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Kaolin-induced hydrocephalus in the newborn rat

M Del Bigio*, O Khan, T Enno and L McPhee

Address: Department of Pathology, University of Manitoba, Winnipeg, Canada

Email: M Del Bigio* - delbigi@cc.umanitoba.ca

* Corresponding author

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Background

Hydrocephalus occurs commonly in fetuses and neonates. The most widely used animal model of this condition has been the H-Tx rat. The genetic defect in this rat has not yet been defined. To complement studies in the H-TX rat, we have used the kaolin model in newborn rats. Our goal was to characterize this model with behavioral and biochemical outcome indicators. Furthermore, we hypothesized that nimodipine, which was protective in rats with hydrocephalus that began at 3 weeks age, would also benefit these animals.

Materials and Methods

Kaolin (25% suspension, 0.02 ml) was injected into the cisterna magna at 1-day age. Animals were weighed daily. Magnetic resonance imaging was used to define the ventricle size at 7 or 21 days. Developmental behavior analyses included observations of the ability to right after being placed on the back, to orient on a slope (negative geotaxis), to hang from a wire, and to walk on a rotating rod. A separate set of rats was administered pimonidazole (50 mg/kg i.p.) prior to sacrifice to detect hypoxic brain damage. The rats were sacrificed and their brains were removed for biochemical and histological analysis. In the drug treatment experiment, nimodipine was administered at doses previously shown to be effective (4–38 mg/kg/day) beginning after MR imaging at 7 days and continuing for 14 days. Additional comparative tests included the water maze test of memory.

Results

Kaolin-injected rats had delayed weight gain and noticeably enlarged heads. They walked with splayed hind limbs and a hunched back. MR imaging at 7 days demonstrated mildly enlarged ventricles and considerable white matter edema. In addition, there were fluid collections outside of the brain particularly dorsal to the cerebellum. At 7 days, geotactic orientation of was delayed in hydrocephalic rats. Biochemical analysis showed reduced ceramide galactosyl transferase, a marker of myelin production, and reduced CNPase, an oligodendrocyte enzyme that seems to play a role in axonal integrity. Myelin basic protein was at not detectable on Western blots in controls or hydrocephalic rats at 7 days. Imaging at 21 days demonstrated severely enlarged ventricles and large extra-cerebral fluid collections. The hydrocephalic rats were impaired in their ability to stay on a rotating rod. Myelin basic protein levels were significantly reduced. GFAP levels were increased.

Pimonidazole adducts were detected in periventricular white matter of hydrocephalic but not control rats. Nimodipine offered no behavioral or biochemical protection when studied in a randomized, blinded experimental manner. The highest doses were fatal.

Conclusion

The kaolin model can be used to complement the H-Tx rat model of hydrocephalus. Nimodipine does not appear to be an effective treatment when administered at this early age. This either suggests differences in the pathophysiology of brain damage at different ages or differences in the toxic potential of nimodipine. It also raises questions about the applicability of this type of treatment.