Of flies, mice, and men

Editorial

In 1995 Nusslein-Volhard and Wieschaus were awarded the Nobel Prize for identifying genes that control the development of the fruit fly Drosophila [1,2]. To the surprise of many, it has since been shown that some of the same genes play a critical role in the development of the human nervous system[3]. Why is this relevant to those working with children who have complex neurological problems? This question can be answered by considering some developmental abnormalities of the brain which are now better understood because of recent advances in genetics.

Holoprosencephaly is a dramatic abnormality where the brain fails to divide into two hemispheres and associated mid-facial defects are present. The primary cerebral vesicle (telencephalon) does not cleave and expand laterally. Environmental factors may be important as holoprosencephaly is at least 20 times more common in infants of diabetic mothers than in the general population. However, in many cases the condition is determined genetically. There is evidence that mutations of several different genes can cause holoprosencephaly in humans[4,5]. One of these genes, on chromosome 7q36, codes for a protein called sonic hedgehog which has a role in the early development of the human nervous system. It is homologous to a protein called hedgehog that is secreted by cells in the developing fruit fly and is crucial in determining the complex structure of the adult fly. Research has shown that mice deficient in the sonic hedgehog gene have malformations of the frontal areas of the brain and have a single eye socket (or cyclopia): an eye abnormality seen in association with holoprosencephaly in humans.

Another severe abnormality of the brain is lissencephaly in which the brain is smooth with only the primary and sometimes a few secondary gyri. Two types of lissencephaly can be distinguished by CT or MRI scan. In type I the cortex is like that of a 13-week fetus: thick with white matter forming a thin rim along the ventricles. In type II lissencephaly the cortex is thinner and characteristic trabeculae penetrate the cortex from the white matter.

Type I lissencephaly is found in Miller-Dieker syndrome, in which postnatal growth failure and characteristic facial features, sometimes associated with microcephaly and congenital heart disease are apparent. The most common cause of type I lissencephaly is mutation of a gene on chromosome 17p13 called LIS1, or PAFAH1B1[5]. This gene has been remarkably conserved through evolution and, in non-mammalian organisms, seems to have a role in the translocation of the nucleus via a microtubule-based mechanism. Mutations of the homologous gene in mice have been shown to cause abnormalities of cortical development ranging from subtle defects in heterozygotes to lethal malformations in homozygotes.

Schizencephaly is a term used to describe clefts which traverse the full thickness of the human cerebral hemisphere, connecting the ventricle to the subarachnoid space. These are described as type I or 'fused-lip', when the walls of the cleft are opposed, and type II or 'open-lip', when cerebrospinal fluid separates the walls. Clinical features are variable, depending on the site and size of the lesion. Epilepsy is common and sometimes the only associated problem is isolated partial seizures. However, there may be hemiplegia, quadriplegia, and speech and learning difficulties of variable degrees. Diagnosis is best made by MRI scanning.

It has been thought that the clefts usually result from destruction of brain tissue, possibly due to vascular insufficiency. However, there is now evidence that some are genetic; familial cases have been described and some sporadic cases in humans are associated with mutations in the gene EMX25. This is homologous to the fruit fly gene called empty spiracles. It encodes a protein that has been shown to be necessary for normal development of the cerebral cortex in mice.

This brief description of the genetic mutations associated with three different types of brain malformation illustrates the striking similarities between different species. There are genes that control development that are common not only to mice and men but also to invertebrates, as shown by the studies of Drosophila. This may be humbling for humans, but it is reassuring to know that there is uniformity in these fundamental processes. There are continuing opportunities to understand more about the complexities of human brain development by studying (supposedly) more simple species.

Better imaging techniques during and after pregnancy allow the identification of brain malformations earlier and with more precision. We do not know the causes of many of these abnormalities and it is all too easy to blame them on environmental factors or viral infections in the absence of a better explanation. It seems likely that increasing numbers of these malformations will be found to be genetically determined.

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References

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