Cancer Of The Cerebellum And Cerebellum Tumors

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SUMMARY: Malignancies of the central nervous system (CNS) are the most common solid tumors of childhood, constituting approximately a quarter of all pediatric tumors. Despite the advances being made in the field of pediatric neuro-oncology, they are still the most common cause of cancer-related deaths in children. Nowadays, it is becoming more and more evident that the cerebellum is essential in a wide range of not only motor, but also higher cognitive functions, leaving cerebellar tumor patients (mostly children) with a vast array of deficits and impairments, as well as psychological changes. Such deficits and impairments affect children not only while the tumor is present, but some also remain even after the tumor itself is removed, leaving the child with permanent damage not easily compensated or recovered from.

FUNCTIONS OF THE CEREBELLUM

Even though the cerebellum has originally been associated with just motor function, especially movement coordination, Jeremy D. Schmahmann and Janet C. Sherman broke new ground when they coined the term ‘cerebellar cognitive affective syndrome’. The term pertains to a clinical entity including impairment of spatial cognition as well as visual–spatial organization and memory; difficulties with executive functions such as verbal fluency, planning, abstract reasoning and working memory; language deficits including agrammatism and dysprosodia; and even personality changes accompanied by disinhibited and inappropriate behavior. Schmahmann and Sherman noticed the aforementioned deficits and impairments performing neurological examinations, bedside mental state tests, neuropsychological studies and anatomical neuroimaging on 20 patients with cerebellar lesions. As a conclusion, the deficits were attributed to the disruption of neural circuits linking the cerebellum with prefrontal, posterior parietal, superior temporal and limbic cortices.

By that time, Schmahmann had already come across some findings regarding the cognitive aspect of the cerebellar function, in his 1996 study on nonhuman primates. He had concluded that the anatomical basis of the cerebellar contribution to cognition and emotion in fact lies in the incorporation of associative and paralimbic pathways into the cerebrocerebellar circuit. He had also noted that within the cerebellum, cognitive and behavioral functions are organized topographically. For instance, he attributed affective and autonomic regulation and memory that is emotionally relevant mostly to the archicerebellum, vermis, and fastigial nucleus. To the cerebellar hemispheres and dentate nucleus he attributed executive, visual-spatial, language, and other mnemonic functions.

Many other groups of scientists have reported similar findings. For instance, Levisohn et al. found that children who had undergone excision of cerebellar tumors, later experienced problems with visual spatial functions and expressive language. Furthermore, they reported that 8 of 14 patients with damage to the vermis, that had previously been stable personality-wise, presented with dramatic mood swings and uncharacteristic giddiness. Also, patients with early infantile autism have been reported to have abnormalities in the cerebellum on both morphometric and neuroimaging studies. Most recently, a detailed neuro-psychological examination has been conducted by Gottwald et al. in 2004, of 21 patients with cerebellar lesions due to hematoma or tumor, as well as of 21 controls. Their study has in part confirmed that lesions of the left cerebellar hemisphere lead to non-verbal deficits, while those of the right lead to verbal ones. Patients with a lesion of the right hemisphere presented mostly with a greater impairment than those with a left-sided lesion, which was explained as a result of the contralateral connection of the cerebrum and the cerebellum. To be exact, the cerebral hemisphere crucial for right hand movements and dominant for language functions, i.e. the left hemisphere, is connected with the right hemisphere of...
The discovery of the role of the cerebellum in both cognition and affect came as no surprise, since it is well known that more than half of all the neurons in the brain are in fact located in the cerebellum, as well as the fact that the cerebellum is connected to nonmotor cortical and subcortical areas including the limbic system, the prefrontal cortex and the brain stem nuclei. Cortical areas such as parietal and superior temporal, as well as the dorsolateral prefrontal cortex, project to the cerebellum via the pons, forming the corticopontocerebellar pathway. Also, deep cerebellar nuclei connect with certain cerebral areas through the cerebellothalamic tract, as well as via the red nucleus.

There are three functional subdivisions of the cerebellum in regard to the connections that the cerebellum makes with other central nervous system (CNS) structures: vestibulocerebellum, spinocerebellum and corticopontocerebellum (also known as cerebrocerebellum). Vestibulocerebellar fibers connect the lateral vestibular nuclei with the flocculonodular lobe of the cerebellum, which is, together with the lingula, the oldest part of the cerebellum, also known as archicerebellum. The function of the vestibulocerebellum is self-explanatory - it is involved in vestibular reflexes, spatial orientation and postural maintenance. The spinocerebellum is phylogenetically known as paleo-cerebellum. Spinocerebellar axons end in the vermis and the intermediate zones of the cerebellar cortex, as well as in the fastigial and interposed nuclei of the cerebellum, delivering proprioceptive input from muscles, joints and tendons. Spinocerebellum, therefore, integrates sensory input with motor commands so as to produce adaptive motor coordination. It projects output fibers to rubrospinal, vestibulospinal, and reticulospinal tracts.

Cerebrocerebellum (or corticoponto-cerebellum) is phylogenetically the newest part of the cerebellum and is therefore known as neocerebellum. It is also the largest of the three functional subdivisions of the cerebellum. It comprises the lateral hemispheres and the dentate nuclei. This part of the cerebellum is extensively connected with the cerebral cortex: afferently via the pontine nuclei and efferently via the ventral lateral (VL) nucleus of the thalamus. Its role lies in in the planning and timing of movements, as well as in cognitive functions of the cerebellum.

**Tumors of the cerebellum**

The posterior cranial fossa is the most common location of childhood CNS tumors, while in adults only 5% of all CNS tumors originate in that area. The adult tumors that do arise there are usually aggressive, as opposed to the lower grade of the majority of childhood CNS tumors.

The most frequently found childhood CNS tumors are astrocytomas, medulloblastomas and ependymomas. They all typically originate in the cerebellar area. Other CNS tumors, such as choroid plexus papillomas and germ cell tumors, can also appear in children, but much less frequently. Interestingly, meningiomas and metastatic lesions, which are a relatively common occurrence in the adult population, are exceptionally rare in children. The three most common childhood cerebellar tumors will be further discussed in this article.

**Astrocytoma**

Astrocytomas are the most common CNS tumor in children. They are a type of gliomas, comprising 75% of them. Microscopically, astrocytomas are divided into 4 grades, according to their level of differentiation. The lower the grade is, the better is the differentiation, and vice versa. Astrocytomas of higher grades (II – IV) are found more often than those of grade I.

Diffuse astrocytomas range from grades II – IV and are mostly found in adults, typically in the cerebrum. On the other one, pilocytic astrocytomas (grade I astrocytoma) predominantly appear in the cerebellum of children. For the purposes of this article, only pilocytic and diffuse cerebellar astrocytomas will be further discussed.

**Pilocytic astrocytoma**

Pilocytic astrocytoma is the most common childhood tumor of the CNS. It is mostly a noninfiltrative, low-grade tumor. However, when a pilocytic astrocytoma appears in an adult, it is more likely to be high-grade than low-grade. The low-grade, noninfiltrative ones constitute approximately 10% to 20% of all childhood primary CNS tumors and 30% to 40% of all posterior fossa tumors. They are most often diagnosed by the end of the first decade of life and in the first half of the second, with the average age at diagnosis being 11 years. Macroscopically, they are either solid or cystic, the latter being more common.

Histologically, two types of cells can be found in pilocytic astrocytoma: elongated, bipolar neoplastic astrocytes clustered in fascicles (“pilocyte” literally means “hair cell”) or sparse and often microcystic stellate astrocytes. Rosenthal fibers and eosinophilic granular bodies (“protein droplets”), indicating chronicity and degeneration, are also typically found. Nuclear atypia is not uncommon and can lead to a benign pilocytic astrocytoma being incorrectly graded as malignant.

The signs and symptoms of pilocytic astrocytoma are dependent on the location of the lesion. Early stages of the illness are...
usually dominated by unsteadiness and dysmetria, followed by unilateral appendicular ataxia and finally truncal unsteadiness as the tumor progresses from lateral regions of the cerebellum toward the midline. In later stages, however, cerebellar symptoms are usually clouded by signs of increased intracranial pressure (due to fourth ventricle blockage and hydrocephalus), such as headache, nausea and vomiting. However, if the tumor is originally located in the vermis or elsewhere in the midline of the cerebellum, both truncal unsteadiness and signs of increased intracranial pressure will occur earlier in the course of treatment. Anorexia, developmental delay and, later, regression of intellectual and motor abilities of the child have also been found to occur. Nystagmus, palsies of the abducens nerve, papilledema and head tilt are also not uncommon at the time of diagnosis. Increased intracranial pressure may also cause a phenomenon called the “sunsetting sign” which manifests in infants and very young children. In those children, upgaze is impaired and the eyes seem to be forced downward. Surgical treatment of pilocytic astrocytoma offers a very successful outcome, since the tumor can usually be resected in total. In such cases, no further treatment is required in the vast majority of children. However, if a cystic infiltrative astrocytoma is misdiagnosed as a typical cystic pilocytic astrocytoma, parts of the cyst wall may get overlooked and left behind, in which case a recurrence of the tumor is to be expected unless further treatment is initiated. In case a truly noninfiltrative cystic pilocytic astrocytoma is not resected in total, other treatment modalities may still not be necessary. Instead, a second attempt of total resection is preferred in case of progression (although there is no certain evidence to support a second resection being more beneficial than radiotherapy, as concluded by Leibel et al. in 1975 and Garcia et al. in 1990). The reason for such preference may be the fact that the efficacy of radiotherapy in managing both incompletely and completely resected pilocytic astrocytoma is unproven. There is even less evidence that would support the use of chemotherapy in children with pilocytic astrocytoma.

**Diffuse cerebellar astrocytoma**

This infiltrative type of astrocytoma is usually found in adults, ranging from grade II to IV (glioblastoma multiforme (GBM)). They are poorly circumscribed and highly infiltrative. Vascularity and necrosis is often evident in GBMs. Histological characteristics of GBM include hypercellularity and mitoses. The signs and symptoms vary depending on the site and grade of the tumor, but are in general similar to those caused by pilocytic astrocytoma. Low-grade diffuse astrocytomas have a more subtle presentation than pilocytic astrocytoma, but tend to cause earlier and more pronounced midline cerebellar deficits. Higher grade lesions usually cause a more abrupt progression of signs and symptoms, especially in case of glioblastoma multiforme in which signs and symptoms of increased intracranial pressure are often dominant over cerebellar deficits. Both low and higher grade diffuse astrocytomas are unlikely to be resected in total because of their infiltrativeness. Nevertheless, the extent of resection is highly indicative of the outcome and long-term prognosis. It was reported by Campbell et al. in 1996 that patients who underwent total resection had a median survival of over 60 months, while those who underwent limited resection had a survival rate of only 10.5 months on average. A multi-institutional trial carried out by Children’s Cancer Group between 1985 and 1991 concluded that post-operative radiation and chemotherapy was twice as effective (in terms of survival rate) in patients who underwent a greater than 90% resection than those who had less than 90% of the tumor removed. Evidence suggesting a positive effect of radiotherapy on survival rates and long-term disease control in patients with subtotally resected low-grade diffuse astrocytoma, is scarce. On the other hand, it has been observed to be effective in relapse control of higher grade diffuse astrocytoma. Several studies reported that chemotherapy was beneficial only in patients who underwent tumor resection, as opposed to tumor biopsy. Intensive chemotherapy administered prior to radiation was most beneficial in patients who had a gross tumor resection.

**Medulloblastoma**

Medulloblastoma is a malignant tumor of childhood. It is the most common malignant brain tumor in children and the second most common of all CNS tumors in children (after pilocytic astrocytoma). They make up as much as 16% of all primary childhood CNS tumors. These tumors can present in young adults as well, but rarely after the age of 30. According to the current World Health Organization (WHO) classification, there are four morphologic variants of medulloblastoma: classic medulloblastoma, desmoplastic medulloblastoma, medulloblastoma with extensive nodularity and advanced neuronal differentiation, and large cell medulloblastoma. Rarely, two other related neoplasms can be found: melanotic medulloblastoma and medullo-myoblastoma. In those two forms, tumor cells differentiate into melanocytes or myocytes, which indicates that medulloblastoma cells are indeed multipotent embryonic
cells. All medulloblastoma variants are malignant.

Medulloblastomas typically appear in the vermis but can also appear in the cerebellar hemispheres. They are mostly well circumscribed. Necrosis can often be found. Medulloblastomas are known for their ability to grow rapidly and infiltrate the fourth ventricle. They often metastasize to other parts of the CNS (via cerebrospinal fluid) and, rarely, outside the CNS.

Histologically, the neoplastic cells that form medulloblastomas are in fact neuroectodermal cells. It is a typical “small-round-blue-cell” tumor, named so because of the hyperchromatic nuclei and scant cytoplasm of the neoplastic cells. The cells may organize in various patterns, such as unstructured nests or pseudorosettes (commonly referred to as Homer-Wright rosettes). Indications of glial and neuronal differentiation can also be noticed. Since it is a highly malignant tumor, mitotic figures are usually numerous. Atypical teratoid/rhabdoid tumor (ATRT) can sometimes resemble a medulloblastoma, especially the large cell variant, leading to a misdiagnosis. Immunophenotyping techniques can be used to distinguish the two, as well as the fact that medulloblastomas are in general less heterogeneous and pleomorphic than ATRTs. The most common signs and symptoms that patients with medulloblastoma present with include headache, vomiting and ataxic gait. In this case, vomiting often occurs when the child awakens. Aside from headache and vomiting, increased intracranial pressure (due to the obstruction of the fourth ventricular outlet) can also lead to lethargy, nausea, papilledema and sight difficulties. As a manifestation of ataxia, speaking and movement coordination can become impaired. Medulloblastoma located in the cerebellar hemispheres (more commonly found in adults more than in children) can result in progressive clumsiness, as well as difficulty standing and walking alone. The tumor can also damage the cranial nerves, especially the abducens and facial nerve, resulting in palsy. Medulloblastomas have also been found to cause hydrocephalus and, in case of a hemorrhage in the tumor, even acute neurological compromise up to and including coma. It is approximated that, at the time of diagnosis, as much as one third of all children diagnosed with medulloblastoma will present with disseminated disease. This percentage is even higher in children younger than 2 years of age at the time of diagnosis. In adult patients, the estimated rate of dissemination at the time of diagnosis varies from 10% to 20%.

The treatment of medulloblastoma includes a therapeutic triad consisting of surgery, radiotherapy and chemotherapy. The goal of surgery in treating medulloblastoma is complete resection, since total or almost total removal of the tumor leads to the highest 5-year survival rates. Of course, this only applies if the tumor had not metastasized. Solely removing the tumor is sometimes not enough. Permanent ventriculoperitoneal (VP) shunting will be required after surgery in as much as 30% to 50% of children diagnosed with medulloblastoma, so as to treat or prevent hydrocephalus. Establishing a diagnosis early, while the tumor is still small, minimizes the need for such shunting. It is important to stress that ventriculoperitoneal shunting itself can cause certain complications, especially in young children. These complications include CSF infection, intraventricular hemorrhage, VP shunt perforations of the gastrointestinal tract and bilateral papilledema to name a few. Therefore, some surgeons prefer placing a catheter between the third ventricle and cisterna magna at the time of surgery, so as to avoid the aforementioned complications. Furthermore, shunt modification may be required in young children to keep pace with growth. External ventricular drainage can be of help in patients needing CSF diversion before or immediately after surgery.

Medulloblastoma is a relatively radiosensitive tumor. Since it usually spreads through CSF, irradiation is craniospinal and aims to involve the entire subarachnoid space.

Medulloblastomas are much more sensitive to chemotherapy than they are to radiotherapy. In fact, according to Friedman and Oakes, they are “one of the more chemosensitive brain tumors of the pediatric population”. The German Oncology Group recently carried out a randomized study which concluded that treating medulloblastoma with radiotherapy and chemotherapy during and after radiation, resulted in “excellent” survival rate. On the other hand, pre-radiation chemotherapy has not, to date, proven beneficial to patient survival. Using chemotherapy as the primary treatment for medulloblastoma in children younger than 3 years of age has also proven disappointing.

Risk assessment is done by taking into account three factors: the patient’s age, localization/dissemination of the tumor and successfulness of the resection. Patients older than 3 years of age whose tumor had not disseminated by the time of diagnosis and was resected totally or nearly so are categorized as patients with average-risk disease. After undergoing craniospinal and local radiotherapy, those patients have a 60% to 65% chance of 5-year progression-free survival (PFS). They account for the majority of medulloblastoma patients - approximately 60% to 70% (possibly more in adults).

Patients with disseminated disease at the time of diagnosis or those whose tumor could only be partially resected, as well as children under the age of 3, are categorized as patients with poor-risk disease. They have an approximately 40% likelihood of 5-year PFS after treatment with craniospinal and local radiotherapy. Positive CSF cytology 2 to 3 weeks after surgery
is associated with poorer outcome, even though free-floating tumor cells found after surgery have been known to disappear spontaneously in some patients. The methods of detecting free-floating tumor cells include lumbar CSF cytology and ventricular fluid analysis, with the former being the more sensitive one.

**Ependymoma**

Ependymomas arise from ependymal cells that line the ventricular system and can originate anywhere throughout the CNS. They occur in both children and adults. They are the third most common brain tumor in children, constituting 10% of all primary childhood CNS tumors and between 10% and 20% of the posterior fossa tumors in patients younger than 15 years of age. Approximately two-thirds of childhood ependymomas are located infratentorially and one-third supratentorially, and vice versa in adults. Pediatric ependymomas often extend throughout the fourth ventricle, with possible penetration of the foramen of Luschka. Histologically, ependymoma tumor cells form two characteristic arrangements: anuclear perivascular pseudorosettes and true rosettes that encircle a central lumen, with the former being more common than the latter. Anaplasia can also be found. More than 5-10 mitoses per high power microscopic field, alongside with leptomeningial metastases, can be associated with increased malignancy.

Ependymomas present with various clinical signs and symptoms, which are initially nonspecific and nonlocalizing. Signs and symptoms secondary to increased intracranial pressure can occur early in the course of illness. Otherwise, ependymomas may sometimes mimic brainstem lesions, in which case they can cause multiple cranial nerve palsies prior to the appearance of signs and symptoms of increased intracranial pressure. If they induce cerebellar deficits, they may clinically resemble medulloblastomas, making it difficult to tell the two apart. Since infratentorially located ependymomas tend to infiltrate the upper part of the cervical cord, they may prompt neck stiffness and head tilt.

As it was in patients with astrocytoma or medulloblastoma, both prognosis and survival rates for ependymoma patients are proportional to the extent of tumor resection, concluded Sutton et al. in 1991. It has been reported by Perilongo in 1997 that ependymoma patients that underwent a total resection had approximately a 30-80% better chances of 5-year PFS than those with a subtotal resection. The fact that ependymomas almost always recur at the primary site of the tumor, (implying that they develop from residual ependymoma cells) also indicates that a total resection should be done. However, a third of all ependymomas infiltrate adjacent brain structures or envelop cranial nerves, rendering them unavailable for total resection. Postoperative radiation is generally considered the adjuvant therapy of choice when treating ependymoma. Local radiotherapy is generally recommended, even to patients whose tumor was resected in total. Chemotherapy has proven beneficial only in delaying radiotherapy in very young patients. When added to surgery and radiotherapy, chemotherapy has not been found to increase survival rates in children older than 2 years of age, as reported by Grill in 2001.

**Functional recovery after tumor resection**

Whether or not brain surgery is better compensated at a young age, resulting in better restitution of function has been a matter of debate for quite some time now. Different studies and reports have reached different conclusions. For instance, both Little (1862) and O’Donoghue (et al., 1986) concluded that “lesions in the cortex or in subcortical regions such as the cerebellum experienced at a young age had less effect on later functioning than similar lesions occurring later in life”. On the contrary, studies conducted by Dennis et al. (1996, 1999) suggested that recovery is not necessarily linearly dependant on the age at which surgery was conducted.29

More recently, an elaborate and extensive study by Konczak et al. in 2005, that included 22 cerebellar patients and 14 healthy controls, set out to determine the connection between recovery and age at which the brain damage had happened, as well as if and how recovery depends on the site of the lesion. Among areas of examination, they took close interest in working memory, postural control and upper limb function. The results of the study demonstrated that damage which happened at a younger age is not better compensated than the one that happened in later childhood or adolescence. Hence, they concluded that age at surgery is a poor indicator of functional recovery. In fact, the site of the lesion proved to be a much better predictor of recovery. Specifically, they found that the lesion site with the worst compensation were the deep cerebellar nuclei, regardless of the age at which surgery was conducted.29
Furthermore, the neuropsychological aspect of cerebellar (or any other, for that matter) brain tumors, should not be overlooked. For instance, a 2014 case study reported a patient who presented only with a headache and personality changes, including pronounced pensiveness and apathy, as well as suicidal tendencies (which he had not experienced previously), without any other neurological disturbance. A computed tomography (CT) scan revealed a mass located in the left frontoparietal and left cerebellopontine angle. After a successful surgical resection of the tumor, the patient no longer experienced suicidal tendencies, but the personality changes persisted. In conclusion, pharmacological and psychological treatment ought not to be excluded from non-surgical management and post-operative treatment of brain tumors, since psychiatric and psychological condition is crucial in regard to the quality of life of both the patient and his family.30

Advances in diagnosis and treatment

Cerebellar tumors are a complex medical issue, primarily because of their prevalence in the young population. Consequently, tremendous effort is being put into finding and developing new techniques in all related fields. The aims vary – from establishing an earlier diagnosis with more effective surgery and adjuvant therapy, to achieving a faster and more complete recovery, to a higher quality of life and helping patients and their families deal with the disease and its consequences. A multidisciplinary team of experts is usually required in order to diagnose, treat and overall help such patients. Knowledge of genetic and molecular pathogenesis is crucial in better understanding the underlying causes of cerebellar tumors in order to treat such tumors the best way possible. Molecular studies have also been quite useful in the improvement of tumor diagnosis, due to newly identified molecular tumor markers. Additionally, a promising new treatment option lies in gene therapy.

The evolution of imaging technology has - been a turning point in a majority of disciplines dealing with cerebellar tumors. The invention of magnetic resonance imaging (MRI) served as a milestone in radiology and led to the development of numerous different imaging techniques, now used in many aspects of neuro-oncology, including diagnosis, surgical assessment and evaluating the response to therapy. It is now possible to identify certain tumors based solely on their MRI characteristics. MR spectroscopy has proven useful in distinguishing between different types of tumors, as well as between the tumor and normal brain tissue. Metabolic imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), are able to assess the quantity of cellular metabolism of the tumor which indicates proliferation and can help distinguish between high grade tumors. Functional MRI and magnetoencephalography (MEG) are used to distinguish a tumor from surrounding functional and vascular structures, which has proven more than useful in pre-operative mapping and image-guided neurosurgery. Intra-operative MRI and ultrasound systems are also used to such effect, helping improve safety during surgery, as well as the extent of tumor resection.

Conclusion

Modern neuroimaging coupled with intra-operative guidance imaging has led to earlier diagnosis, better understanding of the anatomical relation between a tumor and surrounding functional structures, as well as to a safer and more extensive surgical resection of a tumor. As a result, more than one third of patients with a benign fourth ventricle tumor will need no further post-operative treatment, such as radiotherapy or chemotherapy. Additionally, more than 50% of malignant fourth ventricle tumors are nowadays curable using radiation and chemotherapy. Even so, there is still room for improvement. In that regard, further multi-disciplinary collaboration is sure to yield even better results in the future.

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Fig. 6 Conventional MRI and diffusion tensor tractography (DTT) images of a 6-year-old patient with cerebellar tumor. (Kim M-S et al., 2014)