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Neuroepithelial denudation in the hyh mutant mice with congenital hydrocephalus produces agenesis of corpus callosum and alteration in the cerebral cortex

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Background

Hyh mutant mice suffer a congenital hydrocephalus triggered by ependyma denudation [1]. Additional pathological events have been observed: the absence of corpus callosum (ACC) and the reduction in the thickness of the cerebral cortex in this mutant. These two alterations frequently appear associated with human and animal hydrocephalus. Crossing the midline by callosal axons requires the presence of three types of midline glial cells (glial wedge, glial sling and indusium griseum glial cells) and also the correct guidance provided by pioneering axons. This crossing occurs about E-16.5 and pioneering axons appear around E-15.5 [2]. Development of cerebral cortex begins at E-12, continues until postnatal life, and requires proliferation and migration of progenitor cells from subventricular regions.

The aim of this work is to clarify the nature of the relationship between hydrocephalus and ACC and abnormal neurogenesis.

Materials and methods

Control and hydrocephalic *hyh* mice (Jackson Lab., USA) were used. To study the ACC mice from E-15.5 to PN-1 were used. Antibodies against NCAM (callosal axons), GFAP (midline glial cells) and β-III tubulin (neuroblast) were used. DiI tracing at E-17.5 were used to show crossing of midline by callosal axons. Alteration of the cerebral cortex was studied from 1 to 120 postnatal days. Digital photographs were taken and Noesis Visiolog software was used to measure the thickness of the cerebral cortex. Data obtained were statistically processed using Microsoft Office Excel and Sigmastat32 software. The ventricular surface was studied at E-15.5 by scanning electron microscopy. Organotypic slice culture and DiI labelling at E15.5 were used to analyze growth of pioneering axons and migration of neuroblast [2,3].

Results

At PN-1 hydrocephalic mice, corpus callosum is missing. In these animals, however, other commissural formations are present and the lateral ventricles are collapsed, indicating that the ACC is a phenomenon preceding lateral ventricles dilatation. In addition, DiI tracing at E-17.5 shows that in hydrocephalic animals callosal axons do not cross the midline. This led us to study the midline glial cells and pioneering axons. It was found that in E16.5 hydrocephalic mice, the midline glial populations are altered and alterations appear to be associated with the denudation of discrete areas of the lateral ventricles. In hydrocephalic mice, pioneering axon elongation, labelled with DiI at E15.5, has a wrong direction and do not cross the midline. In hydrocephalic mice, cerebral cortex shows a statically significant reduction of its thickness that is especially significant at PN-3, when dilatation on lateral ventricles is not yet apparent. In addition, neuroblast-like cells are detected on the ventricular surface of hydrocephalic mice by use of immunochemistry, scanning electron microscopy, and DiI labelling of organotypic slice culture.

Conclusion

i) Denudation of the ependyma would alter the midline glial cell populations associated with the crossing of callosal fibres, and subsequently alter the direction of the pioneering axons, resulting in the absence of corpus callosum. ii) The denudation of the ependyma layer would result in the disorganization of the germinal areas leading to abnormal neuroblast migration and, probably, to a reduction of the thickness of the cerebral cortex. iii) Detachment of the neuroepithelial cells in hydrocephalic foetuses should not only be associated to the pathogenesis of congenital hydrocephalus but also to abnormal neurogenesis and agenesis of corpus callosum.

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