Simultaneous clinical manifestation of subependymoma of the fourth ventricle in identical twins

Case report

Peter Clarenbach, M.D., Paul Kleihues, M.D., Eberhard Metzel, M.D., and Johannes Dichgans, M.D.

Departments of Neurology, Neuropathology, and Neurosurgery, University of Freiburg, Freiburg, West Germany

At the age of 22 years, identical twin brothers simultaneously developed symptoms of intracranial pressure. Radiological investigation revealed cerebellar midline tumors with occlusive hydrocephalus of the third and lateral ventricles. At operation, subependymomas with identical histological features were found in the fourth ventricle in both twins. This is the first report of subependymomas in identical twins. The clinical data suggest that this tumor type is of maldevelopmental origin.

Key Words • twins • subependymoma • fourth ventricle • maldevelopment • tumorigenesis • congenital malformation

The occurrence of brain tumors in siblings and twins, which has been reported frequently since Besold’s first observation of third-ventricle tumors in two sisters, suggests a prenatal and possibly genetically determined origin. In the past, such cases have also been taken as evidence for the validity of the Cohnheim-Ribbert theory postulating the persistence and subsequent dedifferentiation of multipotential embryonic cells as a common principle of tumor origin. We are reporting the simultaneous development of subependymomas of the fourth ventricle in 22-year-old identical twin brothers. To our knowledge, this is the first time that the familial occurrence of this tumor type has been reported, and the first case of simultaneous manifestation of a brain tumor in adult twins.

Case Reports

The patients (Cases 1 and 2) were born in 1953 after a normal pregnancy, labor, and delivery. Two placentae and three allantoic membranes were found. Uniovularity was confirmed by the following concordant serological data: A2, Ms5 k, Fy a+, b+ 1k a+, b- ccddee Hp2-1 Gc2-1 Gm(+1, -2, b+) Inv-1 SEP (AB) PGMI-1 AKl-1 ADAl-1 T1(CC) C3(FS) GPT2-2 6-PGD (AA) EsD1-1 GLO2-2.

The family history revealed no parental consanguinity. Their mother, now 66 years old, shows no neurological symptoms. Their father died of myocardial infarction at the age of 40 years. So far, no neoplastic diseases have occurred in the older brother or in the two older sisters. The twins developed normally until March, 1975, when both brothers, Case 2 more than Case 1, complained of early vomiting, disturbances of balance, and pulsating headaches.

Examination. Upon admission to our clinic in December, 1975, Case 2 displayed papilledema of about 3 diopters in both eyes, his visual acuity was reduced to 0.7 and 0.6, respectively, and his visual field showed impairment of the inferior segments with enlargement of the blind spot. Case 1, investigated upon our request, showed no disturbance of vision and only minimal papilledema.

Both brothers showed reduced pupillary light reflexes, but prompt contractions on convergence. The retinal fundus had a particularly red appearance in both brothers. The vestibulo-oculomotor system...
Fig. 1. Preoperative computerized tomography scans of Case 1 (left) and Case 2 (right), showing the tumor of the fourth ventricle (arrows).

Fig. 2. Preoperative ventriculography of Case 1 (left) and Case 2 (right), showing an enlargement of the third ventricle and the occlusion of the fourth ventricle by the tumor (arrows).
Subependymoma in identical twins

showed the following major disturbances in both twins: approximately symmetrical impairment of fixation suppression of vestibulo-ocular reflexes, horizontal gaze nystagmus, cogwheeled smooth pursuit, impaired optokinetic nystagmus, and central positional nystagmus. In addition, Case 2 showed spontaneous nystagmus to the left and directional preponderance to the left at rotation. Case 2, again more than Case 1, showed cerebellar ataxia of posture and gait. Otherwise motor performance was normal and cutaneous sensitivity undisturbed.

In both patients angiography and computerized tomography (CT) scans (Fig. 1) showed a tumor in the posterior fossa extending from the midline into the right cerebellar hemisphere, and a pronounced occlusive hydrocephalus. Ventriculography indicated an intraventricular growth in the fourth ventricle in both cases (Fig. 2).

**Operations.** At operation on Case 2 (January 13, 1976), a midline tumor was found which displaced both cerebellar hemispheres laterally and the lower vermis cranially; caudally it reached the upper edge of the C-2 vertebra. It was well demarcated from the medulla oblongata, which was, however, depressed. The cerebellar tonsils, the corpus restiforme of the brain stem, and the floor of the fourth ventricle were infiltrated on the right side.

A similar situation was found during the surgical treatment of Case 1 (January 26, 1976). A midline tumor of the posterior fossa reached down to the C-2 vertebra, infiltrating the right corpus restiforme, the cerebral peduncles, and at several separate points in the medulla oblongata. In both patients subtotal resection was performed, followed by placement of atrioventricular shunts.

**Pathological Examination.** Microscopic examination of the tumor led to the diagnosis of subependymomas with largely identical histopathological features. Isomorphous glial cells with rounded or slightly elongated nuclei were embedded in a dense fibrillary matrix. The cytoplasm of the tumor cells was usually small and difficult to distinguish. Mitoses were not observed in either of the two cases. Often, focal aggregation of tumor cell clusters were surrounded by large non-cellular fibrillary areas (Fig. 3 left). Staining with phosphotungstic acid hematoxylin revealed the presence of a dense network of glial fibers (Fig. 3 right). A search for blepharoplasts in the perikaryon of the tumor cells was unsuccessful. In both cases there was a clear demarcation of the
TABLE 1

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Age of Twins at Diagnosis or Death</th>
<th>Type of Tumor</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joughin, 1928</td>
<td>32 yrs glioma rt hemisphere</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 yrs glioma lt hemisphere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoppe, 1952</td>
<td>40 yrs meningioma lt sphenoidal wing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53 yrs glioblastoma posterior central region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zülich, 1956</td>
<td>3 mos medulloblastoma cerebellar midline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mos medulloblastoma cerebellar midline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Griepentrog &amp; Pauly, 1957</td>
<td>8 wks medulloblastoma fourth ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 wks medulloblastoma fourth ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kjellin, et al., 1960</td>
<td>38 yrs astrocytoma rt temporal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 yrs astrocytoma rt temporal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brady, 1962</td>
<td>14 yrs spongioblastoma fourth ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 yrs spongioblastoma fourth ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fairburn &amp; Urich, 1971</td>
<td>3 yrs mixed glioma cerebellum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 yrs mixed glioma lt parietal hemisphere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedzimir, et al., 1973</td>
<td>9 yrs meningioma rt frontal falx cerebri</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 yrs meningioma tuberculum sellae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarenbach, et al., 1979</td>
<td>22 yrs subependymoma fourth ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 yrs subependymoma fourth ventricle</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Case reports in which the uni-ovularity of the twins can be regarded as proved, and histological diagnosis has been obtained.

Discussion

The prenatal origin of certain brain tumors was first suggested by Müller in 1938, and has since become the basis of theories of the pathogenesis of tumors of the central nervous system. Case reports of familial brain tumors are not sufficient to support these theories. Data from unselected series are controversial. Only familial tumors occurring concurrently in identical twins allow us to assume a prenatal origin and to discuss pathogenetic mechanisms. Nine such cases have been described (Table 1), including the present case. The feature of particular interest in our case is the identical time course of tumor growth, suggesting that not only histology and topology but also growth dynamics were prenatally determined.

The characteristic histology of this type of tumor (namely, clusters of glial cells in a dense matrix of glial fibers) was present in both of our cases. Subependymomas originate, as in the present cases, most frequently from the subependymal region of the fourth ventricle, and are considered to be benign and slow-growing, with relatively sharp demarcation from the adjacent brain tissue. There has been some dispute as to whether subependymomas consist of neoplastic ependymal cells or subependymal astrocytes. Recent electron microscopic and tissue culture studies support the original interpretation, that is, that subependymomas are of mixed composition and originate from the pluripotential cells of the subependymal layer.

The following pathogenetic mechanisms should be considered in this report of familial brain tumors. Tumors could be the result of autosomal recessive inheritance, which is accepted as the origin for the phacomatoses, which include von Recklinghausen's neurofibromatosis, Bourneville's tuberousclerosis, von Hippel-Lindau's syndrome, and neurocutaneous melanosis. The family history of our patients, however, does not show any evidence of inheritance.
Subependymoma in identical twins

In laboratory animals, tumors of the nervous system have been selectively induced transplacentally by a wide range of chemical carcinogens. However, tumors induced by chemicals are usually highly malignant. This is also true for the only tumor type known to date to be transplacentally induced in man, namely, vaginal carcinomas in girls whose mothers were treated with diethylstilbestrol during pregnancy.

Finally, maldevelopmental origin of human brain tumors has to be considered. Congenital tumors of this type include, besides the above-mentioned inherited phacomatoses, teratomas, dermoid and epidermoid cysts, cholesteatomas, and related hamartomas. These tumors are thought to originate from maldevelopmental ectopias, and are usually slow-growing and of benign character.

This theory correlates well with the main features of the tumors described in the present report, that is, the midline localization in the fourth ventricle, the non-proliferative histological aspect, and the favorable course following subtotal resection without evidence of recurrence within 2 years.

In conclusion, our observation suggests a prenatal origin of subependymoma, and favors the view that this type of tumor is of maldevelopmental origin.

Acknowledgment

We wish to thank Dr. Christoph Ostertag, Department of Neurosurgery, University of Freiburg, for providing the computerized tomography scans.

References

27. van der Wiel HJ: Biologie und Pathologie der Hirn- Geschwülste. Berlin: August Hirschwald, 1878

Address reprint requests to: Peter Clarenbach, M.D., Department of Neurology, University of Freiburg, Freiburg, West Germany.