Child's Brain 11: 126-134 (1984)

Neuropathologic Features, Including Pontine Schwannosis, in a Four-Year Survivor of Probable Reye's Syndrome with Secondary Möbius Syndrome

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Key Words. Schwannosis - Reye's syndrome - Möbius syndrome

Abstract. Frequent seizures and loss of motor, language, and intellectual skills necessitated care in an institution for the physically and mentally handicapped for 4 years after diagnosis of presumed Reye's syndrome in a 10-month-old boy. Möbius syndrome was diagnosed and bilateral tarsorrhaphy performed for exposure keratitis. Postmortem examination revealed multiple old boundary zone infarcts in the cerebral cortex, small cavitated infarcts in basal ganglia and thalami, diffuse neuronal loss and gliosis, and a focus of old necrosis in the pons; brain stem herniation during the acute phase of Reye's syndrome was responsible for the latter lesion. Irregular congeries of proliferated peripheral nerves, confirmed by ultrastructural study, were ramifying in the gliotic pontine tegmentum. The pathologic substrate for the neurovegetative state in a long-term survivor of probable Reye's syndrome appears to be multifocal cerebral infarction.

Introduction

For prognostication and treatment, patients with Reye's syndrome have been assigned clinical grades on the basis of neurologic and EEG criteria [3, 18]. Patients in the higher stages of the disease have a high mortality rate or severe neuropsychiatric deficits [3, 5, 6, 18, 22, 32]. The neuropathology of acutely fatal Reye's syndrome has been documented as massive cerebral edema with accompanying intracranial compartment shifts [5, 25, 32]. In such cases, hemorrhages and acute infarcts affect the brain stem, as in other situations with elevated intracranial pressure [19]. The dysmetabolic state and bland necrosis of neurons in the cerebral

© 1984 S. Karger AG, Basel 0302-2803/84/0112-0126 \$ 2.75/0 cortex account for the EEG features; ischemia, mechanical compression, and necrosis of the vital cardiocirculatory and respiratory centers in the medulla oblongata result in extreme EEG abnormalities and are the ultimate cause of death. Infarction and hemorrhages in pons and midbrain are strategically located in the reticular formation with its function in arousal and wakefulness. In contrast to the central nervous system, regeneration in the peripheral nervous system is well established. Aberrant proliferation of Schwann cells and regenerating axons have been described as Schwannosis in the spinal cord, brain stem and basal ganglia [2,9,11,27]. Schwannosis of the brain stem as a sequel to transtentorial herniation has not previously been reported. The unique case is presented of a patient with presumed severe Reye's syndrome who survived in a neurovegetative state for 4 years, who had the clinical features of Möbius syndrome, and who exhibited proliferation of aberrant peripheral nervous tissue in the pons.

Case Report

At the age of 10 months, this white male infant with normal gestation, delivery and development had an upper respiratory tract infection complicated by otitis media. Seizures, muscular rigidity, and coma suggested meningitis on admission to the local hospital. Antibiotics were administered despite CSF findings which did not support that diagnosis. The subsequent hospital course and laboratory data led to the diagnosis of Reye's syndrome; on review of the hospital chart, results of liver function tests could not be located though the tests had been ordered. During appropriate therapy, cardiorespiratory arrest occurred, which was reversed. Severe neurologic damage (loss of previously acquired motor and sensory skills) necessitated transfer to an intermediate-care institution for mentally retarded. During the ensuing 4 years of life he manifested opisthotonus and hypertonus, facial diplegia (Möbius syndrome), no response to auditory, visual, or tactile stimuli (except withdrawal and grimacing to moderately painful stimuli), and no verbalization. He was frequently thrashing about wildly. EEG demonstrated diffuse slowing; seizures were ultimately controlled. Bilateral exposure keratitis and corneal ulceration necessitated tarsorrhaphy. The patient expired unexpectedly and his body was transferred to Georgetown University Hospital for postmortem examination.

Materials and Methods

Sections of multiple paraffin blocks of the brain were stained with luxol fast blue-hematoxylin cosin, Bodian, phosphotungstic acid hematoxylin, Holzer, Nissl, Masson's trichrome, reticulin, and periodic acid-Schiff. After diagnosing the neuropathologic lesion in the pons by light microscopy, a portion of the area was obtained from the corresponding tissue in the stock bottle and processed for electron microscopy. Subsequently, the entire brain stem was processed through paraflin.

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Neuropathology

The brain, weighing 1,100 g, had unremarkable external features. On sectioning the cerebral hemispheres, cortical atrophy was evident in the depths of the sulci, along the arterial boundary zones. Small foci of old, cavitary necrosis were recognized in the thalami and putamina. At microscopy, multiple microinfarcts were present in the cerebral cortex (fig. 1), thalamus, subthalamus, and putamina (fig. 2). These foci were characterized by neuronal fall-out, residual necrotic detritus, accumulation of debris-laden macrophages, and gliosis. More diffuse astrocytosis was evident throughout the cerebral cortex and thalami. The hippocampi exhibited neuronal loss in Sommer's sector. Purkinje cell numbers were significantly reduced with corresponding Bergmann astrocytosis.

The pontine tegmentum contained a zone of gray discoloration and gelatinous consistency, measuring $0.9 \times 0.8 \times 0.5$ cm (fig. 3). Microscopically, the peripheral rim of this area was composed of closely packed, congested vessels. The center contained debris, lipophages, and intertwining fascicles and conglomerates of Schwann cells and axons (fig. 4). Connective tissue accompanied these congeries; at the margins, a haphazard dmixture of collagen, reticulin, and astroglial fibrils were present. By electron microscopy (fig. 5), some axons in this region were surrounded by oligodendroglial-derived myclin; others were myelinated by Schwann cells with their distinctive basement membranes. The cause of death was acute pulmonary congestion, edema and early bronchopneumonia.

Discussion

Unqualified proof of Reye's syndrome does not exist in this case, but the infant was managed and diagnosed as a victim of Reye's syndrome. Marked cerebral edema and intracranial hypertension in the acute phase

Fig. 1. Old microinfarct in the temporal cortex is characterized by neuronal loss, gliosis, and focal collections of macrophages. (LFB-HE × 63.)

Fig. 2. A similar microinfarct of the putamen reveals a central collection of debris-laden scavenger cells surrounded by a zone of gliosis. LFB-HE × 100.

Fig. 3. Photograph of midpons depicts remote tegmental necrosis. LFB-HE. × 2.5.

Fig. 4. Peripheral axons and Schwann cells course as irregular and contorted bundles among debris and residual macrophages in the pontine tegmentum. $PTAH \times 100$.





Fig. 5. Electron photomicrograph from pontine tegmentum demonstrates some residual axons surrounded by central (oligodendroglial-derived) myelin (arrows) as well as several Schwann cells surrounded by basement membrane and enclosing small myelinated axons. Interspersed are bundles of collagen and glial processes crowded with filaments. (Uranylace-tate/lead citrate, \times 6,000.

of the disease resulted in brain stem herniation and cardiorespiratory arrest; this caused the boundary zone infarcts, multifocal microinfarcts and brain stem necrosis. The subsequent psychomotor deficits with extreme mental retardation and seizure activity seen in this patient have a structural basis in the multifocal lesions of the cerebral hemispheres, basal ganglia and brain stem. Purkinje cell loss may be related to the initial cardiocirculatory arrest and, at least partly, responsible for the poor seizure control; but epileptic seizures may cause cerebellar degeneration [30]. Opisthotonus and postural abnormalities can be ascribed to the multiple infarcts in basal ganglia and other components of the extrapyramidal system (thalami, red nuclei, midbrain tectum and pontine reticular formation). Neuronal loss and astrocytosis of the thalami resulted from transsynaptic degeneration secondary to multifocal cerebral cortical and basal ganglionic necrosis.

The total destruction of the pontine tegmentum, a consequence of transtentorial herniation with secondary brain stem hemorrhages and infarction, account for the clinical features of the Möbius syndrome (facial diplegia, ocular immobility, poor head control and exposure keratitis). Classically, the Möbius syndrome is due to agenesis or hypoplasia of the motor nuclei in the brain stem, sometimes with an hereditary pattern. either autosomal dominant [33] or with chromosomal translocation [37]. However, Towfighi et al. [35] have recently reclassified 15 published cases into groups of either primary or secondary brainstem lesions, peripheral nerve involvement, or myopathy. Secondary forms may be due to intrapartum hemorrhage in the brain stem [4], multifocal necrosis in the pons [34, 35], peripheral neuropathy [28], dysplasia of the facial musculature with intact cranial nerve motor nuclei [24], or facioscapulohumeral dystrophy [13]. In our case, facial diplegia resulted from destruction of the internal genu of each facial nerve. Exposure keratitis and corneal ulcer, necessitating tarsorrhapy, can be explained by the destruction of the chief sensory nuclei of the trigeminal complex. Necrosis of the trapezoid body and its nuclei and lateral lemnisci interrupted the central auditory connections, accounting for deafness. Tactile stimuli could not be perceived because of interruption of the medial lemnisci, but the response to moderately painful stimuli can be explained by the preservation of the lateral spinothalamic tracts situated more laterally.

The aberrant ramification of proliferated Schwann cells and peripheral axons within the CNS has been termed Schwannosis [29], myelinated and nonmyelinated neuromas [9, 10], hyperplasia of sheath elements [27],

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focal axonal proliferation [23] and traumatic neuroma [16]. Predisposing lesions in the CNS have been destructive [infarction, trauma, herniated disc, syringomyelia; 15, 17, 36], demyelinative [multiple sclerosis; 8, 11], neoplastic [Schwannoma, ependymoma; 11, 29], and dysmetabolic [subacute combined degeneration, diabetes mellitus; 2, 9, 10, 23]; no predisposing lesion was apparent in 1 case [7].

Feigin and Popoff [8], Feigin and Ogata [9] and Feigin and Budzilo*vich* [10] contend that neuromas of the CNS take origin from heterotopic or dysgenetic perivascular nerves and that Schwann cells derive from maturation of multipotential mesenchyme. However, the failure to demonstrate Schwannosis in spinal cords of children under 16 years of age, its increasing prevalence with advancing age, and the multitude of basically destructive lesions of the CNS with which Schwannosis has been associated suggest a different pathogenesis [2]. Such lesions have been seen most commonly in the cord, a comparatively small structure of central nervous tissue in continuity with and proximity to the substantial anterior and posterior nerve roots. The brain stem with its cranial nerves is the component of the CNS next most commonly afflicted. In the cord and brain stem an origin from injured and abberrantly regenerating motor and sensory nerve roots appears acceptable. Schwannosis of the basal ganglia demands a different explanation. The autonomic plexus accompanying the internal carotid arteries and their major branches represents the likely source. Supplying the basal ganglia, the lenticulostriate arteries are also surrounded and innervated by vasomotor fibers [21, 31]. Thrombosis and especially thromboembolism may at times evoke an intense local vasculitis (1) so that the accompanying autonomic nerves are injured, concurrent with infarction of the basal ganglia, and stimulated to aberrant proliferation into the healing infarct.

Acknowledgement

The authors express gratitude for competent assistance to Mr. Dale Gibson, HT (ASCP), Mrs. Marilyn Davis and Mrs. Elizabeth Ergueta.

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