Fatal CNS Dysgenesis with Severe Microencephaly, Mental Retardation, Seizures and Paucity of Myelin, Autosomal Recessive Trait?*

Gerhard Neuhäuser, Gabriele M. ZuRhein, Elisabeth G. Kaveggia, and John M. Opitz

1 The Harry A. Waisman Center on Mental Retardation and Human Development of the University of Wisconsin, 2 the Wisconsin Clinical Genetics Center of the Department of Medical Genetics, and the Departments of 3 Pediatrics and 4 Pathology of the University of Wisconsin Center for Health Sciences and Medical School, Madison, WI 53706, USA; 5 Central Wisconsin Colony and Training School, Madison, WI 53704, USA

Abstract. Siblings are reported with severe mental retardation, spastic cerebral palsy and seizures; in addition they had progressive or intermittent jaundice and recurrent infections; they died at 3 and 4 years respectively. Neuropathological studies in one showed a small brain with an almost complete lack of myelin in cerebral white matter, brain stem, cerebellum and anterolateral parts of the spinal cord. The condition most likely represents a dysgenesis of myelin (dysmyelination), possibly due to an inability of oligodendrocytes to form myelin and/or metabolic defects in the process of myelination. This mental retardation condition is probably inherited as an autosomal recessive trait and may represent a special type of a primary CNS developmental defect.

Key words: Familial mental retardation – Seizures – Microcephaly – Cerebral atrophy – Myelin dysgenesis – Jaundice.

Introduction

The clinical and even neuropathological differentiation of degenerative CNS diseases and non-progressive mental retardation syndromes caused by pre-, peri- or postnatal lesions may be very difficult, particularly in infants and young children. Developmental and various secondary changes (deformities, degeneration and deterioration) can give the impression of a slowly progressive course in an otherwise “static” mental retardation syndrome; environmental influences also have to be taken into account to explain the course of the patient's condition. Comprehensive anamnestic data and careful longitudinal evaluation of growth,

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Address for offprint requests: Dr. G. Neuhäuser, Univ.-Kinderklinik, Loschgestr. 15, D-8520 Erlangen, Federal Republic of Germany
neurological and mental functions can give helpful information in this respect; further, a positive family history may help to elucidate the natural course of the disorder by allowing comparison with other affected individuals. However, if a progressive condition is suspected, most often extensive neuroradiological, metabolic-biochemical and occasionally biopsy studies are required. However, despite all efforts, it is sometimes impossible to diagnose the condition during the patient’s lifetime or to settle whether true degeneration or deterioration is the explanation for the patient’s apparent progressive course.

Neuropathological evaluation of patients with severe mental retardation is therefore essential in defining the etiology and pathogenesis of underlying “static” and progressive CNS lesions. In examining 891 patients with mental and neurological defects in infancy and early childhood Gross et al. (1968) showed that clinical data and laboratory tests yielded a diagnosis in only 24 percent, whereas by neuropathological evaluation alone a diagnosis was possible in 80 percent. The etiology could be proved with a high degree of certainty in 90 percent of patients if both clinical findings and neuropathological results were considered.

In a study of severely mentally retarded patients at Central Wisconsin Colony (CWC) a clinical/genetic classification was used to define sub-groups according to clinical picture, pathogenesis and etiology (Kaveggia et al., 1971, 1975; Opitz et al. 1971; Opitz, 1976). Neuropathological findings are particularly important in the diagnosis of multiple congenital anomalies/mental retardation (MCA/MR) syndromes and of “isolated” CNS defects as well as in degenerative CNS disorders. Patients with a clinical picture of seizures, cerebral palsy, hypotonia or “pure” mental retardation, in whom MCA or CNS defects cannot be shown by clinical methods, have to be reclassified if an anomaly of the brain or of other organs is found at autopsy. These data are essential for genetic counseling in severe mental retardation, because the recurrence risk might be quite different, i.e. low in most MCA/MR syndromes but high in true degenerative diseases.

A small group of patients at CWC has been difficult to classify; some have been put, without great conviction, into the seizure group, others into the cerebral palsy group, and others into the group with presumed primary CNS developmental defects. These patients are generally severely impaired from birth and show variable mixtures of profound mental retardation, seizures and cerebral palsy-like manifestations, and the initially apparently progressive nature of their condition is usually very difficult to classify as either true degeneration or as deterioration. Most of these cases are familial, presumably on the basis of recessive inheritance. It is therefore obvious that a far greater number of chance isolated cases (rather than familial cases) of these disorders must be present in that patient population, crying for correct diagnosis in order to prevent recurrence through genetic counseling.

We report the findings of two sibs who had an almost identical mental retardation syndrome complicated by spasticity, seizures, jaundice and recurrent respiratory tract infections. Neuropathological studies in one patient showed among other findings almost total absence of myelin in the cerebral white matter and in some spinal areas. The condition may be inherited as an autosomal recessive trait.