HETEROTOPIC GLIAL NESTS IN THE SUBARACHNOID SPACE: HISTOPATHOLOGIC CHARACTERISTICS, MODE OF ORIGIN AND RELATION TO MENINGEAL GLIOMAS*

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The occurrence, in the subarachnoid space, of heterotopic nests composed of neuroglial tissue has been recognized since the original report, in 1907, of a case by Wolbach (1) whose description of heterotopic glial nests was substantiated by O. T. Bailey (2) in 1936. The essential anatomic features of the discrete structures reported by these authors are: 1) they are composed of mature astrocytes whose nuclei tend to be grouped in the center of the nest, 2) they are invested by a delicate connective tissue sheath, 3) the circumferential neuroglial fibers are arranged in an arched manner similar to the marginal glia of the spinal cord, and 4) they may contain ependymal-lined canals.

The origin of these heterotopic glial nests has generally been ascribed to embryonic neurogenic elements which mature after wandering into the subarachnoid space, this hypothesis having been supported by Wolbach (1), O. T. Bailey (2) and P. Bailey and Bucy (3). Oberling (4), however, has suggested that glial tissue in the meninges is derived from meningoblasts which are capable of differentiation into glial elements. These hypotheses have not adequately accounted for the presence of a sheath about the neuroglial nests, the central distribution of nuclei within the nests, nor the architectural arrangement of glial fibers.

Gliomatous tumors in the meninges have been reported by many investigators (2, 4–8). O. T. Bailey has said that primary gliomas of the meninges make up a definite group of meningeal tumors, and has postulated that the neoplasms arise from heterotopic glial tissue in the subarachnoid space (2). This explanation for the origin of primary extramedullary gliomas, without any apparent attachment to the brain or spinal cord, has been supported by reports of other investigators (5, 8–10).

MATERIALS AND METHODS

In this investigation we carried out a pathologic evaluation of 50 cases in which heterotopic glial nests were demonstrated in the subarachnoid space. The tissues in 50 cases, which individually demonstrated from 1 to more than 100 heterotopic glial nests, were studied histologically, and the histopathologic characteristics of the heterotopic structures.

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and of the entire central nervous system were recorded. In addition, the routine microscopic sections of the central nervous system obtained in 100 consecutive necropsies were surveyed for neuroglial heterotopia; only one instance of glial heterotopia was noted in this “control group” of cases. An additional group of 80 cases of various congenital malformations of the brain and spinal cord was studied. Twenty of these latter cases demonstrated the presence of heterotopic glial nests in the subarachnoid space. The principal stains used were the hematoxylin and eosin, and the Mallory phosphotungstic acid hematoxylin stains. Occasionally, the cresyl violet, Orlandi, van Gieson and Cajal gold sublimate stains were employed.

A primary aspect of this study was an inquiry into the origin of extramedullary heterotopic glial structures. All the histologic sections were examined for evidence of faulty migration or maturation of embryonic neural elements, and signs of cellular activity and mitotic figures were searched for, in an attempt to corroborate the theory that such heterotopic structures arise from cell rests. In addition, segments of the neuraxis in 15 cases which demonstrated subarachnoid heterotopic glial nests were studied by means of serial sections to determine whether these nests might originate from the neuraxis by a “pinching off” process. The serial sections were cut every 8 microns, and every fifth section was stained and examined. These sections were stained either with hematoxylin and eosin or by the Mallory phosphotungstic acid hematoxylin technic.

**RESULTS**

**Gross Anatomic Characteristics of the Heterotopic Tissue.** The presence of subarachnoid nests of glial tissue was seldom detected grossly in our series of cases, although in the original case reported by Wolbach there were many minute, barely visible, translucent elevations, giving a finely sanded appearance to the pia-arachnoid over the dorsal surface of the cervical spinal cord (1). In only one instance in our series were small tubercle-like masses, which were subsequently noted microscopically to be heterotopic glial structures, observed in the meninges. In one case a small neuroglial mass 3 mm. in diameter was observed in the arachnoid over the posterior surface of the medulla. In 12 cases the leptomeninges over the brain stem appeared adherent to each other and to the brain, and the arachnoid appeared thickened and opaque. In each of these 12 cases microscopic examination revealed glial nests in the subarachnoid space to be responsible for the leptomeningeal adhesions. In the remaining 36 cases there was no gross evidence of glial tissue in the subarachnoid space.

**Position of the Heterotopic Islands.** The most frequently affected level of the neuraxis was the medulla oblongata, there being heterotopic structures in the subarachnoid space at this level in 53 per cent of the cases in our series. The second most commonly affected site was the lumbar sacral region of the spinal cord, the subarachnoid space of which contained glial nests in 20 per cent of the 50 cases. The relative frequency of location of extramedullary neuroglial nests is noted in Figure 1. Subarachnoid glial nests were present at two or more levels of the neuraxis in 30 per cent of cases. There was equal distribution over the four quadrants of the brain stem and spinal cord as seen in cross section. In 10 per cent of cases, the glial islands lay in close relationship to dorsal or ventral nerve roots, the most frequently involved single root being that of the twelfth cranial nerve. In many instances the glial nests in the subarachnoid space lay adjacent to, and in close relationship with, penetrating blood vessels.
Fig. 1. Relative frequency of location of subarachnoid heterotopic glial structures. The total exceeds 100 per cent due to the occurrence of nests at multiple levels in several cases.

Size and Fiber Architecture. The discrete glial nests varied from less than 0.1 mm. to 3.0 mm. in size. There were several subarachnoid glial masses, less insular in nature, which were considerably larger. These latter masses were con-
sidered analogous to the benign meningeal gliosis described by Oberling (11, 12) rather than to the heterotopia of Wolbach.

These glial nests assumed four types of architectural pattern. The most common type was that described by Wolbach (1). In this type the islands are round or oval, with a central mass of disorganized glial fibers in which astrocytic nuclei are grouped and which is surrounded by a circumferential layer of isomorphic glial fibers (figs. 2a and b).

A second architectural variant was one in which there was no marginal layer of isomorphic glial fibers, with generalized distribution of the astrocytic nuclei. The third type was composed of sheets of glial fibers of varying shape, such as oblong, square or flame-shaped (fig. 3). In several instances large masses of glia, forming a fibrillary reticular network, were seen in the subarachnoid space, constituting the fourth variant of isolated extramedullary glial nests.

**Cellular Inclusions of the Heterotopic Nests.** The cell type which predominates is the mature astrocyte. Immature neurogenic elements were not seen in any of our cases. In 3 instances ganglion cells were present in or adjacent to glial islands. Ependymal-cell inclusions were noted in more than half of these cases; in several
instances they were arranged in a manner simulating the central canal of the spinal cord (fig. 4). Oligodendrocytes were frequently present, and several islands contained small round cells similar to those in the granular layer of the cerebellum (fig. 5).

*Presence of a Sheath About the Glial Islands.* The neuroglial nests described by Wolbach were “all invested with a very delicate sheath of connective tissue derived from the pia or arachnoid (1).” O. T. Bailey stated that the neuroglial

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**Fig. 3.** Flame-shaped heterotopic glial structure in the subarachnoid space. This type of nest does not demonstrate a pial sheath (hematoxylin and eosin stain ×165).

**Fig. 4.** Extramedullary glial island containing a central canal lined by ependymocytes (Mallory phosphotungstic acid hematoxylin stain ×100).
nests observed by him lay wholly within the subarachnoid space, and were
surmounted by connective tissue below and by arachnoid cells above (2). Free­
man reported a heterotopic island of gray matter in the meninges of the pons,
and described a distinct meningeal sheath about the heterotopic tissues (13).

Fifty per cent of the heterotopic islands examined in our investigation were
surrounded by a thin delicate membrane which in some instances was similar
to pia mater and in others simulated arachnoid. In a few instances a double­
layered sheath was present, in which case there was both a pial and an arach­
noidal component in the membrane. All the type 1 islands, that is, those which
were round or ovoid with an arched marginal layer of glia, were invested with a
pial sheath or with a combined pial-arachnoidal membrane. The type 2 islands

Fig. 5. Granular cell inclusions in glial heterotopia observed in the subarachnoid space
adjacent to the cerebellum (hematoxylin and eosin stain X280).

demonstrated either an arachnoidal capsule or none at all. The remaining archi­
tectural variants never possessed a sheath.

Mode of Origin of Subarachnoid Heterotopic Glial Nests. Detailed microscopic
study of several hundred individual subarachnoid heterotopic glial structures
and of the representative sections of the brain and spinal cord in each case
provided no evidence to suggest a wandering of immature cells into the subarach­
noid space, with subsequent maturation of glial nests. The heterotopic islands
were not observed to contain spongioblasts or ependymoblasts. Not a single
mitotic figure was observed in any of the nuclei present in these nests.

More than 100 individual glial islands, in 15 cases, were examined by means of
serial sections. This study proved conclusively, contrary to previous hypotheses
(1–4), that these glial islands originate as protrusions from the brain or spinal
FIG. 6. Formation of a glial nest traced by serial sections (hematoxylin and eosin X50). 
a. Early curling of the marginal glia with evagination of the pia mater. b. Formation of the 
same glial protrusion further advanced. c. "Pinching off" of curled-up glial peninsula. d. 
Glial nest appearing to lie completely free in the subarachnoid space and surrounded by a 
pial sheath.

cord, which are "pinched off" the neuraxis and come to lie in the subarachnoid 
space. The formation of glial nests occurs by one of three different mechanisms, 
each producing a characteristic type of heterotopic structure.

FIG. 7. Formation of subarachnoid glial nests by curling up of marginal glia. a. Glial 
peninsula covered by pia. b. The same glial nest in cross section, appearing to lie free in 
the subarachnoid space. Many nests do become detached from the neuraxis. c. Architectural 
characteristics of a heterotopic nest formed by this mechanism; a pial sheath, centrally 
grouped nuclei, and isomorphic circumferential fibers are demonstrated.
The most common mechanism is a piling up of subpial, marginal glia, with a curling of this glia on itself. This results in a peninsula of glia, covered by pia mater, with isomorphic circumferential fibers and a central collection of astrocytic nuclei. Such a mechanism accounts for all the histologic characteristics of the type 1, or Wolbach type, of glial nest. The formation of such a heterotopic structure is pictured in Figures 6 and 7.

Heterotopic bodies may also be formed by the streaming of marginal glia through a pre-existent pial defect (figs. 8 and 9) or by direct invasion of the leptomeninges (fig. 10) even though no pial defect exists. The nature of their development by protrusion through a pial defect or by invasion of the leptomeninges precludes the possibility of formation of a pial sheath about such islands.

Fig. 8. Formation of a subarachnoid glial nest by streaming of glia through a pial defect. Note absence of pial sheath and scattered distribution of astrocytic nuclei (hematoxylin and eosin stain X320).

Relation of Subarachnoid Heterotopic Glial Nests to the Disease States in Which They Occur. It is beyond the scope of this study to describe all the neuropathologic conditions with which glial heterotopia is associated. The absolute incidence of such heterotopia cannot be determined due to the impossibility of studying a large number of consecutive necropsy specimens of brain and spinal cord by serial section. However, the routine preparations in 100 consecutive cases were examined, and in only 1 case were heterotopic glial nests demonstrated. This incidence of 1 per cent contrasts markedly with an incidence of 25 per cent that occurred in 80 cases of congenital malformation of the nervous system. The principal cause of death in 16, or 32 per cent, of the 50 cases in which subarachnoid heterotopic glial nests were demonstrated was spina bifida with attendant complications. Congenital hydrocephalus was the cause of death in 7, or 14 per cent, of the cases in the entire series, while syringomyelia and prematurity of birth each accounted for death in 4 cases.
In 38, or 76 per cent, of the 50 cases in the series congenital anomalies of the nervous system were demonstrated; spina bifida, congenital hydrocephalus, and
syringomyelia and hydromyelia (figs. 11 and 12) being the most common anomalies present. It is of interest to compare the neurologic anomalies in which glial heterotopia was noted with those in which marked abnormality of ependymal-cell maturation was observed. In another study an analysis of 15 cases in which major, non-neoplastic ependymal-cell abnormalities were observed re-

Fig. 11a. Subarachnoid nests of glia in a case of syringobulbia. The irregular, streaming appearance of these heterotopic structures is characteristic of that found in cases of syringomyelia and syringobulbia, in contrast to the type pictured in Figures 2 and 3, which is most frequently observed in cases of spina bifida (MH X4). b. Two of the subarachnoid nests shown in a. Note absence of pial sheath, and distribution of nuclei throughout the nest (MH X30).
revealed 7 instances of premature stillbirth, in 3 of which the fetuses were anencephalic monsters (14). The cyto-architecture in cases in which markedly abnormal ependymal cells were demonstrated was more disorganized than that seen in the present series of cases and immature neural elements were more frequently observed in the former group.

Although in 27, or 54 per cent, of the 50 cases in this study pathologic evidence of increased intracranial pressure was demonstrated, it appears that such increased pressure is incidental to the lesions predisposing to glial heterotopia, and is not causally related to the glial protrusions. It is the nature of the intra-

Fig. 12a. Glial island in the subarachnoid space in a case of hydromyelia (hematoxylin and eosin ×6). b. Subarachnoid glial island pictured in a. Note the extrapial situation of this nest, and the absence of an encapsulating sheath (hematoxylin and eosin stain ×45).
medullary gliosis, rather than the status of dynamics of the cerebrospinal fluid, which results in peninsular glial protrusions into the subarachnoid space. A luxuriant diffuse gliosis was present throughout the brain and spinal cord in the majority of cases in which glial heterotopia was demonstrated, this gliosis being more active in the subpial marginal area. This subpial gliosis is particularly abundant in cases of spina bifida, and pathologic examination of the nervous system in 34 cases of spina bifida revealed that in 16, or 47 per cent, subarachnoid glial nests were present. The margin of the neuraxis often demonstrates a peculiar “scalloping” of the circumference in such cases (fig. 13). Leveuf (15) and Fischer (16) also have observed glial heterotopia in cases of spina bifida. The latter author also noted the “scalloping” of the margin of the brain stem and spinal cord in such cases.

**Fig. 13.** “Scallop” of the periphery of the medulla oblongata. This finding is noted frequently in cases of spina bifida and is often associated with subarachnoid glial heterotopias (hematoxylin and eosin stain X165).

Relation of Subarachnoid Heterotopic Glial Nests to Meningeal Gliomas. Primary meningeal gliomas have been reported by Cushing and Eisenhardt (6), O. T. Bailey (2), and others (5, 8). Heterotopic or extramedullary gliomas have been reported in other sites, particularly in the nasal region (17–21) and over the sacrum (22). Those authors who discussed the origin of meningeal gliomas universally mentioned the likelihood that heterotopic glial structures were the source for such growths (2, 5, 8, 9, 10). Roussy, Cornil and Leroux (8) also offered, as an alternative hypothesis, the possibility that meningeal gliomas were derived from the arachnoid itself. However, the latter theory has not been widely accepted in this country inasmuch as Oberling’s contention that neuroglial elements are differentiated in the meninges from bipotential meningoblasts has not been corroborated histologically or embryologically.

A study of 15 cases of primary extramedullary spinal gliomas (23) corroborated the thesis that heterotopic gliomas arise from heterotopic glial nests. The
evidence which the last-mentioned study produced in favor of this hypothesis is summarized briefly as follows: 1. There was no apparent attachment of any extramedullary tumors of the central nervous system. 2. There was no evidence of a primary neoplastic process within the brain or spinal cord in any of the cases. 3. Many of the tumors were encapsulated by a sheath similar to the leptomeningeal capsule encountered in glial heterotopia. 4. Sixty-seven per cent of the extramedullary gliomas were present in the lumbosacral region. This frequency is strikingly similar to the frequency with which epidermoid tumors (24) and heterotopic ganglion cells (25) are located in the lumbosacral region. The origin of epidermoid tumors from cutaneous tissue "pinching off" by the neural tube cannot be doubted. Moreover, Humphrey said that the presence of heterotopic sensory ganglion cells is accounted for by a "pinch off" of neural crest primordium as the neural folds close (25). The origin of gliomatous neoplasms from heterotopic glial tissue similarly "pinched off" from the neural tube is held likely. 5. Twenty per cent of heterotopic gliomas demonstrated roentgenologic evidence of spina bifida occulta. Other congenital anomalies such as clubfoot, undescended testes and spondylolysthesis were also observed. The frequent association of glial heterotopia with congenital anomalies has been pointed out earlier in the present report. 6. The histologic characteristics of the extramedullary gliomas were strikingly similar to those of heterotopic glial bodies.

**SUMMARY AND CONCLUSIONS**

Small islands, nests, or peninsulas of glial tissue may be present within the subarachnoid space of human subjects. The occurrence of these nests has been called "glial heterotopia."

These heterotopic structures are rarely observable grossly as small tubercle-like granules over the leptomeninges. More commonly, however, the presence of heterotopic glial tissue in the subarachnoid space results in an opaque thickening of the leptomeninges, very often simulating a picture of a chronic adhesive arachnoiditis. In approximately 80 per cent of cases the presence of subarachnoid heterotopic glial tissue cannot be detected by gross examination of the nervous system.

The most frequent site of occurrence of subarachnoid heterotopic glial tissues is at the level of the medulla oblongata. The second most commonly affected site is at the lumbosacral level of the spinal cord.

Neuroglial nests were found to demonstrate four distinct architectural patterns, the most common being that originally reported by Wolbach. This type consists of a glial island enclosed in a pial sheath. Astrocytic nuclei are grouped centrally and the circumferential glial fibers run isomorphically in an arched manner similar to that of the subpial marginal glia of the spinal cord.

Subarachnoid heterotopic glial structures are formed by the protrusion of mature glia from the neuraxis. In some instances these glial protrusions are "pinched off" and come to lie free in the subarachnoid space or, rarely, in the extraspinal tissues.
It is likely that primary extramedullary gliomas arise from neoplastic activity in extramedullary heterotopic glial tissue.

REFERENCES