Dandy-Walker Like Malformation in a Fischer-344 Rat

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ABSTRACT

A spontaneous cerebellar malformation was found in a 32-day-old male Fischer 344 rat. The cerebellar malformation was composed of a vermis defect and markedly dilated fourth ventricle. The cerebellar hemispheres were separated, with the left hemisphere being smaller than the right one. Degenerative/inflammatory lesions consisting of macrophage/lymphocyte infiltration, spheroidal calcium depositions, and astrocytic gliosis were seen adjacent to the cerebral aqueduct. Abnormally arranged hyperplastic ependymal cells were observed beneath the fourth ventricle in the medulla oblongata. The gross findings of the present case resemble those of the human Dandy-Walker malformation. While a precise mechanism remains to be elucidated, degenerative/inflammatory lesions in the present rat may be involved in the pathogenesis of this malformation.

Keywords. Cerebellar malformation; vermis defect; fourth ventricle; histopathology; scar lesions; spontaneous

INTRODUCTION

Dandy-Walker malformation is a well-known cerebellar malformation, characterized by agenesis of the vermis, cystic dilatation of the fourth ventricle, and enlargement of the posterior fossa (4). Recently, developmental arrest of the hindbrain was proposed for the pathogenesis of the Dandy-Walker malformation (4). However, the precise pathogenesis for the Dandy-Walker malformation remains to be elucidated.

In rats, spontaneous developmental abnormalities of the central nervous system are extremely rare (14). We found a spontaneous cerebellar malformation in a Fischer 344 (F344) rat, resembling the human Dandy-Walker malformation. Histopathology revealed that the affected rat had old degenerative/inflammatory lesions in the brainstem that may be associated with the pathogenesis for the cerebellar malformation. The present paper describes the macroscopic and histopathological findings of the rat cerebellar malformation.

MATERIALS AND METHODS

Pairs of F344 (Crl: F344) rats were purchased from Charles River Japan Inc and mated to obtain the neonates for another study. These animals were kept in a clear polycarbonate case in a room conditioned at 22 ± 4°C and on a 12-hour light–dark cycle. All animals were given a standard commercial laboratory food (MF; Oriental Yeast Co Ltd, Tokyo, Japan) and tap water ad libitum.

We found a small-sized male neonate in a litter (7 male and 2 female) at 2 weeks of age. The growth retardation gradually became conspicuous with age. No neurological abnormality was observed clinically. The rat was euthanized with ether at 32 days of age and subjected to necropsy.

The removed organs were fixed in 10% neutral-buffered formalin and embedded in paraffin. Histologic sections from brain and visceral organs were stained with hematoxylin and eosin (H&E). Sections were also stained with Goodpasture-Gram stain, Zhiel-Neelsen, Grocott’s methenamine silver, and periodic acid–Schiff reaction. Selected sections were processed for glial fibrillary acidic protein (GFAP, Dako, Denmark, 1:500), keratin (Dako, prediluted), and ED-1 (Chemicon, 1:400) immunohistochemistry. Briefly, the deparaffinized sections were treated for 0.3% hydrogen peroxide and masking was carried out with 5% skim milk. The sections were incubated with the primary antibodies and then processed for labeled streptavidin biotin peroxidase procedure (Dako LSAB kit, Dako). Immunoreactivities were visualized by diaminobenzidine tetrachloride.

RESULTS

Necropsy revealed a defect of the cerebellar vermis and dilatation of the fourth ventricle (Figure 1). The cerebellar hemispheres were separated, with the left hemisphere being smaller than right one (Figures 1 and 2). Because of the lack of the vermis and the dilated fourth...
vitreous, the midbrain and the cerebral aqueduct were seen from the dorsal view of the brain. Histologically, the cerebellar vermis was completely absent. The cerebellar nuclei were confirmed in both sides of the cerebellar hemispheres. The laminar structure of cerebellum was well preserved throughout in both remaining hemispheres. No structural abnormality was found in the cerebrum, brain stem, and ventricle system of the cerebrum.

Small focal infiltrates of lymphocytes and macrophages (including hemosiderin-laden cells) and occasional depositions of spheroidal calcium were detected around the cerebral aqueduct in the colliculus caudalis (Figure 3a, b). Hyperplastic and hypertrophic GFAP-positive astrocytes were seen around the degenerative/inflammatory lesions (Figure 3c, d). No infectious agent such as bacteria and fungus was detected by special stains. Neither obstruction nor stenosis of the aqueduct was observed by histopathological examination using the serially sectioned slides. There was no choroid plexus in the midportion of the fourth ventricle, whereas the lateral choroid plexus was observed. Hyperplasia of abnormally arranged ependymal cells with infiltration of hemosiderin-laden macrophages that were clearly demonstrated by ED-1 immunohistochemistry was found beneath the fourth ventricle in the medulla oblongata (Figure 4). The hyperplastic ependymal cells were positively stained with keratin immunohistochemistry (data not shown). Hemosiderin-laden macrophages were also scattered around the dilated fourth ventricle in the other part of the medulla oblongata. No degenerative/inflammatory lesions were found in the cerebrum.

DISCUSSION

In humans, various malformation syndromes of the cerebellar vermis agenesis have been classified (1, 4). The Dandy-Walker malformation is the best known disease with vermis agenesis (1, 4). There are 3 essential diagnostic criteria for Dandy-Walker syndrome: agenesis of the vermis, cystic dilatation of the fourth ventricle, and enlargement of the posterior fossa (4). The gross findings in the present rat coincided with these criteria. Thus, we diagnosed the present case as Dandy-Walker syndrome.

In animals, a few reports of the cerebellar vermis defect have been recorded in dogs (3, 6, 10, 13), in sheep (7, 10-12), in calves (5, 8), and in a foal (2). Most of these cases were referred to as Dandy-Walker malformations. Congenital brain malformations resembling Dandy-Walker syndrome have been induced in rats by 6-aminonicotinamide injection during the prenatal period (9, 15). To the best of our knowledge, however, the present case is the first spontaneous Dandy-Walker malformation in rats.

Several theories exist on the pathogenesis of Dandy-Walker malformation. Early speculation was foraminal atresia during cerebellogenesis (4). However, the fourth ventricle foramina are usually patent, and embryologically the foramina become patent only after the paired cerebellar primordia fuse and the anterior membranous area becomes incorporated into the vermis (4). An alternative hypothesis is that developmental arrest of the hindbrain may play a role in the pathogenesis (4).
FIGURE 4.—Abnormally arranged hyperplastic ependymal cells are observed beneath the fourth ventricle in the medulla oblongata. a) Low-power magnification of focal hyperplasia of ependymal cells. HE. X 10. b) High-power magnification of ependymal hyperplasia. HE. X200. c) Scattered ED-1-positive macrophages in the lesion. X200.

The present case had degenerative/inflammatory lesions around the cerebral aqueduct and hyperplastic ependymal cells in the fourth ventricle. Based on histological findings, these changes were considered to be old lesions. Neither atresia nor stenosis of the passage of cerebrospinal fluid was seen. In humans, etiologic arrests for the Dandy-Walker malformation may occur in the early stage of gestation (4, 9).

Special stains for bacteria, fungus, and protozoa failed to detect any infectious agent. However, this result could not rule out the possibility of infectious etiology during the early stage of gestation. It may be considered that a multifocal inflammatory lesion could destroy primordia of the cerebellar vermis, resulting in the vermis defect in the present rat. While a precise mechanism underlying the vermis defect and cystic dilatation of the fourth ventricle remains to be elucidated, this degenerative/inflammatory process may be involved in the pathogenesis of the present anomaly.

REFERENCES