First hope for a prevention for congenital hydrocephalus

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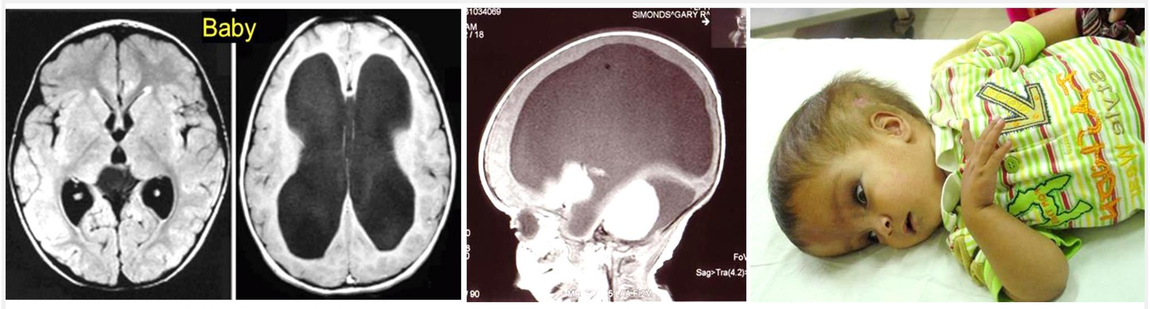
Cerebrospinal fluid (CSF) is pumped into the brain ventricles at a rate of 0.3ml/min giving a total of 4-5 times the volume held in the fluid spaces in and around the brain every day. Any imbalance between production and drainage results in HYDROCEPHALUS:

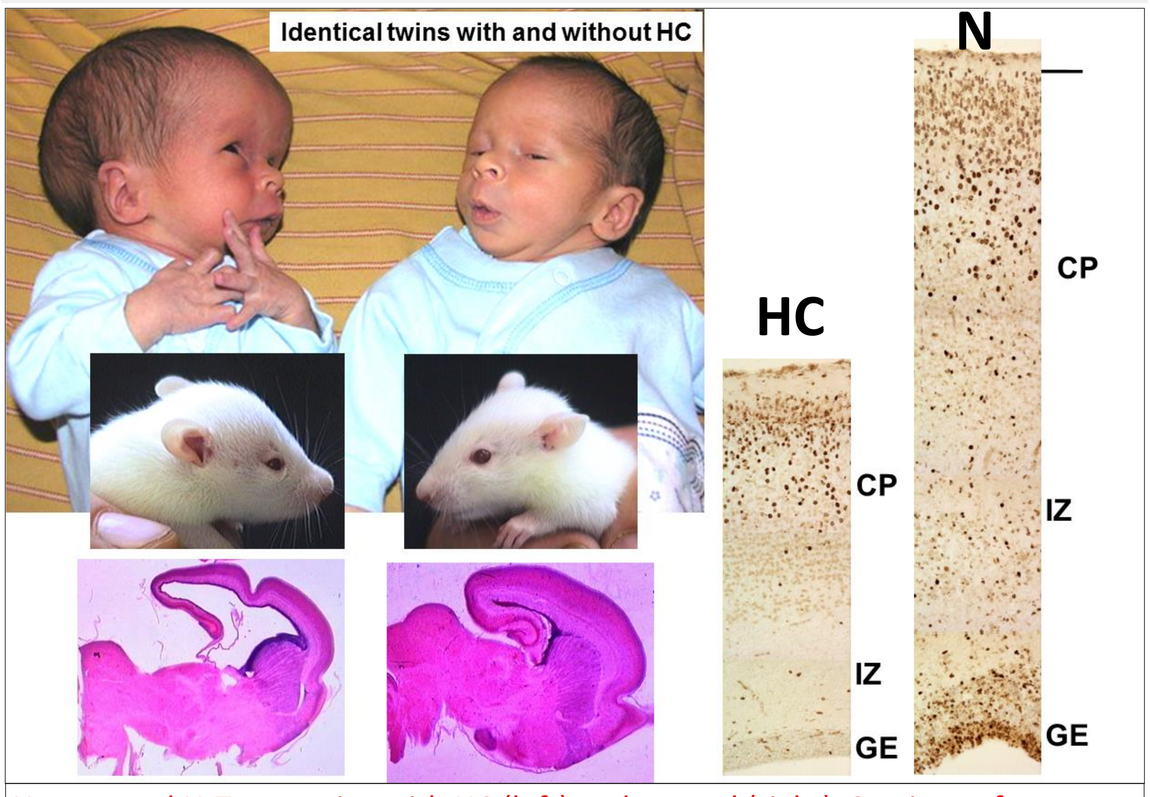


MRI scans of (left to right) normal neonate, hydrocephalic neonate shown in horizontal sections and hydrocephalic neonate in sagittal section. Neonate with hydrocephalus showing enlarged cranium and sunset eyes.

CONGENITAL HYDROCEPHALUS (HC) affects 1:500 live human births globally (NIH, USA). UNTREATED hydrocephalus results in raised intracranial pressure, brain damage, neurological deficits, and can cause death. TREATMENT involves surgical drainage procedures to decompress the brain and prevent further CSF accumulation.

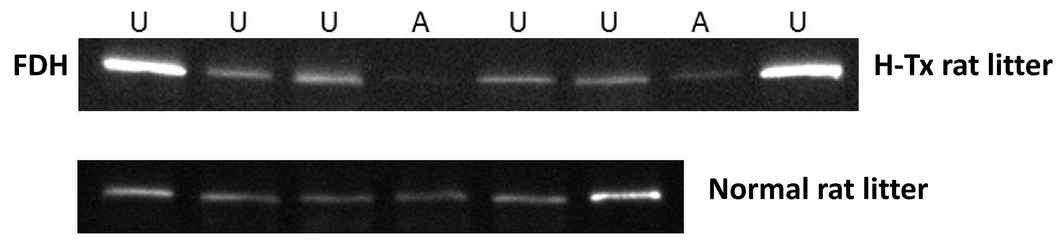
Congenital hydrocephalus is distinct from other causes of HC in having no brain damage but an arrest in development. Current treatments do not recover lost development or damage resulting from raised pressure and account for nearly $1 billion healthcare costs in USA alone and 50-80% of the workload of neurosurgeons.

Over the past 20 years OUR RESEARCH has found CSF to be a critical physiological element in the orchestration of normal development of the cerebral cortex. Composition changes underlie the cause of hydrocephalus and thus addressing these can prevent and/or treat the condition.



Human and H-Tx rat twins with HC (left) and normal (right). Sections of rat brains show enlarged ventricles in HC BUT identifying new born cells in the developing cortex (right) demonstrates that **rather than being a damaged brain the congenital HC brain suffers from poor development** with fewer cells generated from the germinal epithelium (GE) but which show normal migration into the cortical plate (dark brown cells in CP).

We identified a folate imbalance in the CSF of affected individuals and using Western blots (below) can show the decrease in the folate binding protein and enzyme, 10-formyl tetrahydrofolate dehydrogenase (FDH) in affected (A) compared to unaffected (U) rats.



FDH in the CSF is needed to transport normal folate (5-methyl THF) into cells. Cells in affected brains fail to divide due to this missing FDH. **Alternative forms of folate may supply cells directly, so we supplemented pregnant mothers** with folic acid, tetrahydrofolate (THF) or folinic acid (red arrows in the diagram below) and also a combination of THF and folinic acid. We then examined the offspring.

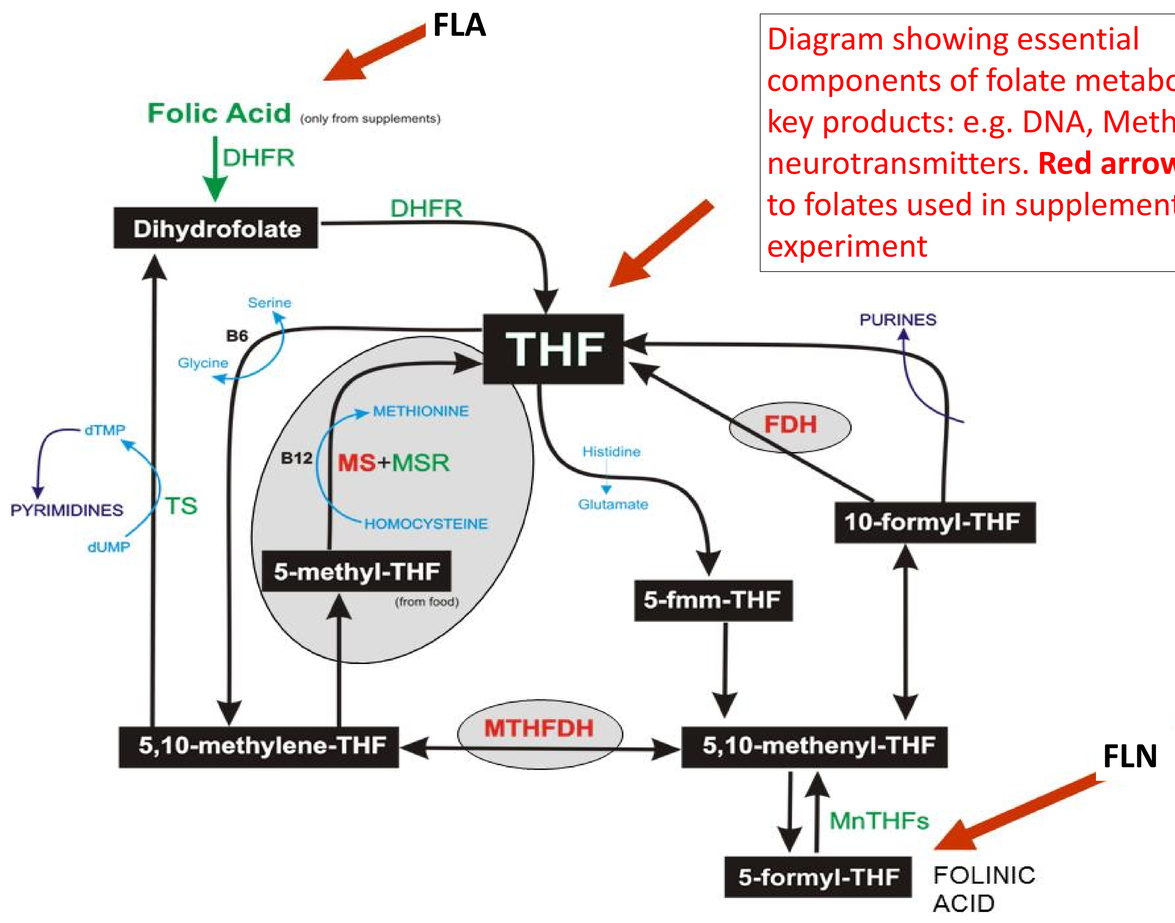
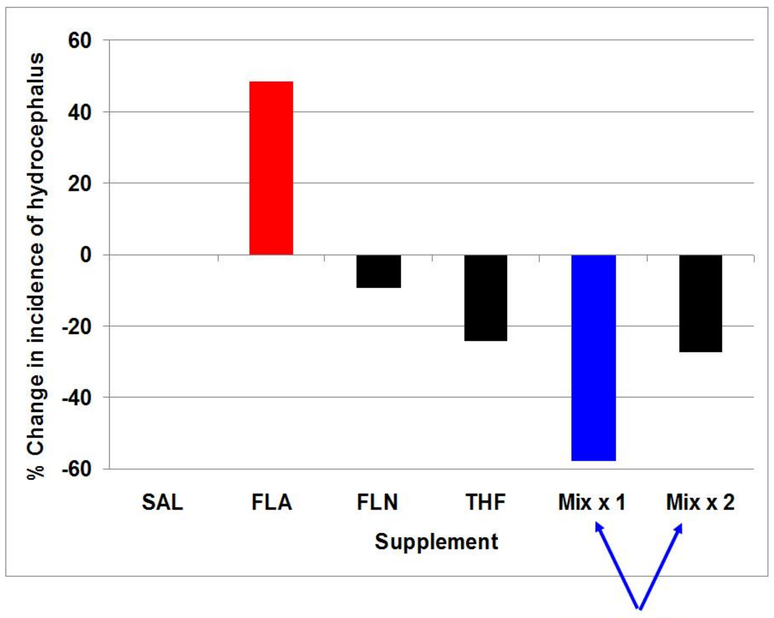
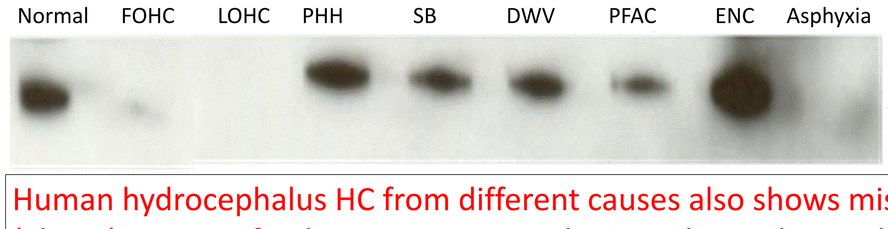


Diagram showing essential components of folate metabolism and key products: e.g. DNA, Methylation, neurotransmitters. **Red arrows** point to folates used in supplementation experiment

Folic acid (red bar) **gave increased incidence** of hydrocephalus in the susceptible HTx rats.
Folinic acid (FLN) or **tetrahydrofolate** (THF) gave **decreased incidence**
Combinations of FLN+THF gave a **synergistic maximum decrease in incidence** (blue bar).

The effect was dose dependent:
Mix 1 and Mix 2 are different doses.
Adjusting the dose will improve efficacy.





Human neonatal CSF Western blot for FDH

Human hydrocephalus HC from different causes also shows missing CSF FDH in Western blots (above). FOHC is fetal onset or cogenital HC similar to that in the H-Tx rat. LOHC is late onset (infection induced) HC. PHH is post-haemorhagic HC. SB is spina bifida with HC. Neonates suffering Asphyxia also shows loss of FDH. Encephalocoels (ENC) have raised FDH.

CONCLUSIONS: A common feature of hydrocephalus and perinatal asphyxia is a loss of FDH from the CSF. Cells cannot access available folate in the CSF. Folic acid precipitates this condition in susceptible fetuses. Combinations of two natural folate metabolites can bypass the FDH block and supply cells directly to prevent hydrocephalus and maximise brain development. **Hydrocephalus is NOT associated with a FOLATE DEFICIENCY but is associated with a folate IMBALANCE that can be rectified with natural folate supplements.**

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