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Analysis of Causative Factor Contributing to Reccurent Neural Tube Defects : A Case Report

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Neural tube defects (NTD) become a concern in developing countries, with rare recurrence risk 2-5%. Folate and cyanocobalamine deficiencies are the common cause of NTD , while other cause are MTHFR enzyme mutation and the presence of Maternal Serum Folate Reseptor Auto-antibodies.; Case Description: A multigravida (GIV P3001), 35 year old mother having anencephalic babies on second and fourth pregnancy with was examined at antenatal clinic Dr. Soetomo Hospital. She was tested negative for TORCH, Ultrasound examination revealed positive Frog sign, cerebellum located outside cranial lobe with cervical spine defect to upper femoral region. Termination of pregnancy was performed, a female 300 gram stillbirth baby was delivered. Open upper cranium was observed with intact brain structure and non closure of cervical spine. After postpartum period, maternal serum folate and cobalamin level were observed within normal values. Maternal serum homocysteine levels was also observed. MTHFR enzyme has a critical role at converting methylentetrahydrofolate to active tetrahydrofolate, and converting homocysteine serum to methionone used for protein synthesis. The mutant MTHFR C677T have 30% lesser converting function in metilathion chain. The decrease of this conversion in metilathion proccess resulting in increase unconverted homocysteine serum level accumulation. The serum of maternal NTD's pregnancy contain Folate Reseptor Auto-antibodies that binds to folate receptor and blocking cellular folate uptake.Conclusion : Mother with history of NTD pregnancy should encourage to take routine daily 400-800 mcg folic acid supplementation, routine antental care is mandatory, ealy ultrasound examination should be performed for monitoring and diagnosis.

Neural tube defects (NTDs) are severe birth defects of the central systema nervosum that originate during embryogenesis and result from failure of the morphogenetic process of ectoderm closure (see sidebar). In higher vertebrates, the ectoderm is generated by the processes that shape, bend, and fuse the neural plate, and fusion within the dorsal midline progressively seals the ectoderm because it forms. If closure isn't completed, the neuroepithelium remains exposed to the environment and consequently subject to degeneration and neuronal deficit. the sort and severity of those open NTDs vary with the extent of the body axis affected. Thus, failure of closure within the prospective brain and medulla spinalis leads to anencephaly and open rachischisis (myelomeningocele), respectively.

Although the unifying feature of open NTDs is incomplete ectoderm closure, evidence points to several different possible causes, both genetic and environmental. In humans, it appears that the majority NTDs are multifactorial, resulting from an additive contribution of several risk factors, which are each individually insufficient to disrupt ectoderm closure (the multifactorial threshold model). The challenge of identifying the first explanation for NTDs in individual patients is highlighted by the various candidate genes and environmental factors indicated by epidemiologic studies and experimental models. Moreover, the potential for gene-gene and gene-environment interactions introduces further potential complexity.

To achieve closure, the neuroepithelium must bend to bring the ideas of the neural folds into apposition. Bending occurs during a stereotypical manner at hinge points: a median hinge point (MHP) within the midline and paired dorsolateral hinge points (DLHPs) that arise laterally (Shum & Copp 1996). The morphology varies along the body axis with differing modes within the upper (MHP only), mid-spine (MHP and DLHPs), and caudal (DLHPs only) regions of the first spinal ectoderm

The mechanisms underlying neuroepithelial bending aren't fully understood, but one notable feature of the MHP is that the predominance of wedge-shaped cells (wider basally than apically) compared with

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nonbending regions (Schoenwolf & Smith 1990). At neural plate stages, the neuroepithelium may be a pseudostratified epithelium during which nuclei move to the basal pole during S-phase, due to interkinetic nuclear migration. Prolongation of S-phase at the MHP provides a possible means by which regulation of the cell cycle may contribute to cell wedging and hence MHP formation (Schoenwolf & Smith 1990).

Bending is regulated by signals emanating from nonneural tissues dorsal and ventral to the neural folds (reviewed by Greene & Copp 2009). The MHP is induced by signals from the notochord, located immediately ventral to the midline of the neuroepithelium (Smith & Schoenwolf 1989, Ybot-Gonzalez et al. 2002). At the molecular level, notochord-derived Shh induces the ground plate of the ectoderm at the MHP (Chiang et al. 1996, Placzek & Briscoe 2005). However, this action isn't essential for spinal ectoderm closure, which completes within the absence of a floor plate in mouse embryos lacking Shh or Fox A2 (Ang & Rossant 1994, Chiang et al. 1996). Thus, the MHP could also be functionally important in floor plate development but isn't essential for ectoderm closure.

The neural folds within the cranial region bend within the midline and dorsolaterally as within the mid-spinal region, but the closure process appears morphologically more complex. The folds are initially biconvex, with the ideas facing faraway from the midline, then switch to a biconcave shape allowing the ideas to approach within the midline. the extra complexity of cranial compared with spinal neurulation appears to be reflected during a more extensive genetic underpinning and a greater sensitivity to disruption, a minimum of in rodents. Exencephaly occurs in approximately 3 times as many knockout mouse models as does rachischisis and is that the NTD type most ordinarily induced by teratogens.

Cranial neurulation may believe specific contributory factors that aren't involved within the spinal region like expansion of the mesenchyme underlying the neural folds. Moreover, disruption of the actin cytoskeleton prevents closure within the cranial but not the spinal region. Similarly, exencephaly is observed, but spinal neurulation completes successfully in null mutants for several cytoskeletal components (e.g., n-cofilin, vinculin) . Nevertheless, apically located actin microfilaments are present throughout the neuroepithelium and functional disruption of the cytoskeleton-associated proteins MARCKS-related protein or Shroom3 causes both spinal and cranial NTDs suggesting that regulation of the actomyosin cytoskeleton plays a task in closure in both regions. Shroom proteins appear to play a key role: Expression of Shroom in Xenopus is sufficient to induce apical constriction of epithelial cells, whereas functional disruption inhibits neural fold bending and suppresses closure.

NTDs are often diagnosed prenatally by ultrasound. However, where diagnostic procedure isn't routinely available and/or induced abortion isn't an option, many babies with NTDs are born. Postnatal medical aid for babies born with open rachischisis usually involves surgery to shut and canopy the lesion. Multiple subsequent surgeries are commonly required to alleviate tethering of the medulla spinalis , treat hydrocephalus, and/or address orthopedic and urological problems.

As open NTDs arise early during pregnancy, there's a protracted period during which secondary neurological damage may occur due to exposure of nerve tissue to the amnionic fluid environment. These considerations provided impetus for the event of in utero fetal surgery for rachischisis , which can improve neurological outcomes compared with postnatal repair, although with fetal and maternal risks. Experimental models of rachischisis are getting used to research the possible combination of surgical intervention with additional therapy, intended to remediate neural damage. Examples include the implantation of biodegradable scaffolds to market neural regeneration and/or neural stem cells to populate the damaged medulla spinalis.

Various teratogenic agents induce NTDs in rodent models. In humans, teratogens that are related to NTDs include the anticonvulsant Depokene and therefore the fungal product fumonisin. Other nongenetic risk factors include maternal fever and excessive use of hot tubs, according to the induction of NTDs by hypothermia in rodent models.

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Maternal obesity and diabetes are well-recognized risk factors for NTDs. Determining the explanation for diabetes-related NTDs is hampered by the complexity of the diabetic milieu, although hyperglycemia alone is sufficient to cause NTDs in cultured rodent embryos. NTDs may result from increased oxidative stress, altered expression of genes like Pax3, and neuroepithelial cell apoptosis. Recent findings suggest that activation of apoptosis signal-regulating kinase 1 (ASK1) in hyperglycemic conditions results in activation of the apoptosis mediator caspase 8 by stimulating the FoxO3a transcription factor.

Experimental models provide systems for analysis of the developmental events of ectoderm closure, and fundamental cellular and morphological processes still be defined in additional detail. in theory , NTDs may result from insufficiency of 1 or more of the key driving forces (e.g., cellular properties and/or morphogenetic movements) that are necessary to realize closure, for instance , through mutation of a PCP gene. Alternatively, a genetic lesion or environmental insult may disrupt the closure process even where the underlying machinery is unbroken , for instance through induction of aberrant cellular behaviors like excess apoptosis. Experimental models require careful analysis to disentangle these possibilities. A key challenge are going to be to know how the molecular and cellular determinants of neurulation relate to the biomechanical forces required to fold the neuroepithelium to realize closure.

Advances in exome and whole-genome sequencing may help researchers begin to know the genetic basis of NTDs in humans. The multifactorial complexity of NTDs means analysis of knowledge from such studies will present a serious challenge. Moreover, investigators will got to integrate genetic data with information on epigenetic and environmental factors to get a more complete understanding of the explanation for individual NTDs.

Folic acid supplementation provides a way to scale back NTD risk and represents a serious public health advance. Nevertheless, the heterogeneity of NTDs suggests that primary prevention could also be achieved best by multiple interventions, and use of additional micronutrients alongside vitamin Bc may provide additional opportunities to further reduce risk.

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