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Clinical and neuropathological evolution of the hydrocephalus developed by the mutant mouse *hyh*

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Background

The *hyh* (hydrocephalus with hop gait) mutant mice develop inherited hydrocephalus. A key feature in this mutant is that there is a foetal-onset ependymal denudation which precedes cerebral aqueduct obliteration and hydrocephalus [1]. Recently, a point mutation in alpha-SNAP protein has been identified as responsible of the *hyh* phenotype [2]. However, preliminary findings from our laboratory have suggested clinical and pathological heterogeneity in the expression of hydrocephalus, indicating that other (nongenetic?) factors may influence the degree of severity of this pathology. This is in accordance with findings in other hydrocephalic mutant strains [3,4]. The present investigation was designed to (a) study the clinical evolution of hydrocephalic mice in order to evaluate whether or not clinical heterogeneity does actually occur, (b) identify nongenetic factors (maternal age, multiparity) that may affect such an evolution, and (c) identify neuropathologic events underlying clinical heterogeneity.

Materials and methods

Mice of the *hyh* strain (B6C3Fe-*a/a-hyh*) were used in this investigation. The expression of hydrocephalic phenotype was studied in 1690 *hyh* mice (231 litters). The clinical evolution of hydrocephalic mice was achieved following up 79 postnatal (PN) hydrocephalic mice, from PN-1 to PN-180. Brain samples of hydrocephalic and non-hydrocephalic mice were studied at different developmental stages with several methods, including light microscopy, immunocytochemistry and scanning electron microscopy.

Results

In agreement with a monogenetic mendelian recessive disease, 22.4% of newborns developed the hydrocephalic phenotype. The male:female ratio was 1 in non-hydrocephalic mice and 2 in hydrocephalic mice. Multiparous females, as compared to primiparous, had litters with a significant reduction of both, frequency of hydrocephalus and sex ratio. Maternal age did not affect these parameters. Two mortality profiles were identified: (i) 70% of hydrocephalic mice died during the first 8 postnatal weeks and (ii) 30% died during the following months with more than 10% still surviving up to 7 months. The degree of severity of the pathology, as evaluated by the rates of body weight increase and mortality, was higher in males than in females. These results lead us to identify two major forms of clinical evolution, namely (a) rapidly progressive, and (b) slowly progressive. The neuropathological analysis showed that during the first 2 PN months the severity of hydrocephalus was variable ranging from moderate (communicating) hydrocephalus to a very severe (non-communicating) hydrocephalus. A common feature to all pathological groups was ependymal denudation. However, these groups differ in several aspects such as (i) precocity of the onset of aqueductal obliteration; (ii) nature and degree of alterations of periventricular structures, such as the hypothalamus; (iii) presence or absence of spontaneous communications between ventricles and subarachnoid space; (iv) intraventricular haemorrhages and (v) mesencephalic compression. Aspects i, iv, and v showed a high correlation with early mortality, whereas spontaneous ventriculostomies together with the absence of ventricular haemorrhages were associated with a less

severe or arrested pathological process leading to a long-term hydrocephalus.

Conclusion

It is concluded that (1) there are nongenetic (epigenetic) factors related with maternal multiparity (hormones? lactation?) that influence the expression of the mutation, (2) there are sex-related factors (genetic? hormonal?) that determine a higher frequency and severity of the disease in males, (3) there is a correlation between early or late mortality and the nature of the CNS alterations, and (4) the *hyh* mutant appears as a unique animal model to investigate long-term hydrocephalus

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