CNS Dysplasia in Dysencephalia Splanchnocystica (Gruber’s Syndrome)* **

A Case Report

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Summary. A macrosomic male infant with multiple malformations survived for 4 days. His external dysplasias comprised macrocephalus, cheilopalatoschisis, auricular anomalies, and unilateral hexadactyly; his internal dysplasias included cysts of kidneys and pancreas, and a patent foramen ovale. The child had frequent generalized convulsions and died of bronchopneumonia. Chromosomal analysis was normal.

The main neuropathological findings were a cleft foramen magnum, micropolygyria and heterotopia of the neocerebrum, hypoplasia of the vermis and central white matter of the cerebellum, diffuse heterotopia of Purkinje cells, and unique heterotopic gray matter in the central cervical cord.

The infant's disorder was classified as Gruber’s syndrome, and this report may be the first detailed description of CNS malformations in this syndrome which, however, are probably not specific for this syndrome. The neuropathological findings were compatible with a heterochronic pathogenesis. This and the familial occurrence of malformations suggest a genetic nature of the syndrome.

Key words: Gruber's syndrome — Heterotopia in spinal cord — Micropolygyria in neocortex — Purkinje cell heterotopia

This report describes the histological anomalies in the CNS in the rare syndrome of Gruber, or “dysencephalia splanchnocystica”. To our knowledge, it is the first report on the detailed CNS findings.

Case Report

The mother was 40 years old. She had had three abortions and one child with multiple malformations consisting of cheilopalatoschisis, cardiac anomaly, and cleft bladder, and died shortly after birth. She had one healthy daughter of 17 years. During her sixth pregnancy (Fig. 1), she had no complications. Because of her unfavorable obstetrical history, Caesarean section was performed at term, when greenish turbid amniotic fluid was observed.

At birth, the male infant was macrosomic (4,650 g in body weight, 60 cm in length), macrocephalic (head circumference 42 cm) and had an Apgar score of 5. Following successful resuscitation and intubation, he was able to breathe spontaneously. Multiple external malformations were noted: they included relatively short extremities and hexadactyly of the left hand and foot, low set and malformed ears, low nuchal hair line, median cheilopalatoschisis, and a short penis.

During the first hours of life, he had repeated generalized convulsions which were insufficiently controlled by diphenylhydantoin and phenobarbital. He had several cardiac arrests. He died aged 4 days from severe respiratory insufficiency due to bronchopneumonia. There were no abnormal laboratory findings in urine and blood nor in the chromosomal analysis.

Fig. 1. Family tree of the present case (arrow). ■ Multiple malformation, [] stillborn, □ infantile death, ♦ abortion, I organic impotence
Pathological Findings (S 836/76)
There were bilateral cystic kidneys: cyst formation being particularly prominent in the distal tubuli. There were smaller cysts in the lower margin of the entire pancreas and a big cyst in the tail. A patent foramen ovale (4 mm in diameter) was noticed in the heart. The lungs showed massive aspiration of amniotic fluid, focal bronchopneumonia, and intraalveolar hemorrhage.

Neuropathological Findings (A 346/76)
The foramen magnum was large and there was a cleft in the crista occipitais externa without a meningoencephalocele. There was intense congestion of meningeal vessels. The frontal and parietal lobes were slightly hypoplastic and micropolygyria was present (Fig. 2). The distribution of the micropolygyria was widespread, exclusively in the neocortex, but the second and third temporal gyri, temporal pole, and the cuneus-calcarineus regions were normal. The lateral ventricles were markedly enlarged. The cerebellum was asymmetrically hypoplastic, particularly the vermis (weight of cerebellum including brain stem was 22 g, total brain weight was 490 g). The fourth ventricle was enormously enlarged dorsolaterally and opened into the foramen of Magendie.

Histologically, the neocortical micropolygyria varied considerably; it partly showed a very irregular structure, including pachygyric micropolygyria but partly a typical four-layered structure, sometimes associated with “overshooting” of nerve cell migration into the molecular layer (Fig. 2). In the cerebral white matter, there were some periventricular circumscribed foci of heterotopic gray matter (Fig. 2) and numerous nerve cells were scattered in the subcortical white matter. The residual periventricular germ cells were normal for the patient’s age.

At the base of the brain near the hippocampus (carrefour temporo-insulo-hippocampique), a large gliomesenchymal dysgenesis was encountered (Fig. 3a), which contained abundant mesenchymal elements, astroglia cells, scattered nerve cells, and occasional myelinated fibers. The pes hippocampi was hyperplastic and the fascia dentata very irregularly shaped.

Fig. 2. Typical four-layered (medial) and atypical (dorsal) microgyria. Note the normal cortical structure of the gyrus cinguli. Arrows indicate heterotopic gray matters (Nissl, × 6)