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

A Case Report

A. Hori[1], H. Orthner[1], A. Kohlschütter[2], K. M. Schott[3], K. Hirabayashi[4], and K. Shimokawa[4]

[1] Division of Neuropathology, [2] Department of Pediatrics, and [3] Department of Pathology, University of Göttingen, Robert-Koch-Str. 40, D-3400 Göttingen, Federal Republic of Germany
[4] Gifu University School of Medicine, Gifu, Japan

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.

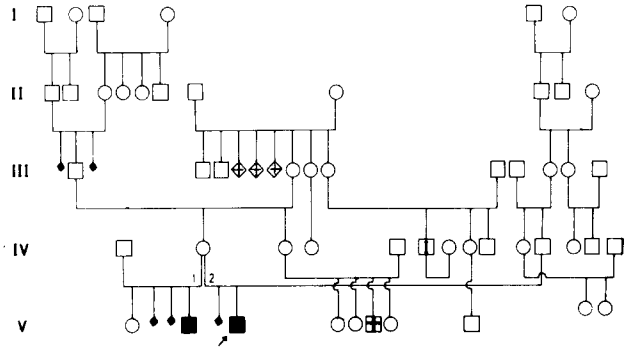

Fig. 1. Family tree of the present case *(arrow)*. ■ Multiple malformation, ⊞ stillborn, ⊕ infantile death, ◆ abortion, *I* organic impotence

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 hexadactylia 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.

* Georg Benno Gruber (February 22, 1884 – July 20, 1977) in memoriam

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Offprint requests to: Dr. A. Hori (address see above)

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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.

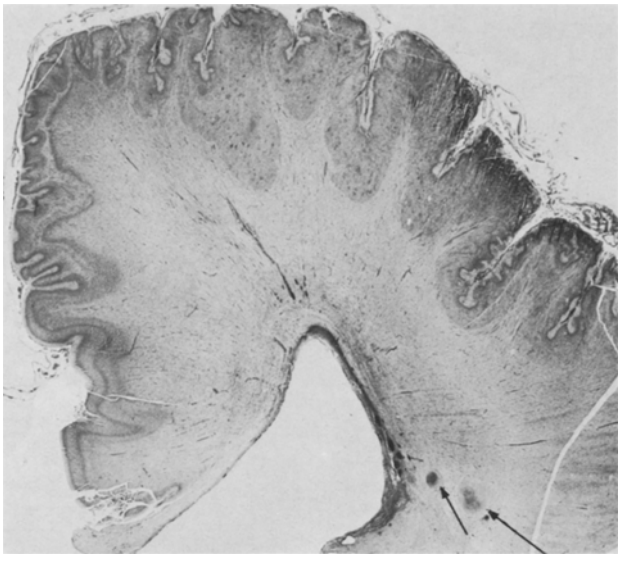

Fig. 2. Typical four-layered (medial) and atypical (dorsal) microgyria. Note the normal cortical structure of the gyrus cinguli. Arrows indicate heterotopic gray matters (Nissl, ×6)

Neuropathological Findings (A 346/76)

The foramen magnum was large and there was a cleft in the crista occipitalis 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-calcaneus 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 dorsolateralwards 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.

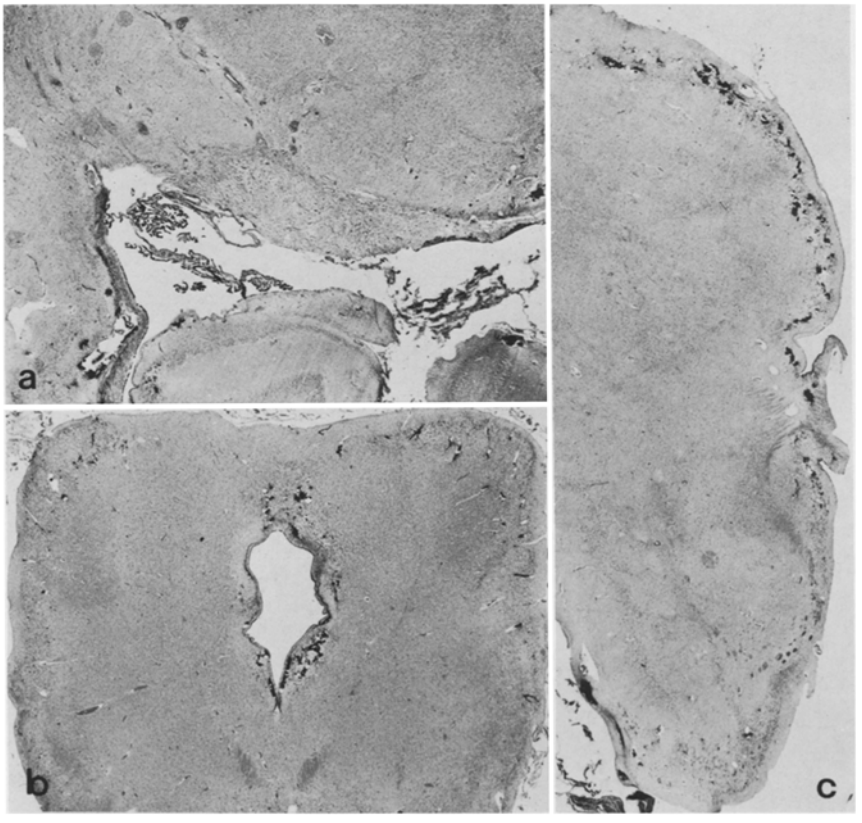

Fig. 3a—c. Gliomesenchymal dysgenesis of the base of the brain and subependymal and tegmental laminar calcification (**a**, **b** H.-E., ×1,8; **c** Klüver-Barrera, ×1,1)

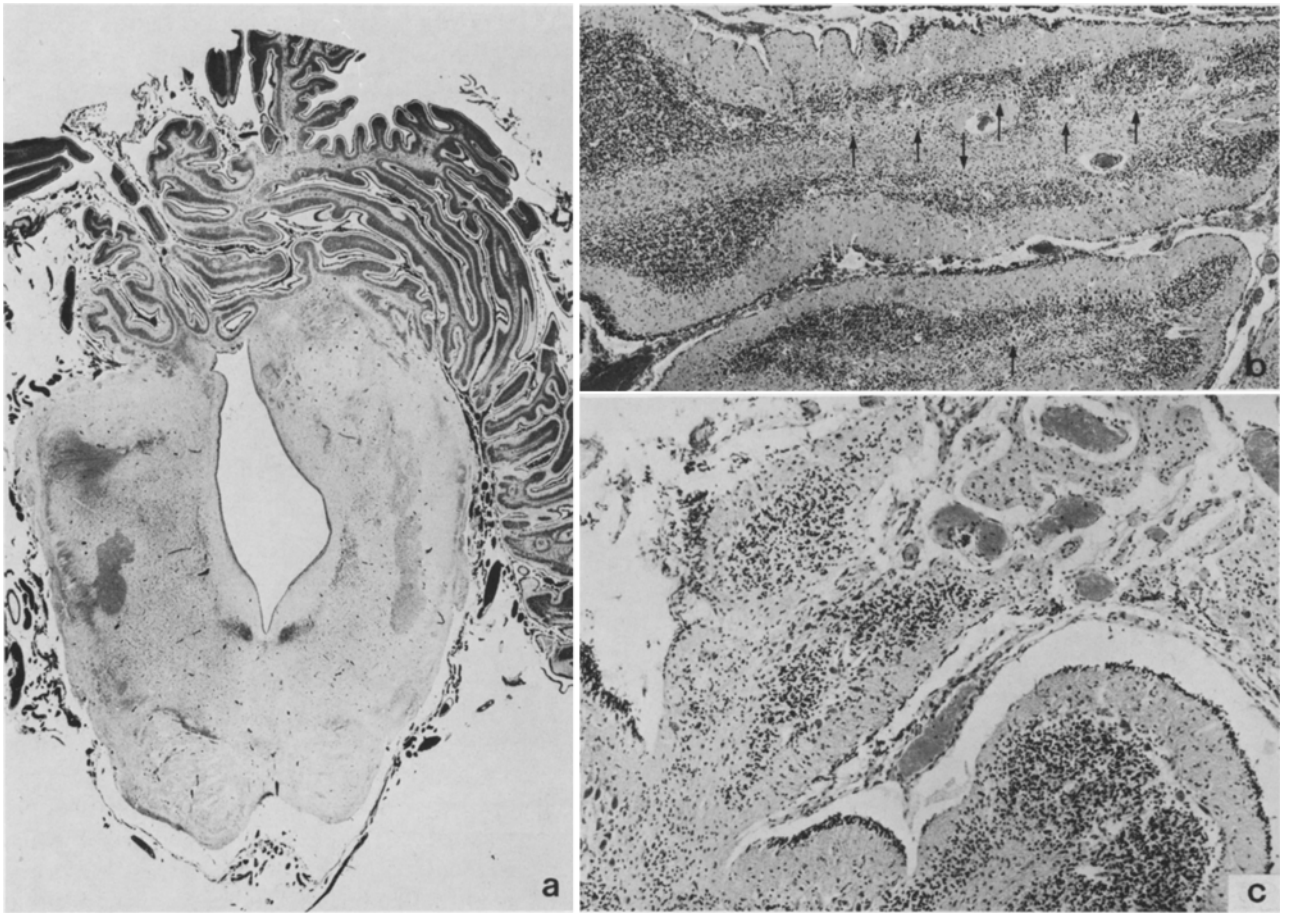

Fig. 4. a Displacement of cerebellar and vestibular nuclei, enlarged fourth ventricle, and hypoplasia of pons (Klüver-Barrera, ×1,1). **b** Reversed Purkinje cell layer (*arrows*) and forme fruste of micropolygyria (H.-E., ×13). **c** Damaged cerebellar cortex (H.-E., ×26)

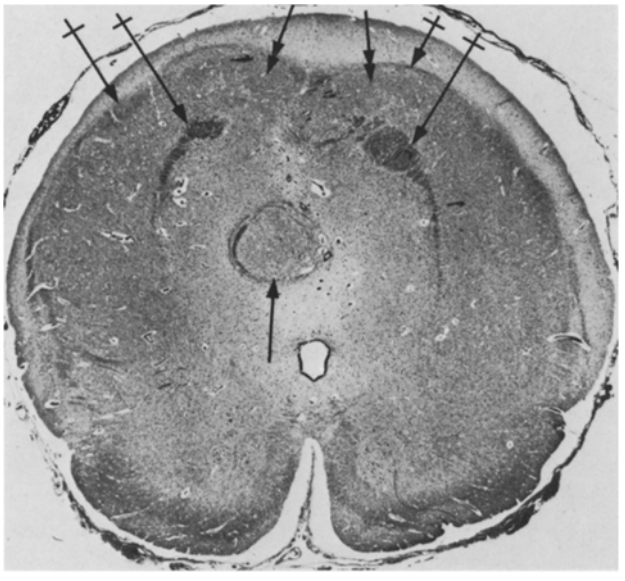

Fig. 5. Upper cervical cord. Heterotopia *(arrow)* surrounded by circular myelinated fibers, presumable posterior fascicles *(crossed arrows)*, displastic dorsal columns (*double arrows*), and multifurcated central canal (Klüver-Barrera, ×2,9)

In the subependymal regions of the thalamus, the hypothalamus, and the hippocampus including the fascia dentata, and in the periaqueductal region, calcified pseudolaminar necroses were found (Fig. 3b, c).

The massa intermedia was very large; no further dysplasias were encountered in the diencephalon and mesencephalon.

The central white matter of the cerebellum was hypoplastic and was largely occupied by masses of compact gray matter which consisted of the incompletely developed dentate nucleus, dorsally displaced hyperplastic vestibular nuclei, a hyperplastic locus coeruleus, and lateroventrally displaced globosus-emboliformis nuclei (Fig. 4a). A flocculo-nodular dysgenesis contained disorganized cortical structures. In only a small part of the cerebellar cortex, rudimentary micropolygyria of the molecular layer was observed (Fig. 4b). Here the Purkinje cells were situated within the inner granular layer and even subcortically. Purkinje cell heterotopia was widely disseminated within the cerebellar white matter, particularly within the lobuli semilunares and the velum medullae. In some parts of the neocerebellum, cortical structures had been replaced by reactive mesenchymal tissue (Fig. 4c).

At the base and on the lateral surface of the hypoplastic pons, subpial islands of ectopic glial tissue were found, which contained glial cells and fibers as well as a small number of mesenchymal elements.

In the dorsolateral region of the medulla oblongata, there were foci of heterotopic gray matter with a structure similar to the inferior olivary body. The olivary nuclei appeared regular in shape, but their medial parts were hypoplastic.

At the upper level of the cervical cord, remarkable dysgeneses were found. Semiserial sections showed ventrodorsal bifurcation of the canalis centralis into several channels. A focus of heterotopic gray matter surrounded by circular myelinated fibers (Fig. 5) was situated in the center of the cord. The sulcus medianus posterior was absent and the posterior columns were fused without a median raphe. There were concentric double semicircular myelinated fiber bundles in the common posterior region (dystopic-dysgenetic posterior fascicles?). Between these concentric bundles, paired gray matter foci were observed (nuclei of spinal tract of trigeminal nerve?). The anterior horns and anterior spinal tracts could be identified easily.

Discussion

Diagnostic Criteria

The multiple malformation syndrome, "dysencephalia splanchnocystica", described by Gruber in 1934, is characterized by a posterior encephalocele, by cysts of the kidneys, pancreas and liver, and by polydactyly. In addition, aplasia of the olfactory tracts, microphthalmia, club foot, and occasionally a cleft palate and retarded differentiation of genital or other organs may be associated (Gruber 1933/34). Some of these features may be absent. Therefore, the following syndromes are thought to represent subcategories of the Gruber syndrome: the Grauhan syndrome (dysphalangy, cheilopalatoschisis, and urogenital malformations); the Hanhart syndrome III (cleft palate of variable expression, renal aplasia, possibly also other dysplasias in brain or urogenital organs); and the Allemann syndrome (renal malformation, drumstick fingers and toes). The autosomal recessive Meckel syndrome is at least closely related to the Gruber syndrome, or both are even the same in phenotype, though in the former, cystic lesions are recognized mostly only in kidneys (Mecke and Passarge 1971).

Although there was no encephalocele in the present case, the abnormally large foramen magnum and the cleft of the crista occipitalis may be a "forme fruste" of the posterior encephalocele. Microgyria of the cerebrum, the hypoplasia-dysplasia in the cerebellum, unilateral hexadactyly and cyst formation in the pancreas and kidneys fulfil the typical criteria of the Gruber syndrome. Gruber stressed the familial occurrence of this syndrome. In our case, the family tree is compatible with a dominant or polygenetic mode of inheritance, but evidence in support of either hypothesis is insufficient (Fig. 1).

Neuropathological Consideration

Several exogenic factors are known to induce cerebral micropolygyria. Intrauterine carbon monoxyde intoxication, for example, may cause micropolygyria due to cortical necroses (Hallervorden 1949; Bankl and Jellinger 1967) while an impaired fetal blood supply may cause regional micropolygyria (Richman et al. 1974). Focal or non-systemic micropolygyria may also be seen in toxoplasmosis, cytomegalia, or porencephalies. Additional miscellaneous causes may be responsible for micropolygyria and faulty migration, to which category the present case may belong.

The dorsal displacement of the vestibular nucleus and the ventral displacement of the globosus-emboliformis nuclei in the present case appear to correlate with the hypoplasia of the central white matter of the cerebellum and the enlargement of the fourth ventricle. The hypoplasia of the vermis may relate to the hypoplasia of the medial part of the inferior olivary bodies.

The Purkinje cell heterotopia, widely found in the white matter, velum medullae, and within the inner granular layers may be due to a disturbed migration of the Purkinje cells.

The heterotopic gray matter outside the base of the pons was first described in a 55-year-old male by Freeman (1926); presenting histologically as a cerebral structure in the leptomenix. Hori and Iizuka (1975) demonstrated "neuronal ectopia" of the pontine surface in a 43-year-old male as an incidental finding. The ectopic pontine parenchyma in the present case can be compared with neuronal ectopias (Freeman 1926; Hori and Iizuka 1975) and the subpial glial ectopia (Cooper and Kernohan 1951) and also with gliomesenchymal dysgenesis, identical to that on the base of the brain, which may also often be found in many forms of brain malformation.

Dysplasias in the medulla oblongata and the upper cervical cord were conspicuous, and precise identification of anatomical status in the dorsal parts of the cervical cord was almost impossible. Friede (1975) described aplasia of the dorsal tracts associated with generalized impaired muscle development in a 3-day-old male. Since Pick (1878) described heterotopic gray matter in the dorsal tract of the lumbar cord, no further reports of heterotopias in the spinal cord have been published for 100 years. The heterotopic gray matter surrounded by myelinated fibers in the central gray matter of the cervical cord in the present case is unique.

Histological dysplasias in the CNS of this case were conspicuous; yet they cannot be regarded as specific for Gruber's syndrome, as no particular type of CNS dysplasia is specific for any syndrome.

Pathogenesis

The malformation of the spinal cord and the medulla oblongata must have developed very early in embryonal life, shortly after the fusion of the neural tube and at the time of migration of the olivary cells, respectively. Disturbed Purkinje cell migration indicates the developmental disturbance during a later

stage of embryonal life. The micropolygyria of the neocerebrum must have developed in the second intrauterine trimester. This discontinuous heterochronic and system-bound teratogenicity renders exogenous teratogenic factors unlikely. Of course, the brain continues to develop after an exogenous teratogenic event occurred at a certain fetal period so that the brain may display a complex development (so-called "secondary adaptive lesions"; Jacob 1958, 1966) as shown in the cerebellar cortex of the present case (Fig. 4c). This dysplasia, however, may have been formed after the complete lobulation of the cerebellar cortex. Calcified necrotic lesions in the thalamus, hypothalamus, etc. have no evident correlation to the brain malformation, but are thought to be secondary lesions. It should be mentioned, however, that similar periventricular foci of mineralization may be seen after intrauterine cytomegalic infection.

Not only the neuropathologic changes but also the splanchnocystic or hexadactylic malformations may be heterochronic. Also the familial occurrence of these various malformations of the case emphasizes endogenic pathogenesis.

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