CHAPTER 1

INTRODUCTION AND PURPOSE OF THIS THESIS

HISTORY

Harvey Cushing in 1931 described his experience with 76 treated cerebellar astrocytoma-like tumors and was the first to separate this group of tumors from other gliomas on the basis of 4 specific properties he had observed (1). The properties of these tumors were a cerebellar localization, frequently a cystic appearance, occurrence at a young age, and most important, a very good prognosis for the patient. Most of the cystic lesions of the cerebellum were previously referred to as "gliomatous cysts". It was Bergstrand in 1932 who first described the specific histologic appearance of these prognostic favorable lesions (2). He found that many of the cells in these tumors were uni- or bipolar spongioblasts, reminiscent of cells found during the late embryonal stage of development. Therefore, he proposed the term "gliocytoma embryonale" for these tumors. He also suggested that these lesions were congenital malformations and considered them to be hamartomas. Bucy and Gustafson could not support this theory and stated that the cerebellar astrocytoma is a neoplastic entity (3). Furthermore, they drew attention to the typical hyaline bodies so often found in these lesions and called them "Rosenthal fibers". Zülch stressed the fundamental difference in the cellular picture between cerebellar astrocytomas and cerebral astrocytomas, the former being a type of "spongioblastoma" (4). Ringertz and Nordenstam described their experience with 140 cerebellar astrocytomas, operated by Olivecrona between the years 1924 and 1948 (5). They also proposed the term spongioblastoma and noted that these tumors not only occur in the cerebellum but also in the cerebral hemispheres and in the brainstem. In 1977 the term "juvenile pilocytic astrocytoma" was introduced by Russell and Rubinstein (6). First in 1979 and later in 1993, the name "pilocytic astrocytoma" was given to these tumors by the World Health Organization in their classification of tumors of the central nervous system (7).

INCIDENCE

Pilocytic astrocytomas account for 6% of all brain tumors in humans, but in childhood for approximately 15% (8). After leukemia, brain tumors are the second most common malignancy of childhood. More than 50% of all pediatric brain tumors are located in the posterior fossa and one-third of these are pilocytic astrocytomas. Most frequently the cerebellar pilocytic astrocytoma occurs between the age of 5 and 10 years, equally distributed among both sexes (9). Two-third of the pilocytic astrocytomas are located in the cerebellum, the remainder in the optic pathways, in the hypothalamic area, in the third ventricle, in the cerebral hemispheres, in the pons, in the medulla oblongata and in the spinal cord. This means that the tumor can actually arise at any location in the central nervous system. The tumor occurs predominantly in the pediatric population. However in a recent series of 131 pilocytic astrocytomas, 28% occurred in patients above the age of 18 (10). Pilocytic astrocytomas are strongly associated with neurofibromatosis 1 (von Recklinghausen's disease): 15% of patients suffering from neurofibromatosis 1 will develop a pilocytic astrocytoma, mostly in the optic pathways and 30% of patients presenting with an optic glioma will appear to have neurofibromatosis 1 (11).
A case of a cerebellar astrocytoma has been described occurring in a child with a deletion of a part

of the long arm of chromosome 18 (12).

A "cystic astrocytoma" with pilocytic areas and Rosenthal fibers has been described in association with Fahr's disease, which is synonymous to idiopathic nonarteriosclerotic cerebral calcification (13).

The occurrence of a cerebellar juvenile pilocytic astrocytoma in a patient with alcaptonuria, later followed by the occurrence of a pituitary adenoma, has been reported (14).

SYMPTOMS AND SIGNS

Presenting symptoms and signs can be divided in those caused by increased intracranial pressure, and those which are the result of local brain dysfunction at the site of the tumor. Headache, vomiting and papilledema are the result of increased intracranial pressure, mostly caused by hydrocephalus due to obstruction of cerebrospinal fluid pathways. In children with a cerebellar tumor in general, gait abnormality, a wide-based gait, gait-ataxia and later on repeatedly falling may occur. Less common features are dysmetria and nystagmus. Sometimes stiffness of the neck or head tilt due to extension of the tumor or the cerebellar tonsils in the foramen magnum may be seen. Seldom there is strabismus, which is then caused by sixth nerve paresis due to increased intracranial pressure.

In babies the increased head size may be the first symptom of a cerebellar tumor, furthermore the raised intracranial pressure may cause split sutures and a bulging fontanelle. Later the child becomes irritable, lethargic and has impaired attention. Occasionally a child may present with extreme drowsiness, bradycardia and slowed respiration.

In the past, when these patients were presented late in the course of their disease, there were also the "cerebellar fits", short periods of coma accompanied by opisthotonic posture.

Pilocytic astrocytomas on other locations give focal symptoms, such as visual disturbances, hypothalamic dysfunction and brainstem symptoms.

MACROSCOPIC APPEARANCE

Pilocytic astrocytomas of the cerebellum show a pink-grey color in most cases. The tumors are in 60%-80% of cases cystic, the remainder is solid (5,15-18). Most often they are located in the vermis of the cerebellum, expanding asymmetrically to one or both cerebellar hemispheres. Sometimes they are confined to one cerebellar hemisphere, showing a lateral position; then they mostly consist of a single large cyst containing a mural tumor nodule. They seldom grow infiltrating, about 8% of cerebellar pilocytic astrocytomas were assumed to infiltrate into the brainstem (19). However, in a recent study 30% of tumors showed brainstem infiltration during surgery (20).

On computed tomography 80% of the cerebellar astrocytomas show contrast enhancement (21). This is probably due to vascular proliferation inside the tumor. In supratentorial low grade astrocytomas contrast enhancement is associated with a poor prognosis, whereas in pilocytic astrocytomas it has no prognostic value.

On magnetic resonance imaging half the number of childhood cerebellar astrocytomas enhanced after gadolinium administration (22). However, in another study the T1-weighted post-gadolinium

MR images of 30 pilocytic astrocytomas at various localizations, showed enhancement in 93% of cases (23). In this study the T1 spin-echo signal of pilocytic astrocytomas was generally decreased and the T2 signal increased. Furthermore, 63% of cases had no associated edema in the surrounding brain and among 4 cases there was evidence of previous hemorrhage.

HISTOLOGY

The histologic appearance of the pilocytic astrocytoma is very distinct. Most tumors have a biphasic pattern, in which areas of loose texture with microcysts and stellate or protoplasmic-type astrocytes alternate with more compact areas containing the typical elongated (piloid) astrocytes with cytoplasmatic fibrillation (10). These two types of areas are present in highly variable proportions among different tumors. Some tumors even may show only one of these two areas. In the microcystic areas eosinophilic granular bodies are often seen. In the more compact areas Rosenthal fibers are almost invariably present. The tumors that only show the more loose textured area with microcysts and lacking the typical piloid areas were formerly referred to as the "diffuse type" of pilocytic astrocytoma. They make up for 15% of the pilocytic astrocytomas (10). Their behavior and prognosis is equal to the biphasic pilocytic astrocytomas.

Mitoses are infrequent, however they do occur in 7 to 20% of the cases but then they are very sparse (24). Necrosis is also rare and can be found in approximately the same frequency (24). Microcalcification is quite frequently found. Vascular proliferation is commonly seen, in such a degree that the picture resembles a vascular malformation, whereas endothelial proliferation is rare. Focal oligodendroglial features can be found in small amounts in the tumor.

Based on the variations in different histologic characteristics many authors have tried to distinguish subgroups among these tumors. The most well known subdivision has been made in the "juvenile pilocytic astrocytoma" and the "diffuse" type (6), the first one showing the typical picture of alternating areas of loose microcystic structure and of solid and compact structure. In the second type there is a more even distribution of glial fibrils and there are small and uniform cells. The diffuse type is supposed to be far less frequent than the juvenile type, it appears in older children and grows more infiltrating. The 25 year survival for the juvenile type is 94% and for the diffuse type 38%. Winston et al. scored all the single microscopical characteristics of 132 cerebellar gliomas and related these to survival (25). This led them to the conclusion that the so called type A cerebellar glioma, consisting of microcysts, Rosenthal fibers, leptomeningeal deposit and focal oligodendroglial components, had a 10 year survival rate of 94%, whereas the type B, consisting of high cellular density, mitosis, necrosis and calcification had a 10 year survival rate of 29%. Another study regarded the uneven distribution of fibrils in connection with lack of high cell density, necrosis and mitosis as the most important favorable factor (26).

In later studies the existence of these subclassifications was not supported and especially the differences in survival could not be confirmed. The features necrosis, mitosis and endothelial proliferation were not related to survival in these studies (10,27-30). Consequently, the conventional Kernohan or St. Anne-Mayo grading systems for astrocytomas do not apply for pilocytic astrocytomas as far as a relation to survival is concerned (31). Also in the WHO-classification the pilocytic astrocytoma is a distinct entity among astrocytic tumors.

The above information about the histology is mainly derived from studies that investigated cerebellar

pilocytic astrocytomas, however it applies also for other pilocytic astrocytomas, on every possible localization.

Most optic pathway and hypothalamic gliomas are thought to be pilocytic. However, it is difficult to establish to which extent, since most studies only speak of "optic glioma" or "low grade glioma", 60% seems to be pilocytic and 40% fibrillary (32). Most optic gliomas occur in early childhood. When they occur in adults they may exhibit characteristics of malignant gliomas and show an aggressive behavior (33). In the brainstem and in the cerebral hemispheres the diffuse (grade 2) astrocytoma far outnumbers the pilocytic astrocytoma (10).

Also malignant forms of pilocytic astrocytomas, with aggressive behavior, exist. They are infrequent and most are reported to occur on the site of a "benign" pilocytic astrocytoma treated many years previously (34,35). Almost all of these patients had undergone radiation therapy many years before and possibly the malignant recurrence was radiation induced. Also primary forms of malignant pilocytic astrocytomas have been described, these tumors showed mitotic activity of more than one per high power field (x250), endothelial proliferation and necrosis (36). The prognosis of these tumors seems to be much less favorable than for the "benign" pilocytic astrocytomas, but still much better in comparison to diffuse fibrillary astrocytomas showing the same histological features.

TREATMENT AND PROGNOSIS

The treatment of first choice is surgical resection; a statement already made by Harvey Cushing and upheld until now. The surgeon must aim for total resection. This is an achievable task for most cerebellar and cerebral hemispheric lesions. However, for deep seated lesions, such as the optic pathway, hypothalamic and brainstem localizations this will often be impossible.

There is some discussion about the cyst-wall, when there is a single cyst with a mural tumor nodule. If this wall shows contrast-enhancement on computed tomography or magnetic resonance imaging, it very likely contains tumor cells, and should be resected (29). In non-enhancing cases resection of the nodule only will be sufficient. When the inner wall of the cyst is smooth and glossy, the presence of tumor cells is very unlikely. On the other hand, when the cyst-wall is thick, not shiny and shows a gelatinous aspect it is probably infiltrated by tumor and should be resected (37). Others advise to biopsy the cyst-wall in all cases and to resect it when tumor cells are seen on frozen sections (30). Recently it was stated that cyst-wall excision did not influence outcome or risk of recurrence (20). Survival after total tumor removal is excellent: Cushing in his well known series of 76 patients established 28 total resections of cerebellar lesions, the 20 year survival among this subgroup was 100% (1). True tumor recurrence, which is recurring tumor after complete resection, is extremely rare for pilocytic astrocytomas (38). Therefore, the prognosis for pilocytic astrocytomas, when resected totally, is excellent.

The problem in treatment for these tumors lies in those patients where total tumor resection is not feasible. In cerebellar tumors this problem occurs when the tumor has infiltrated the brainstem; than total resection is not always possible. Pilocytic astrocytomas of the optic pathways, hypothalamus or basal ganglia are hardly ever totally resectable. Therefore, twenty year survival for chiasmal gliomas in one study of 28 patients was only 43% (39). Nevertheless, even after incomplete resection the prognosis can be very favorable since the tumor remnant may remain "quiescent" for many years (16,18,27,40). It has been reported that pilocytic astrocytomas of the brainstem or the

optic-hypothalamic area behave more benign when associated with neurofibromatosis 1 (41,42). Formerly, radiation therapy was often used to treat the tumor remnant and a beneficial effect was reported several times (9,43-45). Others stated that radiotherapy has no influence on the tumor (1,30,46). Because of the deleterious side effects of irradiation on the developing brain, the use of it is contra-indicated below the age of 4 years and after macroscopically total resection. In the present time it is generally believed that conventional radiation therapy has no place in the treatment of cerebellar pilocytic astrocytomas; exceptions are a different histologic appearance or re-recurring tumor at an inoperable site (8,46). However, radiation therapy is still frequently used in the treatment of optic, diencephalic and brainstem gliomas (47-50). Probably such treated patient series contain pilocytic astrocytomas next to other type of gliomas.

Results of chemotherapy are only reported for the treatment of optic and brainstem gliomas. In two studies a decrease of tumor size was reported (51,52). The best treatment for chiasmatic-hypothalamic gliomas is uncertain. Patient series that were treated with radical surgical (incomplete) resections had no better outcome than those where the tumors were only biopsied and tumor progression was controlled by either chemotherapy in very young infants or radiation therapy in older patients, with 10-year survival rates ranging from 57% to 90% (47-50,53).

Experience with stereotactic radiosurgery is very limited. However, Grabb et al demonstrated a possible beneficial effect among 8 patients with residual pilocytic astrocytomas after surgery: 3 tumors disappeared, 4 decreased in size and 1 remained unchanged after stereotactic radiosurgery (54).

The successful treatment of a patient with a pilocytic astrocytoma depends primarily on the extent or possibility of surgical resection. It is known from older studies that tumors and tumor remnants may remain quiescent for many years (16,18,27,40). Therefore, the neurosurgeon has to make a difficult decision: taking the risk of surgically induced neurological damage when aiming for total tumor resection on one hand or refraining from riskily surgery and accepting residual tumor on the other. This problem, as has been stated before, is especially encountered in the treatment of tumors on deep seated localizations of the brain, such as in the brainstem, the hypothalamus and the optic chiasm.

Different neurosurgical clinics uphold controversial opinions on the best treatment for these patients. These range from very aggressive surgical to strictly conservative expectative attitudes. Advocates of aggressive treatment use as motivation the fact that residual tumors may progress, sometimes even rapidly (55,56). Supporters of the opposite opinion are motivated by the frequently seen benign and quiescent behavior of the residual tumor (39,57).

The use of other treatment modalities such as radiation therapy and chemotherapy, are subject to similar diverging opinions, since it is not known how effective they are.

The existence of these dualistic views is mainly caused by the fact that we do not know what the behavior of the residual tumor will be.

Therefore, it would be very rewarding to find new characteristics of the tumor that can predict behavior, and can be of help in determining prognosis and treatment for patients with residual pilocytic astrocytoma.

THE PURPOSE OF THIS THESIS

1. Determining the frequency and behavior of residual tumor after surgical treatment of pilocytic astrocytomas localized in an operable site: *An extensive literature review is performed on previous patient studies. Medical files of 73 patients with cerebellar pilocytic astrocytomas are retrospectively investigated and follow-up neuroimaging studies are analyzed in order to draw up an inventory of possible manifestations of biological tumor behavior. Patient outcome is listed and a treatment protocol drafted (chapter 2).*

2. Finding methods and techniques to study cell kinetics and proliferative potential, which have been applied to other tumors and not yet to pilocytic astrocytomas: *Two relatively simple tissue staining techniques, AgNOR staining and Ki-67 labeling, are described, including their physiological background and technical properties. The reliability of these techniques is discussed in relation to predictive value on tumor behavior as derived from previous studies (Chapter 3, first two paragraphs).*

3. Exploring recent knowledge and insights in molecular genetics of oncogenesis to understand the paradoxical neoplastic character of pilocytic astrocytomas: *Implications of two genes and the products these genes code for in carcinogenesis are reviewed. The TP53 gene for being the most frequent mutated gene in human cancers and for being involved in the formation of astrocytomas grade II-IV. The Neurofibromatosis 1 gene for the existing relation between von Recklinghausen's disease and (optic) pilocytic astrocytomas. (Chapter 3, last two paragraphs).*

4. Application of cell kinetic studies to tumor material and relating the results to true tumor behavior as observed on follow-up neuroimaging studies of the patient: *AgNOR staining and Ki-67 labeling (MIB1-labeling) are performed on tumor tissues and the results are related to behavior of the residual tumor (Chapters 4 and 5).*

5. Application of molecular genetic studies on tumor tissue to study the role of known tumor suppressor genes: *Immunohistochemical p53 labeling and screening for TP53 mutations are performed in order to establish the role of this gene in pilocytic astrocytomas. The product of the NF1 gene, neurofibromin, is qualitatively and quantitatively studied to test the hypothesis that the NF1 gene functions as a tumor suppressor gene also in pilocytic astrocytomas. (Chapters 6 and 7).*

6. Establishing new parameters that can predict the behavior of the tumor in order to set a rationale for the treatment and follow-up of patients with residual or inoperable pilocytic astrocytomas: *An attempt is made to combine results of the performed studies in order to find a combination of tests that gives a high predictive value on tumor behavior. The role of TP53 and NF1 is discussed. An adjusted treatment and follow-up algorithm is presented. (Chapter 8).*

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