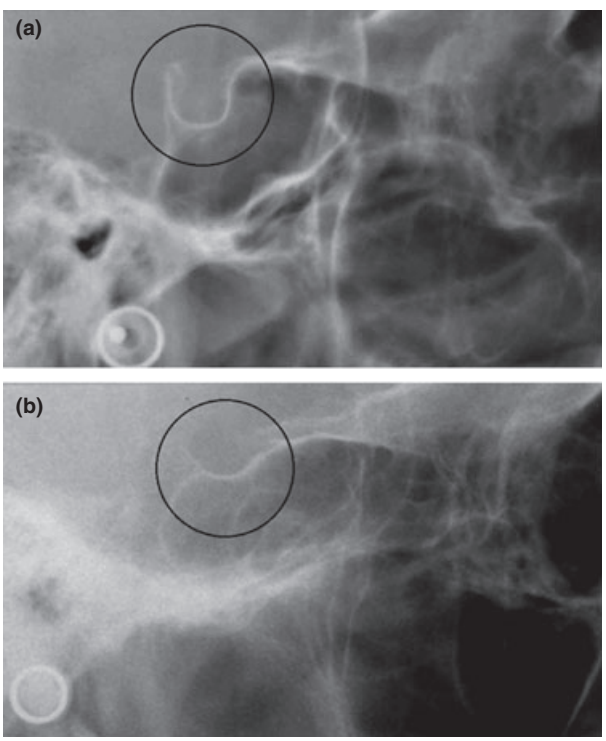

Figure 3. Lateral radiograph of sella turcica (a) and normal morphology (b). Abnormal morphology with diverging anterior and posterior walls in a patient with myelomeningocele.

NTD and Down syndrome

All or at least some cases of NTD and Down syndrome could have a common etiological pathway associated with impaired maternal folate metabolism. Mothers of infants affected with NTD have an increased frequency of mutations in the genes encoding MTHFR, although not necessarily for Down syndrome. The two have common epidemiological features, such as a large maternal contribution to both risk of occurrence and recurrence, increased number of miscarriages, ethnic differences, and maternal age. Although the underlying mechanism for the connection between the disorders needs to be established, direct evidence of the link between the two implies that folate supplementation before conception can reduce the frequency of Down syndrome.[28]

Diagnosis

Obtaining the patient's history and conducting a physical examination and screening are essential. Differential diagnosis includes neonatal meningitis; spinal cord hemorrhage and infarction; spinal epidural abscess; staphylococcal, tuberculous, and viral meningitis; and cervical and lumbosacral disk syndromes.

Prevention and treatment

Primary prevention: folic acid

In high-risk women, folic acid supplementation of 4 mg/day 3 months before conception and during the first trimester is recommended.[29]

Secondary prevention: screening

Maternal serum α-fetoprotein (MSAFP) test is performed on a pregnant woman's blood at approximately 16–18 weeks of pregnancy. High-resolution ultrasound detects NTD after approximately 18 weeks of pregnancy. Amniocentesis samples the amniotic fluid after 15 weeks of pregnancy. If MSAFP levels are elevated, ultrasonography is undertaken to rule out other possible explanations, such as multiple gestations, diabetes mellitus, and fetal malformations. If ultrasonography provides no explanation, amniocentesis is usually performed.[30]

Treatment

Proper medical and surgical care should be rendered by the neonatologist, neurosurgeon, orthopedician, and urologist. Newborns with an open NTD should be kept warm, and the defect covered with a sterile saline dressing. Prompt closure of the defect should be done. The patient should be positioned in a prone position to prevent pressure on the defect.

Conclusion

NTD are of immense importance to the dental profession. The chances of increased caries, plaque, latex allergy, physical impairment, and anesthesia problems in spina bifida patients need to be considered. Alteration of the cranial base angle and prognathic mandible and sella turcica morphology can be predicted from cephalograms. Oral and maxillofacial surgeons and orthodontists have an important role in assessing craniofacial malformations and facial skeleton morphology, and treating craniosynostosis cases with appropriate surgeries. The association between NTD and conditions, such as cleft and Down syndrome, in some studies cannot be ignored.[27,28] Therefore, dentists need to be well educated about these malformations, their etiology, screening, preventive measures, and relevance to the profession.

References

1 Frey L, Hauser WA. Epidemiology of neural tube defects. *Epilepsia* 2003; **44**: 4–13.
2 Sadler TW. Embryology of neural tube development. *Am J Med Genet* 2005; **135**: 2–8.
3 Young DL, Schneider RA, Hu D, Helms JA. Genetic and teratogenic approaches to craniofacial development. *Crit Rev Oral Biol Med* 2000; **11**: 304–17.
4 Shields DC, Kirke PN, Mills JL *et al.* The thermolabile variant of methylenetetrahydrofolate reductase and neural tube defects: an evaluation of genetic risk and the relative importance of the genotypes of the embryo and the mother. *Am J Hum Genet* 1999; **64**: 1045–55.
5 Padmanabhan R. Etiology, pathogenesis and prevention of neural tube defects. *Congenit Anom (Kyoto)* 2006; **46**: 55–67.
6 Steegers-Theunissen RP, Smithells RW, Eskes T. Update of new risk factors and prevention of neural tube defects. *Obstet Gynecol Surv* 1993; **48**: 287–93.
7 Loeken MR. Current perspectives on the causes of neural tube defects resulting from diabetic pregnancy. *Am J Med Genet* 2005; **135**: 77–87.
8 Pippenger CE. Pharmacology of neural tube defects. *Epilepsia* 2003; **44**: 24–32.
9 Lemire RJ. Neural tube defects. *JAMA* 1988; **259**: 558–62.
10 Cherian A, Seena S, Bullock RK, Antony AC. Incidence of neural tube defects in the least-developed area of India: a population-based study. *Lancet* 2005; **366**: 930–1.
11 Botto LD, Lisi A, Robert-Gnasia E *et al.* International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? *BMJ* 2005; **330**: 571.
12 Berry RJ, Li Z, Erickson JD *et al.* Prevention of neural-tube defects with folic acid in China: China-U.S. Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med* 1999; **341**: 1485–90.
13 Bower C, Rudy E, Callaghan A, Quick J, Cosgrove P. *Report of the birth defects registry of Western Australia 1980-2009*. King Edward Memorial Hospital: Western Australia, 2010.
14 Mitchell LE. Epidemiology of neural tube defects. *Am J Med Genet* 2005; **135**: 88–94.
15 Cohen MM. Malformations of the craniofacial region: evolutionary, embryonic, genetic and clinical perspectives. *Am J Med Genet* 2002; **115**: 245–68.
16 Juranek J, Salman M. Anomalous development of brain structure and function in spina bifida myelomeningocele. *Dev Disabil Res Rev* 2010; **16**: 23–30.
17 Jenkinson MD, Campbell S, Hayhurst C *et al.* Cognitive and functional outcome in spina bifida–Chiari II malformation. *Childs Nerv Syst* 2011; **27**: 967–74.
18 Fields HW Jr, Metzner L, Garol JD, Kokich VG. The craniofacial skeleton in anencephalic human fetuses I. Cranial floor. *Teratology* 1978; **17**: 57–66.
19 Acs G, Cozzi E. Antibiotic prophylaxis for patients with hydrocephalus shunts: a survey of pediatric dentistry and neurosurgery program directors. *Pediatr Dent* 1992; **14**: 246–50.
20 Deshmukh SS. Spina bifida. *Indian J Pediatr* 1997; **64**: 57–61.
21 Waters K, Forbes P, Morielli A *et al.* Sleep-disordered breathing in children with myelomeningocele. *J Pediatr* 1998; **132**: 672–81.
22 Helpin ML, Rosenberg HM. Beyond brushing and flossing. In: Batshaw ML, ed. *Children with disabilities*. Paul Brooks Publishing Co: Baltimore, 1977: 643–55.
23 Hudson ME. Dental surgery in pediatric patients with spina bifida and latex allergy. *AORN J* 2001; **74**: 57–72.
24 Martinez-Lage JF, Poza M, Lluch T. Craniosynostosis in neural tube defects: a theory on its pathogenesis. *Surg Neurol* 1996; **46**: 465–70.
25 Kjaer I, Hansen BF, Keeling JW. Axial skeleton and pituitary gland in

human fetuses with spina bifida and cranial encephalocele. *Fetal Pediatr Pathol* 1996; **16**: 909–26.
26 Kjaer I, Wagner A, Madsen P, Blichfeldt S, Rasmussen K, Russell B. The sella turcica in children with lumbosacral myelomeningocele. *Eur J Orthod* 1998; **20**: 443–8.
27 Weingaertner J, Fanghaenel J, Bienengraeber V, Gundlach KK. Initial findings on teratological and developmental relationships and differences between neural tube defects and facial clefting. First experimental results. *J Maxillofac Surg* 2005; **33**: 297–300.
28 Barkai G, Arbuzova S, Berkenstadt M, Heifetz S, Cuckle H. Frequency of down's syndrome and neural tube defects in the same family. *Lancet* 2003; **361**: 1331–5.
29 Werler MM, Louik C, Mitchell AA. Achieving a public health recommendation for preventing neural tube defects with folic acid. *Am J Public Health* 1999; **89**: 1637–40.
30 Milunsky A. Prenatal detection of neural tube defects. VI. Experience with 20,000 pregnancies. *JAMA* 1980; **244**: 2731–5.