Acta Neuropathol (Berl) (1987) 73:320–322

Acta Neuropathologica

Absence of subcommissural organ in the cerebral aqueduct of congenital hydrocephalus spontaneously occurring in MT/HokIdr mice

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Summary. The midbrains of pups with congenital hydrocephalus spontaneously occurring in MT/HokIdr mice were histologically examined. The subcommissural organ (SCO) and the posterior commissure were completely absent in the hydrocephalic brain. The cerebral aqueduct in the hydrocephalic brain was never completely stenosed, though it was somewhat narrowed in its middle region as compared with that in the normal brain. A possible interrelationship between an absence of SCO and a cause of congenital hydrocephalus is discussed.

Key words: Congenital hydrocephalus – Subcommissural organ – Cerebral aqueduct – MT/HokIdr mouse

Congenital hydrocephalus has occurred in many mammalian species including human beings. The pathogenetic mechanisms hitherto proposed for the congenital hydrocephalus can be roughly divided into three; an overproduction of cerebrospinal fluid (CSF) by the choroid plexus, a defect in the CFS absorption mechanism, and obstruction of the CSF flow in the cerebral ventricles. Numerous investigators have accepted stenosis of the cerebral aqueduct as a main cause of congenital hydrocephalus; however, the precise mechanism of aqueductal stenosis remains unclear. Some investigators have regarded aqueductal stenosis not as the cause of congenital hydrocephalus, but the result of cerebral ventricular pressure exerted by a developing hydrocephalus [1, 6, 8, 10, 14].

Recently, we examined the pathogenesis of congenital hydrocephalic rats produced by in utero X-irradiation, and suggested that the maldevelopment of the subcommissural organ (SCO) may be involved in the cause of aqueductal stenosis [11].

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MT/HokIdr mice were derived from the stock of an inbred strain maintained in our institute (Idr). Various congenital anomalies, such as exencephaly, hydrocephalus, cleft lip and palate, polydactyly of hindfoot, etc., have spontaneously occurred in this strain. Congenital hydrocephalus occurred at an incidence of about 1.2%, or in 18 of 1522 living pups, from December 1979 to July 1986. We examined these congenital hydrocephalic brains histologically, and found that the SCO has been completely absent at the anterior end of the cerebral aqueduct.

Materials and methods

Ten hydrocephalic and five normal pups were selected from the inbreeding stock of MT/HokIdr strain. Since the onset of cranial enlargement in affected pups occurs at varying days during the first few weeks of postnatal life, the age of sacrificed hydrocephalic mice ranged from postnatal day 7 to day 26. Normal pups were sacrificed at postnatal day 15 and 20.

They were anesthesized by ether, killed by a cardiac perfusion with 10% formalin, and their brains were fixed with Bodian II solution for 24 h. After dehydration with an ethanol series, they were embedded in paraffin wax. Coronal and sagittal sections were stained with hematoxylin and eosin before light microscopic examination.

Results

In the midbrain of a normal pup, the SCO, consisting of an elongated pseudostratified ependymal cell layer and a hypendymal layer containing glial cells, nerve fibers and vascular elements, was located at the anterior end of the cerebral aqueduct and lining the ventricular surface of the posterior commissure (Figs. 1A, 2A). In all the hydrocephalic brains examined, however, the SCO was completely absent, and the anterior end of the cerebral aqueduct was covered with a common, flattened ependymal cell layer (Figs. 1B, 2B). The posterior commissure was also completely absent in the hydrocephalic brain (Fig. 2B), although

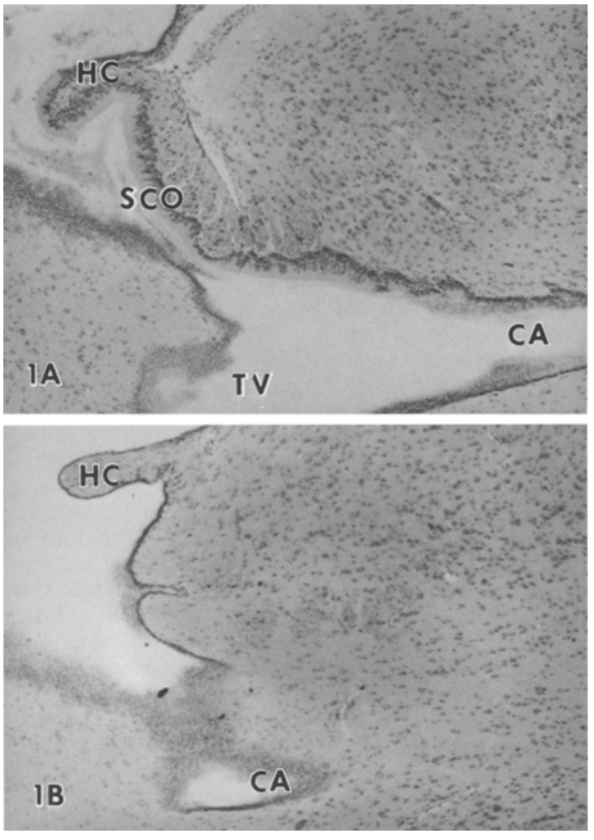

Fig. 1A, B. Sagittal section of the anterior end of cerebral aqueduct. **A** Normal (20-day-old); **B** hydrocephalus (25-day-old). Note the absence of subcommissural organ (*SCO*) in the hydrocephalic brain. *CA* Cerebral aqueduct; *HC* habenular commissure; *TV* third ventricle. × 58

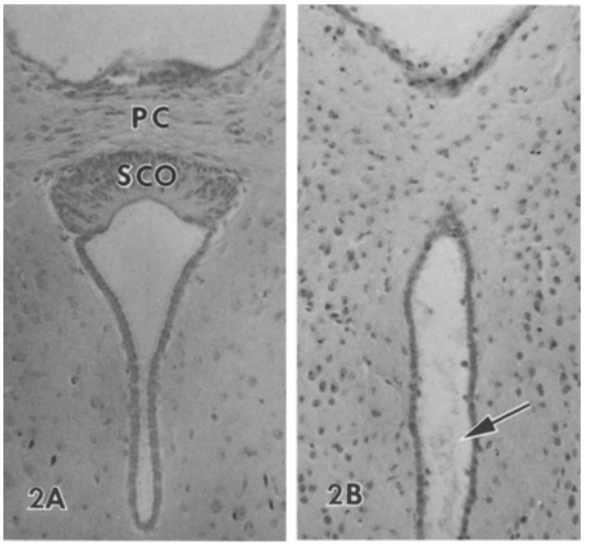

Fig. 2A, B. Coronal section of the anterior end of cerebral aqueduct. **A** Normal (20-day-old); **B** hydrocephalus (17-day-old). Note the absence of subcommissural organ (*SCO*) and posterior commissure (*PC*) in the hydrocephalic brain. *Arrow* indicates eosinophilic amorphous materials in the cerebral aqueduct of hydrocephalic brain. × 132

the habenular commissure was normally present (Fig. 1B). The cerebral aqueduct of the hydrocephalic brain was somewhat narrower in its middle region as compared with that in the normal brain, but never completely stenosed (Fig. 3A, B). No morphological changes were observed in the ependymal cell layer of the cerebral aqueduct either in hydrocephalic or normal brains (Fig. 3A, B). Eosinophilic amorphous materials were numerous throughout the cerebral aqueduct of hydrocephalic brain (Figs. 2B, 3B). These amorphous materials were only found in small amounts, if at all, in the cerebral aqueduct of normal brain.

Discussion

Owing to the low incidence of congenital hydrocephalus in MT/HokIdr mice, and also to the fact that the onset of cranial enlargement in hydrocephalic mice occurs in postnatal life, we could not examine an embryonic development of affected mice. Thus, it has remained uncertain whether the absence of SCO is a primary defect of affected mice or the result of degeneration of pre-existing SCO brought about by an increased CSF pressure exerted by a developing hydrocephalus. In the pathogenetic study of the congenital hydrocephalus experimentally induced in rats by in utero X-irradiation, however, we have shown that the anomaly of SCO is not a result of the hydrocephalic state, but a defect preceding the onset of enlargement of cerebral ventricles [11]. Overholser et al. [9] and Newberne [7] have also shown that the maldevelopment of SCO occurs in an early embryonic stage of congenital hydrocephalic rats, produced by feeding pregnant mothers on diets deficient in vitamin B_{12} or folic acid. These facts suggest that the absence of SCO in congenital hydrocephalic MT/HokIdr mice may be a primary defect and closely related to the cause of congenital hydrocephalus.

Initially described at the beginning of this century, the SCO has been the subject of extensive investigations in many vertebrate species; nevertheless, its specific function is still poorly understood [12, 16]. The SCO has been suggested to be involved in regulation of the water and electrolyte metabolism in body fluid [4]. The relationship between the SCO and the endocrine system has repeatedly been considered [3]. Some investigators have proposed that Reissner's fiber (RF), the secretory product of SCO, has a detoxifying function by binding certain biogenic

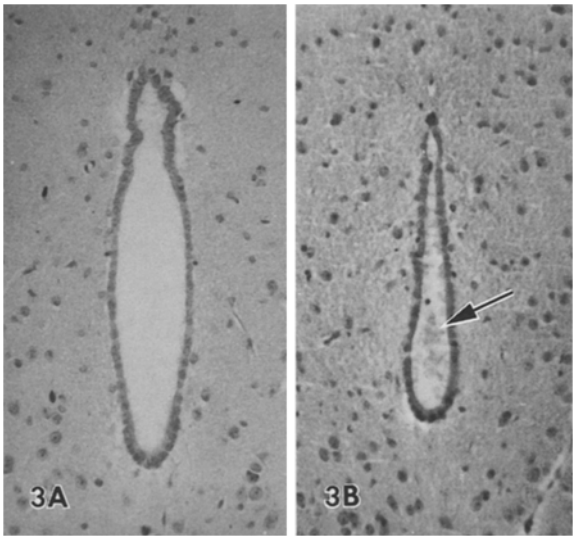

Fig. 3A, B. Coronal section of the middle region of cerebral aqueduct. **A** Normal (20-day-old); **B** hydrocephalus (14-day-old). Cerebral aqueduct in the hydrocephalic brain is somewhat narrower than in the normal brain. Numerous eosinophilic amorphous materials are noted in the cerebral aqueduct of hydrocephalic brain (*arrow*). ×160

amines in the CSF [5]. Diederen et al. [2] have also confirmed the binding capacity of RF with biogenic amines, and have proposed that the SCO and RF are involved in regulation of CSF composition. The cleaning capacity of RF by adhering erythrocytes and cellular debris in the CSF has also been suggested [13]. Woollam and Collins [15] have considered that the RF may be a mechanoreceptor of the CSF pressure, and the SCO may transmit this information to the circumventricular organs and the choroid plexus.

In the present study, the cerebral aqueduct of congenital hydrocephalic mice was never completely stenosed, but some amorphous materials were usually present in it. This fact suggests that the SCO, and its product RF, have a CSF cleaning function in the cerebral aqueduct, and their absence cause an accumulation of certain wastes in the cerebral aqueduct and an obstruction of CSF flow. At present, this is merely one of the possible interrelationships between the absence of SCO and the cause of congenital hydrocephalus derived from the above-mentioned proposed functions of the SCO. The present study may offer some new clues to clarify not only the precise mechanism of congenital hydrocephalus but also the real function of the SCO.

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Received December 16, 1986/Accepted January 16, 1987