Letters to the Editor

Neural Tube Closure

The etiology of neural tube defects is still an enigma. A complex interaction between genetic and environmental factors is considered to be the etiological factor. Recent studies showing that periconceptional folic acid therapy prevents neural tube defects are of great importance, as it may superficially point towards a predominant environmental factor.

In our earlier study from Davangere we showed that neural tube defects were 2.5 times more common in offsprings of consanguineous parents(l). Thus genetic factor may be an important cause of neural tube defects in this part of the world. In our recent study done during a period between April 1993 to March 1995, a total of 7826 births (live and still births) took place in 2 hospitals attached to J.J.M. Medical College. Sixty nine babies were born with neural tube defects; 36 were born to 2209 consanguineous parents and 33 were born to 5617 nonconsanguineous parents. The incidence in consanguineous couple was 16.3/ 1000 births and in non-consanguineous 5.9/1000 births (2.7 times; $p < 0.001$). Out of 69 babies born with neural tube defects, 40 were still born, 10 died during the perinatal period and the remaining were alive at the time of discharge from the hospital. A sincere attempt was made to obtain consent for autopsy in all the cases of neural tube defects who were still born or died in the perinatal period. Permission for postmortem was obtained in only 20 cases. Biopsy was taken from various regions of the gastrointestinal tract (duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, and sigmoid colon) and they were stained with Hemotoxylin Eosin stain. In 8 of the 20 cases, tissues were unsatisfactory for the interpretation. Only 2 cases out of 12, where detailed histopathological information was available, showed myenteric and submucous plexus and ganglion cells within the wall. The remaining 10 cases had craniocaudal extension of absence of myenteric and submucous plexus within the wall. One of the cases out of 10 showed presence of ganglion cells in the terminal ileum. This case had meningomyelocele with gastroschisis, whereas the remaining 9 cases had anencephaly and one of them also had gastroschisis.

Long segment Hirschsprung's disease has been reported in Wardenburg syndrome(2). McKusick explained the long segment Hirschsprung's disease as an autosomal recessive condition, thus implying the role of genetic factors in the defective migration of neural crest cells. Our study reveals that neural tube defects may co-exist with varying degree of long segment Hirschsprung disease indicating that a genetic factor may be involved in the migration of neural crest cells.

Although the pathogenesis of neural tube defects is not completely clear, it has been suggested that abnormalities such as anencephaly are due to defective closure of anterior neural tube at multiple sites(3). Failure of migration of neural crest cells occur in various disorders like Waardenburg syndrome, pigmentary disorders, deafness and intestinal aganglionosis. Neural crest cells migrate from the neural tube throughout the embryo to differentiate into numerous tissues, including the skeleton of the bronchial arches, cranial ganglia, and the peripheral nervous system(4).

Disruption of neural tube defects may be responsible for failure of neural crest cell migration. It is not yet clear as to how the neural crest cell migrate to their targeted sight of implantation like gut, ears, skin, adrenals, *etc.* It is possible that the tissues surrounding the neural crests may have a role in the migration of neural crest cells(4). The co-existence of neural tube

defects and absence of ganglion cells in the intestines suggests that failure of neural tube closure may cause defects in migration of neural crest cells resulting in features like agangliosis within the gut. Thus our observation that neural tube defects are more common in offsprings of consanguineous parents and further a good number of them are associated with defects of neural crest cell migration may indicate a predominant genetic factor in the causation of neural tube defects.

Recent studies have shown that folic acid supplements taken periconceptionally can greatly reduce a woman's risk of having a child with a neural tube defect (NTD)(5). It is clear that folic acid does not act to correct a simple nutritional deficiency, because most pregnant women carrying an affected fetus have levels of folate well above the deficient range(6). Thus, it has been generally assumed that an abnormality in folate metabolism is responsible for a large proporation of NTDs. It is suggested that a cystathionine synthase abnormality was present, based on abnormal methionine loading test results in women with affected offspring(7). Women carrying affected fetuses have significantly higher homocysteine levels than controls(8).

In a recent study(9), genetically determined variant of the 5.10 methylenetetra-hydrofolate reductase gene that specifies a product with reduced enzyme activity, was shown to be associated with NTDs. This finding explains some of the association between elevated homocysteine and NTDs because reductase is important for metabolising homocysteine and also how folic acid supplimentation prevents some of NTDs, by overcoming a partial block in the conversion of 5,10 methylene tetrahydrofolate to 5 methyltetrahydrofolate(9).

There is probably a genetic explanation for NTDs whereby a genetic factor (the abnormal enzyme) and an environmental factor (folate availability) interact to produce NTDs. Genetic screening could identify women who will require folic acid supplements to reduce their risk of having a child with an NTD.

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