sciendo

DOI: 10.2478/rjr-2023-0004

Romanian Journal of Rhinology, Volume 13, No. 49, January - March 2023

LITERATURE REVIEW

Unusual manifestation of cerebellopontine angle medulloblastoma with tinnitus and sensorineural hearing loss

Andreea Elena Bejenariu[1,2,3], Alex Iulian Milea[1,2], Codrut Sarafoleanu[1,2,3]

[1]ENT&HHNS Department, "Sfanta Maria" Hospital, Bucharest, Romania

[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[3]ENT Sarafoleanu Medical Clinic, Bucharest, Romania

ABSTRACT

BACKGROUND. Medulloblastoma is the most common central nervous system embryonal tumor in children. In adults, this tumor is extremely rare, accounting for nearly 1% of primary brain tumors. Raised intracranial pressure signs are common manifestations of posterior fossa tumors, but tinnitus and/or sensorineural hearing loss are very uncommon presenting symptoms.

MATERIAL AND METHODS. Starting from a very rare case of a 39-year-old male with left tinnitus and progressive left sensorineural hearing loss as isolated symptoms of a medulloblastoma, we performed a literature survey using the PubMed, ProQuest, Web of Science, Science Direct, Wiley Online search engines for patients with medulloblastoma and tinnitus and/or sensorineural hearing loss.

RESULTS. All patients found in the relevant literature with auditory dysfunctions presented sensorineural hearing loss. Other frequent manifestations were: ataxia, facial numbness, vertigo, headache, nystagmus. Two patients were found with tinnitus and sensorineural hearing loss as isolated symptoms of medulloblastoma, as in our case, and in two other cases the sensorineural hearing loss was the unique symptom. With refers to the onset of medulloblastoma, just 3 patients had the first symptoms sensorineural hearing loss and tinnitus.

Concerning the tumor location, in patients manifested with isolated tinnitus and sensorineural hearing loss, like our patient, the tumor arised from the internal auditory meatus, extended to the cerebellopontine angle or involved the vestibulocochlear nerve.

With regards to treatment, surgery in association with radiotherapy and chemotherapy was elected in most cases (38%).

CONCLUSION. It is important to pay attention at patients with isolated auditory dysfunction that may mimic significant posterior fossa tumors, such as a medulloblastoma.

KEYWORDS: medulloblastoma, tinnitus, hearing loss.

INTRODUCTION

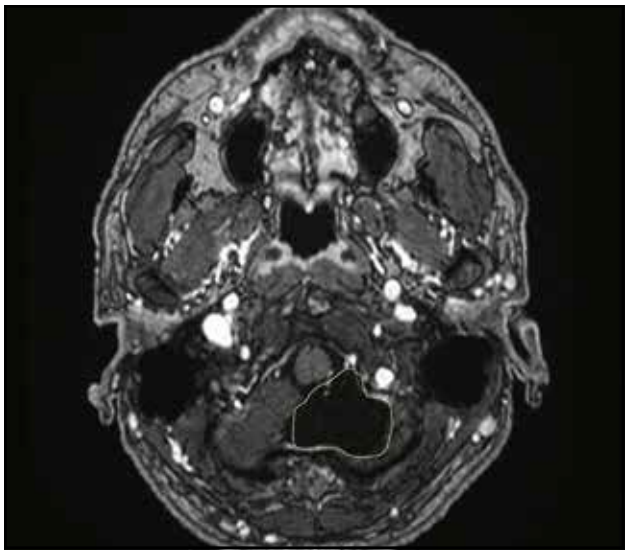
Medulloblastoma is the most common central nervous system embryonal tumor in children. The incidence of childhood medulloblastomas from all paediatric intracranial neoplasms represent approximately 25% and up to 40% of the posterior fossa tumors[1]. In adults, this tumor is extremely rare, accounting for nearly 1% of primary brain tumors and 6% of the posterior fossa tumors[1]. In the literature, there is no specific predominance for male or female[2]. Cerebellar medulloblastoma was first described in 1925 by Baileys and Cushing as a malignant tumor of the cerebellum[3].

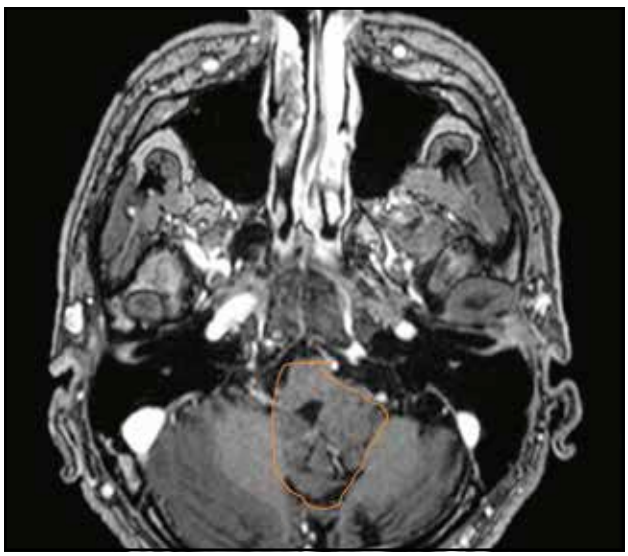
Medulloblastoma is most commonly localised in the midline of the cerebellum, at the level of the apex of the fourth ventricle and vermis and rarely may occur in the cerebellopontine angle or in the cerebellar hemispheres spreading extra-axially[4].

There are some controversies about the origin of cerebellopontine angle (CPA) medulloblastoma. A theory described that CPA medulloblastoma is formed from a remnant of the lateral medullary velum which proliferates into the cerebellopontine angle[5,6]. The origin of extra-axial medulloblastoma in the cerebellopontine angle may appear because of the extension from the midline of the cerebellum through the foramina of Luschka or arising directly from the surface of the external germinal layer of the pons or cerebellum; or it may appear in the tentorial region[7].

Usually, medulloblastoma manifests as a dysfunction of the cerebellum or gives symptoms related to high intracranial pressure. Rarely, it manifests with isolated auditory symptoms (dys-

Corresponding author: Andreea Bejenariu, MD, ENT&HNS Department, "Sfanta Maria" Hospital, 37-39 Ion Mihalache Blvd., District 1, Bucharest, Romania
ORCID: https://orcid.org/0000-0001-6134-9239
e-mail: andreeaelena.bejenariu@yahoo.com
Received for publication: October 13, 2022 / **Accepted:** December 8, 2022





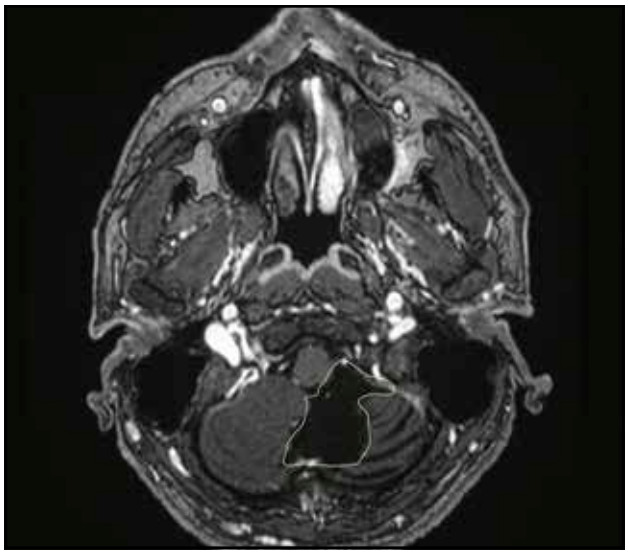


Figure 1. Contrast-enhanced cranio-cerebral MRI (T2 and T1 signal-axial section) reveals a nodular mass in the left side of the Luschka foramen extended to the fourth ventricle and left cerebellar peduncle.

function) with evolution of weeks or even months. In unilateral sensorineural hearing loss, the tumor is localised in the cerebellopontine angle, internal auditory canal, or cerebellum at the level of the fourth ventricle. Cerebellopontine angle medulloblastoma manifests in most patients with headache and vomiting or nausea, followed by ataxia. Some patients may complain about hearing loss, tinnitus, dizziness, fullness sensation of the ear and facial asymmetry if the seventh and eighth cranial nerves are involved when the tumor extends to the porus acusticus[7-9]. When the extension of the tumor involves the sixth cranial nerve or it is a result of hydrocephalus, patients may present with double or blurred vision. Exceptionally, these patients have normal neurological examination[8-13].

MATERIAL AND METHODS

The present literature review began with a 39-year-old male patient who presented to our clinic with left tinnitus and left progressive sensorineural hearing loss, with no other complaints. He did not present any associated neurological manifestations, despite the location of the tumor described on the imaging examination. The MRI (magnetic resonance imaging) scan performed with intravenous contrast showed a nodular lesion (23/16mm maximum axial dimensions) with tissular isointense signal on T2 and T1, slightly hyperintense FLAIR, with non-homogeneous structure due to the presence of areas of hypersignal in T2-weighted images, hyposignal in T2-weighted images, localised on the left side of the Luschka foramen, procident in the fourth ventricle, without a demarcation interface to the left middle cerebellar peduncle and the posterior edge of the medulla oblongata on the left side (Figure 1); symmetrical ventricular system, with dimensions within normal limits, and midline structures in normal position.

On ENT examination, the external auditory canals were clear, tympanic membranes were normal, the nasopharynx looked normal. Weber lateralised on the right ear, Rinne positive bilaterally, but short on the left ear. The audiometric assessment revealed on the pure-tone audiometry a left moderate to severe sensorineural hearing loss on high frequencies (55dB on 2kHz, 90dB on 4kHz and 80dB on 8kHz); there was also a mild decrease in hearing thresholds on 4kHz (35dB) and 8kHz (30dB) in the right ear (Figure 2).

After the diagnosis, the patient was referred to the Neurosurgery Department for specific therapy (surgery and/or gamma knife radiosurgery).

The literature research in the PubMed, ProQuest, Web of Science, Science Direct, Wiley Online databases was performed according to the following inclusion criteria: case reports with medulloblastoma associated with tinnitus and/or hearing loss, articles in English with full access, adult and paediatric patients.

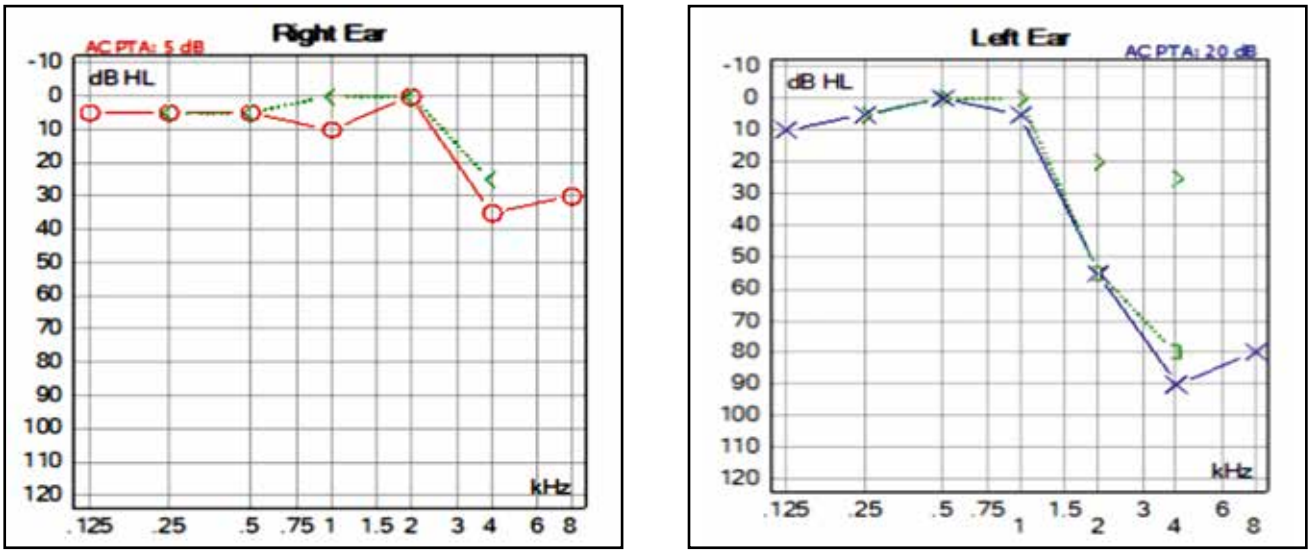


Figure 2. Pure-tone audiometry – left moderate to severe sensorineural hearing loss on high frequencies (55dB on 2kHz, 90dB on 4kHz and 80dB on 8kHz); mild decrease in hearing thresholds on 4kHz (35dB) and 8kHz (30dB) in the right ear.

RESULTS

Following the application of chosen criteria, we found only 21 cases of medulloblastoma associated with auditory dysfunction[5,7,11,14-29] (Table 1). In this study, a gender predominance for male was found (52.3% males, 47.6% females); 38% of the patients were children and 62% of the patients were adults, with a mean age of 23 years (between 2 and 50 years).

Among patients with auditory dysfunction, all of them (21 patients) manifested with sensorineural hearing loss – 81% manifested with unilateral hearing loss and 19% had bilateral hearing loss; 43% of patients related unilateral tinnitus and one of them had transient tinnitus. The most frequent associated clinical manifestations to auditory symptoms were ataxia (48% of cases) followed by facial numbness (38% of patients), vertigo (33% of cases), headache (33% of patients), nystagmus (24% of patients), nausea and vomiting (19% of patients). Only 2 patients (10%) manifested with isolated tinnitus and sensorineural hearing loss[19,24], like our patient, and in 2 cases (10%) the sensorineural hearing loss was the unique symptom[27,28].

Regarding the onset of the medulloblastoma, 3 patients (14%) had the first symptoms tinnitus and sensorineural hearing loss[16,23,24]. Some patients associated other less frequent manifestations such as seizures (10% of patients), ageusia (10% of patients), progressive cranial nerve deficits, facial paralysis, swallowing difficulty, absent corneal reflex, visual impairment, quadriparesis, cognitive impairment, paretic foot musculature (in a patient with leptomeningeal spread).

With reference to the location of the tumor, in patients manifested with isolated tinnitus and sensorineural hearing loss, like our patient, the tumor occurred in the internal auditory meatus, extended to the cerebellopontine angle or it involved the vestibulocochlear nerve. In our patient, the tumor was localised on the left side of the Luschka foramen with extension to the fourth ventricle and left cerebellar peduncle. Even if the mass had contact with the fourth ventricle and cerebellar peduncle, the patient did not have hydrocephalus or other neurological manifestations. In patients with tinnitus, hearing loss and other symptoms (43% of patients), the lesion presented the following localisations: the cerebellopontine angle extended to the fourth ventricle; the cerebellar hemisphere extended to the cerebellopontine angle and the internal auditory meatus; the midline cerebellar or cerebellar vermis extended to the fourth ventricle; the internal auditory meatus extended to the cerebellopontine angle; the cerebellopontine angle compressing the brainstem; the cerebellopontine angle extended to the right porus acusticus and to the foramen magnum.

In most cases (38%), patients were treated by surgery in association with radiotherapy and chemotherapy, while in almost 29% of cases surgery with radiotherapy was the therapeutical choice. The rest of the cases were treated by surgery and chemotherapy (10%) or isolated surgery (10%).

HISTOPATHOLOGICAL AND MOLECULAR CHARACTERISTICS OF MEDULLOBLASTOMAS

Diagnostic criteria from the current classification of medulloblastomas in accordance with the fourth (2016) and fifth (2021) editions of the World Health Organization Classification of Tumors of the Central Nervous System incorporate histopathological characteristics and the molecular features[30] (Table 2).

Histopathological patterns of medulloblastomas

From the histopathologic point of view, medulloblasto-

Table 1. Cases with medulloblastoma associated with auditory dysfunction found in the literature.

Author First published	Age (years) Gender	Initial manifestations	Following manifestations	Lesion localization
Britton et al.[14], 1975	39, M	Progressive right hearing loss Tinnitus Aural fullness	Vertigo Nausea and vomiting Occipital headache Right-sided ageusia Ataxic movements on the right hand Wide-based gait ataxia	From the right cerebellar hemisphere extended to the cerebellopontine angle, with displacement of VII, VIII cranial nerves and partial blockage of the right internal auditory meatus.
Britton et al.[14], 1975	46, F	Progressive right hearing loss	Vertigo Occipital headache Right-sided ageusia Right-sided facial numbness Positional nystagmus, papilledema	From the right cerebellar hemisphere to the right cerebellopontine angle, with obstruction of the right auditory internal meatus and tonsillar herniation on the right side.
Merino et al.[15], 1994	25, F	Sudden left hearing loss	Vertigo Nausea and vomiting Nonlocalized headache Left-sided facial hypoesthesia Anaesthesia of the left external auditory mea-tus	Left cerebellar hemisphere, displacing the fourth ventricle to the right.
Nishizawa et al.[16], 1997	19, F	Tinnitus Sudden right hearing loss	Alternate lateral gaze nystagmus Wide-based gait Right limb ataxia	Lateral recess of the fourth ventricle extended to the right cerebellopontine and cerebellomedullary cisterns.
Mehta et al.[17], 1998	40, M	Sudden right hearing loss Severe vertigo Ataxia	Tinnitus Headache Numbness on the right side of the face Weight loss Hypoesthesia V2, V3 divisions of the right trigeminal nerve Positional nystagmus to the left, right and upward gaze Absent right corneal reflex Mild facial weakness on the right	Right cerebellopontine angle causing distortion of the fourth ventricle.
Park et al.[18], 2004	15, M	Sudden left hearing loss	Facial paralysis on the left side House-Brackmann grade 3	Left cerebellopontine angle cistern and in the internal auditory canal
Magliulo et al.[19], 2005	28, M	Progressive left hearing loss	Left tinnitus	Intracanalicular left internal auditory meatus with extension to the left cerebellopontine angle.
Adeleye et al.[20], 2009	16, F	Right-sided tinnitus Headache	Progressive visual impairment Increasing tinnitus Ataxia Cognitive impairment Seizures Bilateral hearing loss Quadriparesis Bilateral blindness	Cerebellar midline filling up the fourth ventricle causing obstructive hydrocephalus, marked scalloping of the supra-and infratentorial skull bones including the petrous ridge bilaterally.
Lobbes et al.[21], 2010	26, M	Progressive left hearing loss	Right hearing loss Progressive cranial nerve deficits Paretic foot musculature	Left internal auditory canal Right internal auditory canal; bilateral thickening of the cranial nerves III-X Intradural extramedullary lesions on C3 and Th11 thickening of the cauda equina Extensive supratentorial and intraspinal leptomeningeal deposits
Terakawa et al.[22], 2011	19, M	Sudden right hearing loss	Vertigo Facial anaesthesia on the right side	Middle cerebellar peduncle.
Chou et al.[23], 2011	7, F	Transient tinnitus Sudden bilateral hearing loss	Slightly Ataxic gait with left-side deviation	From the cerebellar vermis extended to the fourth ventricle with obstructive hydrocephalus.
Amene et al.[24], 2012	21, M	Tinnitus Sudden right hearing loss	No other neuro-vestibular manifestations	Thickening of the VIII cranial nerve complex, along to other numerous parenchymal lesions that lead to the diagnosis of recurrent metastatic medulloblastoma.

Author First published	Age (years) Gender	Initial manifestations	Following manifestations	Lesion localization
Spina et al.[11], 2013	22, M	Sudden left hearing loss Tinnitus Headache Vertigo Ataxia Right arm weakness Left nystagmus	Mild peripheral deficit of the left facial nerve	A left CPA lesion in contact with the posterior edge of the petrous bone and the tentorium with a supero-medial cyst.
Bahrami et al.[25], 2013	23, M	Sudden right hearing loss	Nausea Vomiting Ataxia	In the right cerebellopontine angle.
Alnaami et al.[26], 2016	7, M	Progressive right hearing loss	Headache Nausea Vomiting Ataxia	In the right cerebellopontine angle extended to the foramen of Luschka and the right internal auditory meatus (IAC) – Crani-al nerve VIII infiltrated with tumor throughout its entire course, the right VII cranial nerve infiltrated with the tumor.
Goudihalli et al.[7], 2018	50, M	Right hearing loss Short duration of facial asymmetry Weak gag	No other neuro-vestibular manifestations	In the right cerebellopontine angle, extending to the porus acusticus and to the foramen magnum.
Roy et al.[27], 2019	2, F	Progressive left hearing loss	Sudden bilateral hearing worsening	From the cerebellar vermis to the roof of the fourth ventricle.
Magg et al.[28], 2019	14, F	Progressive left-side hearing loss	No other neuro-vestibular manifestations	Left cerebellopontine angle originating from the left cerebellar flocculus adjacent to the left cochlear nerve and the brain stem (cochlear nerve partially infiltrated at its entrance into the brain stem).
Magg et al.[28], 2019	14, F	Progressive left-side hearing loss	Mild gait unsteadiness and a slight postural instability	From the caudolateral part of the fourth ventricle up to the left cerebellopontine angle leading to a displacement of the vestibulocochlear nerve.
Thanh Dung et al.[5], 2021	6, F	Progressive right hearing loss Seizure	No other neuro-vestibular manifestations	Right cerebellopontine angle.
Aqel et al.[29], 2022	43, F	Vertigo Headache Vomiting	Tinnitus Progressive left hearing loss Imbalance Swallowing difficulty Unsteady ataxic gait A weak gag reflex on the left side Uvula deviated to the right side (nv IX, X) Left horizontal and vertical nystagmus	Left cerebellopontine angle lesion compressing the brain stem.

mas are classified as follows: classic medulloblastoma; desmoplastic/nodular medulloblastoma; medulloblastoma with extensive nodularity and large cell/anaplastic medulloblastoma (Table 2).

Classic medulloblastomas are by far the most frequent encountered in clinical practice, accounting for 72% of medulloblastomas[31]. The classic type of medulloblastoma is characterized by the absence of mitosis or a persistent mitotic activity, almost round nuclei and the absence of enlarged cell size[32].

Desmoplastic/nodular medulloblastoma is more frequent in adults than the classical variant of medulloblastoma. This histopathological type is characterized by nodules of neurocytic differentiation that contain also embryonal elements, pericellular collagen deposition (identified by reticulin deposition)[32-34].

Medulloblastoma with extensive nodularity is usually described in infants and it is characterised by more nodules (which are predisposed to be irregular and to unite) than primitive elements. There is a pattern described by a connection of adjacent nodules through linear arrangements of neurocytic cells[32].

Large cell/anaplastic medulloblastomas are two variants that were integrated in one variant. Anaplastic medulloblas-

Table 2. Histopathological and molecular classification of medulloblastoma.

Histopathological classification	- classic medulloblastoma - desmoplastic/nodular medulloblastoma - medulloblastoma with extensive nodularity - large cell/anaplastic medulloblastoma
Histopathological classification	- WNT (wingless-type)-activated medulloblastoma - SHH (sonic hedgehog)-activated and TP53-wildtype medulloblastoma - SHH (sonic hedgehog)-activated and TP53-mutant medulloblastoma - non-WNT/ non-SHH medulloblastoma subdivided in group 3 and group 4

tomas are described by increased cytologic pleomorphism, frequent mitotic activity, increased cell size, frequent apoptotic bodies, while large cell medulloblastomas are characterized by round cell morphology, prominent nucleoli and increased cell size[35].

Molecular types of medulloblastomas

Genetically defined medulloblastomas are classified as: WNT (wingless-type)-activated medulloblastoma, SHH (Sonic Hedgehog)-activated and TP53-wildtype medulloblastoma, SHH (Sonic Hedgehog)-activated and TP53-mutant medulloblastoma, non-WNT/non-SHH medulloblastomas (subdivided in group 3 (G3) and group 4 (G4)) (Table 2). Molecular types of medulloblastoma may be identified by immunohistochemistry (by pattern expression of three proteins GAB1, YAP1, beta-catenin), molecular genetics and a diversity of molecular profiling approaches by a variety of nucleic acid-base techniques (such as DNA fluorescence in situ hybridization, RNA and DNA sequencing, RNA expression profiling) and by methylome and transcriptome profiling[36].

In adults, SHH-activated medulloblastoma is the most frequent molecular group accounting for up to 60% of all cases, representing 30% of all medulloblastomas[30,31,37]. Usually, this tumor is located laterally in the cerebellar hemispheres or in the cerebellar vermis and, most frequently, it is associated with desmoplastic medulloblastoma[38,39].

WNT-activated medulloblastoma may be found in roughly 15% of adults with medulloblastoma and it is the least frequent type of medulloblastoma[37]. This tumor usually appears in the midline or near the cerebellopontine angle, involving the brainstem, cerebellar peduncle and extending through the foramen of Luschka[39,40].

When it appears in adults, G3 tumors are highly rare, but G4 tumors are regular, up to 25% of these types of medulloblastomas being present in adults. Statistically, G3 tumors have a frequency of 20% and G4 tumors of 40%[37].

Non-WNT/Non-SHH medulloblastomas are the most frequent types of medulloblastoma and they are usually located in the midline and the fourth ventricle. The most of these tumors are associated with classic medulloblastoma and in some cases with large cell medulloblastoma[37,41].

RADIOLOGIC CRITERIA FOR MEDULLOBLASTOMAS

Craniospinal magnetic resonance imaging is the gold standard diagnostic imaging in medulloblastoma. Computer tomography imaging is recommended in emergency and in patients with contraindications to magnetic resonance imaging.

On magnetic resonance imaging (MRI), medulloblastoma appears as intra-axial mass with slight edema and sharp margins. There are described some MRI characteristics of medulloblastoma such as the specific localisation (a posterior fossa mass with possibly obstructive hydrocephalus), variable enhancement patterns (from strong to mild or even no enhancement identified), variable signal intensity (from hyperintense to hypointense on T2 signal; a decreased T2 signal is a sign for important cellularity), tumor margins (ill-defined or well-defined), diffusion restriction of the tumor compared to the adjacent cerebellar parenchyma, tumors with or without edema, cystic or necrotic changes are mostly small and may appear in up to 50% of cases[42], but calcifications are uncommon in medulloblastomas[4]. It was observed that group 3 from non-WNT/non-SHH medulloblastomas present strong enhancement, while group 4 medulloblastomas show weak enhancement[42].

On T1-weighted images lesions are usually hypointense and on T2-weighted images lesions appear from hypointense to hyperintense, compared to normal grey matter, according to molecular and histopathological subtype. The lesion presents moderate to strong contrast after intravenous administration of contrast agents. It is suggested to achieve diffusion-weighted images on which medulloblastoma appears with restricted diffusion because of the high cellularity of this tumor[43]. In our patient, the magnetic resonance imaging showed a nodular lesion with tissular isointense signal on T1 and T2, slightly hyperintense FLAIR localised on the left side of the Luschka foramen, with extension to the fourth ventricle and left cerebellar peduncle (Figure 1).

With diffusion MRI are evaluated different brain injuries such as abscesses, tumors or ischemia. Apparent diffusion coefficient amount of tumor depends on nuclear area and cellular density and it is useful in differentiating medulloblastoma from other brain tumors[44].

The CT scan usually shows a high-density lesion because of important tumor cellularity in the posterior fossa. On CT, medulloblastoma may appear as a well-defined, hyperdense mass with edema around, on the midline in the cerebellar vermis and frequently compressing the fourth ventricle with obstructive hydrocephalus. Also, CT imaging may be useful in detecting mineralization and haemorrhage areas[43,45,46].

It was reported that in some patients with hearing loss, tinnitus or dizziness, unexpectedly, the computer tomography scan of petrous bones did not show any lesion at the level of the internal auditory canal, but on the MRI examination, a lesion was noted in the cerebellopontine angle as a homogenous solid mass which appeared hyperintense on T2-weighted image[5,33].

DIFFERENTIAL DIAGNOSIS OF CEREBELLOPONTINE ANGLE MEDULLOBLASTOMA

Cerebellopontine angle medulloblastoma sometimes cannot be clearly differentiated from other cerebellopontine angle tumors, such as meningioma, schwannoma, epidermoid cyst, ependymoma, because their radiological and clinical features may not be completely different. For example, it is difficult to differentiate a cerebellopontine medulloblastoma with hearing loss from an acoustic schwannoma. Usually, on MRI images, acoustic schwannoma appears as a hypointense mass on the T1 sequence, and heterogeneous hyperintensity on T2 that appears homogeneous after the contrast substance administration. Patients with acoustic schwannoma may present with unilateral hearing loss,

tinnitus and some of them with vertigo. On CT imaging, it may appear as a heterogeneous mass in the cerebellopontine angle[7,47]. One must keep in mind that the acoustic schwannoma is the most frequent tumor found in the cerebellopontine angle, and the most important tumor with which the differential diagnosis of medulloblastoma should be made[5].

Meningioma commonly appears near the petrosal and sigmoid sinuses, in the posterior part of the petrous pyramid. Most often, it is discovered incidentally. When meningioma is identified in the cerebellopontine angle, it is usually calcified with hyperostosis of the adjacent bone. The signs and symptoms appear late because the tumor grows outside the internal auditory canal. Most of the patients complain about hearing loss and tinnitus[48].

Epidermoid tumors are frequently localised in the posterior fossa and are commonly found in the third and fourth decade of life. In the beginning, most of the patients complain about asymmetric tinnitus and hearing loss and others about headache and instability. Some of the patients may present spasms and facial tic. The CT scan shows a homogenous low-density mass, and MRI reveals a mass with a high signal on T2, a low non-enhancing signal on T1[49].

Ependymoma, in contrast to medulloblastoma, occurs from the floor of the fourth ventricle or cerebellopontine angle. This tumor particularly spreads via the foramen of Luschka or Magendie and it may be attached to the nerve roots and vessels. Calcifications occur in almost 50% of cases and are better identified on CT scan. Ependymoma, in comparison to medulloblastoma, appears on MRI as a heterogeneous mass with intermediate diffusion, commonly enhancing and usually with calcifications[50].

PROGNOSTIC FACTORS

There are several prognostic factors that should be considered in medulloblastomas, such as: age, gender, tumor's location, tumor's size, risk group, histological type, molecular type, stage, involvement of brainstem / the fourth ventricle floor / cerebrospinal fluid, extent of resection, interval between surgery and the beginning of radiotherapy, the dose of cerebrospinal irradiation, use of chemotherapy[51-53].

Regarding the negative prognostic factors, we point out: the residual postoperative tumor, metastasis especially M2-M3, desmoplastic histology and large cell histology compared to classic histology, extent of the medulloblastoma further the posterior fossa, reduction in radiotherapy dose[51,53].

Positive prognostic factors include female, younger age at diagnosis may be a positive factor, limited extension of medulloblastoma at presentation.

The prognosis of medulloblastoma is based on tumor stage, histopathological type, molecular type, treatment of choice, age, extend of resection.

Medulloblastoma stages (Chang classification) is based on pre-operative radiological characteristics and intraoperative ones to determine T stage and M stage[43] (Table 3).

There are some differences regarding the prognosis of medulloblastoma in adults and paediatric patients. Risk stratification in children depends on age less or over 3 years, extend of the tumor, histological type and molecular type. It was observed that infants and children under 3 years had poorer survival rates than older children because of reduced dose of radiotherapy or missing radiotherapy[54].

In children between 0-5 years old, the 5-year survival rate is reported between 30% and 60%. Infants with desmoplastic medulloblastoma compared to classic and anaplastic medulloblastoma, treated with chemotherapy alone, have better survival rates up to 90%[55]. In high-risk patients, survival rates seem to range between 30% and 40% and in average risk patients, survival rates from 70 to 80%[51].

Dufour et al., in a study centered on M stages, reported in patients with M1 a 5-year overall survival rate of 47%, in patients with M2 5-year survival rates of 51% and in patients with M3, 42%[56].

Medulloblastomas metastasize in the spinal canal, leptomeninges and supratentorial regions through the cerebrospinal fluid. Metastases may appear between 38% and 60% of cases and the most frequent metastases are in the spinal canal (58%), but cerebellopontine angle medulloblastomas rarely metastasize in the spinal canal[57,58].

The overall survival rates of medulloblastoma in adults is reported between 70% and 80% after radiotherapy[52,59].

The dose of radiotherapy is a prognostic factor. Abidi et al. reported that the 5-year survival rate was 53% and 10-year survival rate was 34% in patients who underwent craniospinal radiotherapy after surgery[53].

It was observed that postoperative radiotherapy and chemotherapy have improved the prognosis. The dose of chemotherapeutics and radiation may be individualized, and it should be reduced in children with low risk of recurrence[60].

WNT medulloblastoma has a favourable prognosis in the paediatric population with a survival rate at 5 years over 90%;

Table 3. Medulloblastoma TM staging according to Chang[43].

T stage	
T1	Tumor < 3 cm
T2	Tumor > 3 cm
T3a	Tumor > 3 cm extended in the aqueduct of Sylvius and/or the foramen of Luschka
T3b	Tumor > 3cm extended in the brainstem
T4	Tumor > 3 cm extended down over the foramen magnum and/or up the aqueduct of Sylvius
M stage	
M0	No evidence of hematogenous metastasis or gross subarachnoid
M1	Microscopic tumor cells found in the cerebrospinal fluid
M2	Evidence of gross nodular seeding in the cerebellar or cerebral subarachnoid space or in the lateral or the third ventricle
M3	Evidence of gross nodular seeding in the spinal subarachnoid space
M4	Metastases outside de cerebrospinal axes

in adults, the prognosis is worse and they are not classified as a low-risk group as those from the paediatric population[61,62]. WNT-activated medulloblastomas have violent evolution if they remain untreated. Almost all patients that are receptive to current therapeutical management, have long-term survival[30].

The 5-year survival rate is 76% in SHH-activated medulloblastoma and TP53-wildtype medulloblastoma with an intermediate risk disease. TP53 anomalies in SHH medulloblastoma have bad prognosis, being associated with a 5-year survival rate of around 41% and a high-risk disease[63,64]. SHH medulloblastomas have been divided in four subgroups (SHH- α, β, γ, δ) by Advanced Genomics International Consortium[61]. The majority of children have SHH-α and almost all infants have SHH-β, SHH-γ, whereas adults have SHH-δ tumors. It was observed that SHH-β medulloblastomas have worse prognosis with a 5-year survival rate of 67% than 88% 5-year survival rate in SHH-γ medulloblastomas[54]. The adult population from the SHH-δ group present with metastatic medulloblastoma in less than 10%, having a favourable prognosis with 5-year survival rate of 88.5%[65].

In comparison with WNT medulloblastomas and SHH medulloblastomas, Non-WNT and Non-SHH medulloblastomas have the worst overall prognosis. For example, G3 medulloblastomas have an overall survival rate <60%. G3 medulloblastomas appear in around 45% of the infant population and G4 medulloblastomas appear commonly in older paediatric patients[66].

TREATMENT OF CEREBELLOPONTINE ANGLE MEDULLOBLASTOMA

Regarding the management of medulloblastomas, the standard therapeutic approach is surgery accompanied by chemotherapy and/or radiotherapy. A total resection of the tumor should be performed if it is possible. Where a total resection is not possible, a maximum safe resection should be performed. The purpose of the surgery is to procure samples for molecular and histological examination, to decrease the tumor compression effect and the intracranial pressure, solving a possible hydrocephalus. In hydrocephalus, surgery with tumour removal should be taken into consideration. If immediate surgery is not achievable, in hydrocephalus, at least an external ventricular drain is required. Before surgery, vasogenic tumour oedema should be decreased using corticosteroids[43,67,68].

Postoperative radiotherapy is compulsory in patients with intermediate risk (patients with residual tumor less than 1.5 cm^2, M0, M1, classic or desmoplastic histology and WNT or SHH molecular subtype) and hight risk (patients with residual tumor greater than 1.5 cm^2, M2, M3, M4, anaplastic or large cell histology, non-WNT or non-SHH molecular subtype and the presence of SHH p53 mutation)[50]**.** Craniospinal irradiation with sufficient target volume coverage should be performed in association with a local boost to the tumor bed.

To decrease long-term side effects, proton therapy is a possible choice. In children, it is suggested to initiate radiotherapy within 28-42 days after surgery, according to paediatric protocols[69,70]. Proton therapy seems to have some advantages regarding early and late toxicity such as decreasing hematotoxicity, ototoxicity, cardiotoxicity and endocrine dysfunction[71-73].

Gamma Knife stereotactic radiosurgery proved to be beneficial as adjunctive therapy for residual or recurrent medulloblastoma[74,75].

Systemic therapy should be associated in adult patients beside surgery and radiotherapy, regardless of their risk classification, because medulloblastomas are chemosensitive tumours. In adults, especially in Europe, the packer chemotherapy systematic plan is used, which consists in cisplatin, vincristine, lomustine. Tolerance to this therapy is better in children than in adults[76].

In one of those two patients with medulloblastoma manifested only with tinnitus and hearing loss and intracanalicular localisation of the tumor, the left internal auditory meatus extended to the left cerebellopontine angle, the chosen treatment was surgery with total resection of the tumor with preservation of the cranial nerves (VII, VIII, IX, X, XI), followed by radiotherapy and chemotherapy without symptoms at the 7-month follow-up[19]. In the other patient with medulloblastoma and isolated auditory symptoms (tinnitus, hearing loss), the tumor appeared at the level of the VIII cranial nerve complex and other numerous parenchymal lesions were also described, with the diagnosis of recurrent metastatic medulloblastoma. The therapeutic option for this patient was stereotactic radiosurgery, but he died 6 months after his surgery and 8 years after the initial diagnosis. It is important to mention that this patient had 2 recurrences treated by radiotherapy and chemotherapy (first time), chemotherapy and biologics (the second time)[24].

Some authors consider that treatment with COX2 inhibitors which target prostanoid production can have some benefits against medulloblastoma, because it was demonstrated that this tumor is dependent on the activity of prostaglandin E2 for growth. It was observed that the inhibition of prostaglandin E2 synthesis caused a decline in cell viability depending on the concentration of inhibitors. It was noticed that the clonogenic capacity of medulloblastoma cells can be inhibited by COX2 inhibitors and also producing apoptosis[77].

CONCLUSIONS

Medulloblastoma is a very rare tumor in young and adult patients with a precisely particular profile from clinical, prognostic, molecular and therapeutic perspective. It is important to pay attention to patients with isolated auditory dysfunction that may mimic significant posterior fossa tumors. Regardless of the distinctive risk, the standard therapeutic management of medulloblastoma is surgery accompanied by cranio-spinal radiotherapy and multi-modal chemotherapy.

Conflict of interest: The authors have no conflict of interest.
Contribution of authors: All the authors have equally contributed to this work.

REFERENCES

1. Xia H, Zhong D, Wu X, Li J, Yang Y, Sun X. Medulloblastomas in cerebellopontine angle: Epidemiology, clinical manifestations, imaging features, molecular analysis and surgical outcome. J Clin Neurosci. 2019;67:93-8. DOI: 10.1016/j.jocn.2019.06.013.
2. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology, therapy, and late effects. Semin Radiat Oncol. 2010;20(1):5866. DOI: 10.1016/j.semradnoc.2009.09.005.
3. Bailey P, Cushing H. Medulloblastoma cerebelli, a common type of mid-cerebellar glioma of childhood. Arch Neurol Psychiatr. 1999;14:192-224.
4. Jaju A, Yeom KW, Ryan ME. MR imaging of pediatric brain tumors. Diagnostics (Basel). 2022;12(4):961. DOI: 10.3390/diagnostics12040961.
5. Dung LT, Duc NM. Medulloblastoma in the cerebellopontine angle mimicking a schwannoma. Clin Case Rep. 2021;9(4):1948-53. DOI: 10.1002/ccr3.3912.
6. Kadin ME, Rubinstein LJ, Nelson JS. Neonatal cerebellar medulloblastoma originating from the fetal external granular layer. J Neuropathol Exp Neurol. 1970;29(4):583-600. DOI: 10.1097/00005072-197010000-00005.
7. Goudihalli SR, Pathak A, Brar R, Mundi I. Reappraisal of cerebellopontine angle medulloblastomas: Report of a fatal case and lessons learned. Interdisciplinary Neurosurgery. 2018;12:20-3.
8. Murase M, Saito K, Abiko T, Yoshida K, Tomita H. Medulloblastoma in older adults: a case report and literature review. World Neurosurg. 2018;117:25-31. DOI: 10.1016/j.wneu.2018.05.216.
9. Chen CC, Cheng PW, Tseng HM, Young YH. Posterior cranial fossa tumors in young adults. Laryngoscope. 2006;116(9):1678-81. DOI: 10.1097/01.mlg.0000233507.13293.d9.
10. Hadi I, Roengvoraphoj O, Niyazi M, Roeder F, Schuller U, Belka C, et al. Medulloblastoma in adults: A retrospective single institution analysis. Stranhlenther Onkol. 2018;194(3):225-34. DOI: 10.1007/s00066-017-1235-5.
11. Spina A, Boari N, Gagliardi F, Franzin A, Terreni MR, Mortini P. Review of cerebellopontine angle medulloblastoma. Br J Neurosurg. 2013;27(3):316-20. DOI: 10.3109/02688697.2012.741733.
12. Gil-Salu JL, Rodriguez-Pena F, Lopez-Escobar M, Palomo MJ. Medulloblastoma presenting as an extra-axial tumor in the cerebellopontine angle. Neurocirugia (Astur). 2004;15(3):285-9. DOI: 10.1016/s1130-1473(04)70485-6.
13. Akay KM, Erdogan E, Izci Y, Kaya A, Timurkaynak E. Medulloblastoma of the cerebellopontine angle –case report. Neurol Med Chir (Tokyo). 2003;43(11):555-8. DOI: 10.2176/nmc.43.555.
14. Britton BH. Adult medulloblastoma: neurotologic manifestations. Ann Otol Rhinol Laryngol. 1975;84(3 Pt 1):364-7. DOI: 10.1177/000348947508400313.
15. Galvez EM, Meseguer DH, Ortega FG, Mondejar JM. Sudden deafness and cerebellar tumour. J Laryngol Otol. 1994;108(7):584-6. DOI: 10.1017/s0022215100127495.
16. Nishizawa S, Yokoyama T, Hinokuma K, Uemura K. Unilateral sensori-neural hearing disturbance caused by intramedullary cerebellar tumors – three case reports. Neurol Med Chir. 1997;37(9):701-7. DOI: 10.2176/nmc.37.701.
17. Mehta JS, Sharr MM. An unusual cause of acute labyrinthine failure. J Laryngol Otol. 1998;112(2):193-5. DOI: 10.1017/s0022215100140290.
18. Park SY, Kim JH, Kim KT, Kim YJ, Kim TH, Hwang K, et al. A case of medullomyoblastoma of cerebellopontine angle mimicking acoustic neuroma. Yonsei Med J. 2004;45(4):719-22. DOI: 10.3349/ymj.2004.45.4.719.
19. Magliulo G, Parrotto D, Pulice G, Celebrini A, Giangaspero F. Medulloblastoma of the cerebellopontine angle in adulthood. Audiol Med. 2005;3:208-11.
20. Adeleye AO, Balogun JA. Bilateral deafness and blindness from a IVth ventricular medulloblastoma. Br J Neurosurg. 2009;23(3):315-7. DOI: 10.1080/02688690802512858.
21. Lobbes M, Hoeberigs MC, van Genugten J, van Oostenbrugge R, Stokroos R, Cornips EM, et al. A rare case of extra-axial medulloblastoma presenting with multiple cranial nerve thickening. Neuro Oncol. 2010;12:1-6.
22. Terakawa Y, Tsuyuguchi N, Takami T, Ohata K. Medulloblastoma manifesting as sudden sensorineural hearing loss. J Korean Neurosurg Soc. 2011;50(1):51-3. DOI: 10.3340/jkns.2011.50.1.51.
23. Chou YT, Liao PW, Lin MCH, Chou JC, Lin YH, Lin MH, et al. Medulloblastoma presenting with pure word deafness: report of one case and review of literature. Pediatr Neonatol. 2011;52(5):290-3. DOI: 10.1016/j.pedneo.2011.06.009.
24. Amene CS, Yeh-Nayre LA, Crawford JR. Isolated sensorineural hearing loss as initial presentation of recurrent medulloblastoma: neuroimaging and audiologic correlates. Clin Neuroradiol. 2013;23(4):301-3. DOI: 10.1007/s00062-012-0186-6.
25. Bahrami E, Bakhti S, Fereshtehnejad SM, Parvaresh M, Khani MR. Extra-axial medulloblastoma in cerebello-pontine angle: A report of a rare case with literature review. Med J Islam Repub Iran. 2014;28:57.
26. Alnaami I, El-Hakim H, Aronyk K, Pugh J, Lu JQ, Mehta V. A pediatric medulloblastoma presenting as an isolated unilateral sensory neural hearing loss. ZUMJ. 2016;22(5):209-13.
27. Roy CF, Yang L, Daniel SJ. A pediatric medulloblastoma presenting as isolated sensorineural hearing loss: Case report and review of the literature. Int J Pediatr Otorhinolaryngol. 2019;126:109640. DOI: 10.1016/j.ijporl.2019.109640.
28. Magg J, Nägele T, Alber M, Weichselbaum A, Ebinger M, Schuhmann MU. Unilateral hearing loss due to cochlear nerve involvement as isolated symptom of a primary medulloblastoma. Neuropediatrics. 2020;51(2):170-2. DOI: 10.1055/s-0039-3399528.
29. Aqel W, Salman A, Aldarawish A, Bakri I. Medulloblastoma at the cerebello-pontine angle resembling vestibular schwannoma: A case report and review of the literature. Int J Surg Case Rep. 2022;99:107695. DOI: 10.1016/j.ijscr.2022.107695.
30. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-51. DOI: 10.1093/neuonc/noab106.
31. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131(6):803-20. DOI: 10.1007/s00401-016-1545-1.
32. Orr BA. Pathology, diagnostics, and classification of medulloblastoma. Brain Pathol. 2020;30(3):664-78. DOI: 10.1111/bpa.12837.
33. Furtado SV, Venkatesh PK, Dadlani R, Reddy K, Hegde AS. Adult medulloblastoma and the "dural-tail" sign: rare mimic of a posterior petrous meningioma. Clin Neurol Neurosurg. 2009;111(6):540-3. DOI: 10.1016/j.clineuro.2009.02.002.
34. McManamy CS, Pears J, Weston CL, Hanzely Z, Ironside JW, Taylor RE, et al. Nodule formation and desmoplasia in medulloblastomas-defining the nodular/desmoplastic variant and its biological behavior. Brain Pathol. 2007;17(2):151-64. DOI: 10.1111/j.1750-3639.2007.00058.x.
35. McManamy CS, Lamont JM, Taylor RE, Cole M, Pearson AD, Clifford SC, et al. Morphophenotypic variation predicts clinical behavior in childhood non-desmoplastic medulloblastomas. J Neuropathol Exp Neurol. 2003;62(6):627-32. DOI: 10.1093/jnen/62.6.627.
36. Andreiuolo F, Mazeraud A, Chrétien F, Pietsch T. A global view on the availability of methods and information in the neuropathological diagnostics of CNS tumors: results of an international survey among neuropathological units. Brain Pathol. 2016;26(4):551-4. DOI: 10.1111/bpa.12383.
37. Remke M, Hielscher T, Northcott PA, Witt H, Ryzhova M, Wittmann A, et al. Adult medulloblastoma comprises three major molecular variants. J Clin Oncol. 2011;29(19):2717-23. DOI: 10.1200/JCO.2011.34.9373.
38. Hovestadt V, Ayrault O, Swartling FJ, Robinson GW, Pfister SM, Northcott PA. Medulloblastomics revisited: biological and clinical insights from thousands of patients. Nat Rev Cancer. 2020;20(1):42-56. DOI: 10.1038/s41568-019-0223-8.
39. Patay Z, DeSain LA, Hwang SN, Coan A, Li Y, Ellison DW. MR imaging characteristics of wingless-type-subgroup pediatric medulloblastoma. AJNR Am J Neuroradiol. 2015;36(12):2386-93. DOI: 10.3174/ajnr.A4495.
40. Kumar R, Liu APY, Northcott PA. Medulloblastoma genomics in the modern molecular era. Brain Pathol. 2020;30(3):679-90. DOI: 10.1111/bpa.12804.
41. Perreault S, Ramaswamy V, Achrol A, Chao K, Liu T, Shih D, et al. MRI surrogates for molecular subgroups of medulloblastoma. AJNR Am J Neuroradiol. 2014;35(7):1263-9. DOI: 10.3174/ajnr.A3990.
42. Brandao LA, Poussaint TY. Posterior fossa tumors. Neuroimaging Clin N Am. 2017;27(1):1-37. DOI: 10.1016/j.nic.2016.08.001.
43. Franceschi E, Giannini C, Furtner J, Pajtler KW, Asioli S, Guzman R, et al. Adult medulloblastoma: updates on current management and future perspectives. Cancers (Basel).

2022;14(15):3708. DOI: 10.3390/cancers14153708.

44. Yeom KW, Mobley BC, Lober RM, Andre JB, Partap S, Vogel H, et al. Distinctive MRI features of pediatric medulloblastoma subtypes. AJR Am J Roentgenol. 2013;200(4):895-903. DOI: 10.2214/AJR.12.9249.
45. Pant I, Chaturvedi S, Gautam VKS, Sarma P, Satti DK. Extra-axial adult cerebellopontine angle medulloblastoma: Revisiting a rare entity. J Can Res Ther. 2022;18(3):770-3. DOI: 10.4103/jcrt.JCRT_675_20.
46. Bourgouin PM, Tampieri D, Grahovac SZ, Léger C, Del Carpio R, Melançon D. CT and MR imaging findings in adults with cerebellar medulloblastoma: Comparison with findings in children. AJR Am J Roentgenol. 1992;159(3):609-12. DOI: 10.2214/ajr.159.3.1503035.
47. Kohan D. Rare tumors of the cerebellopontine angle. In: Kohan D, Heman-Ackah SE, Chandrasekhar SS. Neurotology. Oxford University Press, New York; 2014, p.55-62.
48. Eskey CJ, Belden CJ, Pastel DA, Vossough A, Yoo AJ. Neuroradiology Cases (Cases in Radiology). Oxford University Press, USA; 2012, p.187-8.
49. Baloh RW, Honrubia V, Kerber KA. Tumors. In: Baloh RW, Honrubia V, Kerber KA. Baloh and Honrubia's clinical neurophysiology of the vestibular system, 4 edn. Contemporary Neurology Series. Oxford University Press, New York; 2011, p.339-351.
50. Franceschi E, Seidel C, Sahm F, Pajtler KW, Hau P. How we treat medulloblastoma in adults. ESMO Open. 2021;6(4):100173. DOI: 10.1016/j.esmoop.2021.100173.
51. Rutkowski S, von Hoff K, Emser A, Zwiener I, Pietsch T, Figarella-Branger D, et al. Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. J Clin Oncol. 2010;28(33):4961-8. DOI: 10.1200/JCO.2010.30.2299.
52. Buglione M, Ghirardelli P, Triggiani L, Pedretti S, Pasinetti N, De Bari B, et al. Radiotherapy for adult medulloblastoma: Long term result from a single institution. A review of prognostic factors and why we do need a multi-institutional cooperative program. Rep Pract Oncol Radiother. 2015;20(4):284-91. DOI: 10.1016/j.rpor.2015.03.003.
53. Abidi R, Boussarsar A, Yahyaoui S, Aissaoui D, Mousli A, Kochbati L, et al. Survival and prognostic factors in adult medulloblastoma: the Salah Azaiz Institute experience. Br J Neurosur. 2021;1-4. DOI: 10.1080/02688697.2021.1895969.
54. Robinson GW, Rudneva VA, Buchhalter I, Billups CA, Waszak SM, Smith KS, et al. Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial. Lancet Oncol. 2018;19(6):768-84. DOI: 10.1016/S1470-2045(18)30204-3.
55. Ashley DM, Merchant TE, Strother D, Zhou T, Duffner P, Burger PC, et al. Induction chemotherapy and conformal radiation therapy for very young children with non-metastatic medulloblastoma: Children's Oncology Group study P9934. J Clin Oncol. 2012;30(26):3181-6. DOI: 10.1200/JCO.2010.34.4341.
56. Dufour C, Beaugrand A, Pizer B, Micheli J, Aubelle MS, Fourcade A, et al. Metastatic medulloblastoma in childhood: Chang's classification revisited. Int J Surg Oncol. 2012;2012:245385. DOI: 10.1155/2012/245385.
57. Mohan M, Pande A, Vasudevan MC, Ramamurthi R. Pediatric medulloblastoma: A review of 67 cases at a single institute. Asian J Neurosurgery. 2008;2:63-69.
58. Singh M, Cugati G, Symss NP, Pande A, Vasudevan MC, Ramamurthi R. Extra axial adult cerebellopontine angle medulloblastoma: An extremely rare site of tumor with metastasis. Surg Neurol Int. 2011;2:25 DOI: 10.4103/2152-7806.77178.
59. Vigneron C, Antoni D, Coca A, Niederst C, Jarnet D, Meyer P, et al. Adult medulloblastoma: Retrospective series of 21 patients. Cancer Radiother. 2016;20(1):14-7. DOI: 10.1016/j.canrad.2015.07.156.
60. Zhang ZY, Xu J, Ren Y, Li KKW, Ng HK, Mao Y, et al. Medulloblastoma in China: clinicopathologic analyses of SHH, WNT, and non-SHH/WNT molecular subgroups reveal different therapeutic responses to adjuvant chemotherapy. PLoS One. 2014;9(6):e99490. DOI: 10.1371/journal.pone.0099490.
61. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, et al. Intertumoral heterogeneity within medulloblastoma subgroups. Cancer Cell. 2017;31(6):737-54.e6. DOI: 10.1016/j.ccell.2017.05.005.
62. Clifford SC, Lusher ME, Lindsey JC, Langdon JA, Gilbertson RJ, Straughton D, et al. Wnt/ Wingless pathway activation and chromosome 6 loss characterize a distinct molecular sub-group of medulloblastomas associated with a favorable prognosis. Cell Cycle. 2006;5(22):2666-70. DOI: 10.4161/cc.5.22.3446.
63. Kool M, Jones DTW, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, et al. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. Cancer Cell. 2014;25(3):393-405. DOI: 10.1016/j.ccr.2014.02.004.
64. Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC, et al. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol. 2013;31(23):2927-35. DOI: 10.1200/JCO.2012.48.5052.
65. Remke M, Ramaswamy V, Peacock J, Shih DJH, Koelsche C, Northcott PA, et al. TERT promoter mutations are highly recurrent in SHH subgroup medulloblastoma. Acta Neuropathol. 2013;126(6):917-29. DOI: 10.1007/s00401-013-1198-2.
66. Northcott PA, Lee C, Zichner T, Stütz AM, Erkek S, Kawauchi D, et al. Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature. 2014;511(7510):428-34. DOI: 10.1038/nature13379.
67. Seidel C, Heider S, Hau P, Glasow A, Dietzsch S, Kortmann RD. Radiotherapy in medulloblastoma—evolution of treatment, current concepts and future perspectives. Cancers. 2021;13(23):5945. DOI: 10.3390/cancers13235945.
68. Thompson EM, Hielscher T, Bouffet E, Remke M, Luu B, Gururangan S, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol. 2016;17(4):484-95. DOI: 10.1016/S1470-2045(15)00581-1.
69. Packer RJ, Sutton LN, Elterman R, Lange B, Goldwein J, Nicholson HS, et al. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg. 1994;81(5):690-8. DOI: 10.3171/jns.1994.81.50690.
70. Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. Lancet Oncol. 2016;17(3):287-98. DOI: 10.1016/S1470-2045(15)00167-9.
71. Liu KX, Ioakeim-Ioannidou M, Susko MS, Rao AD, Yeap BY, Snijders AM, et al. A multi-institutional comparative analysis of proton and photon therapy-induced hematologic toxicity in patients with medulloblastoma. Int J Radiat Oncol Biol Phys. 2021;109(3):726-35. DOI: 10.1016/j.ijrobp.2020.09.049.
72. Zhang R, Howell RM, Homann K, Giebeler A, Taddei PJ, Mahajan A, et al. Predicted risks of radiogenic cardiac toxicity in two pediatric patients undergoing photon or proton radiotherapy. Radiat Oncol. 2013;8(1):184. DOI: 10.1186/1748-717X-8-184.
73. Eaton BR, Esiashvili N, Kim S, Patterson B, Weyman EA, Thornton LT, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. Neuro Oncol. 2016;18(6):881-7. DOI: 10.1093/neuonc/nov302.
74. Germanwala AV, Mai JC, Tomycz ND, Niranjan A, Flickinger JC, Kondziolka D, et al. Boost Gamma knife surgery during multimodality management of adult medulloblastoma. J Neurosurg. 2008;108(2):204-9. DOI: 10.3171/JNS/2008/2/0204.
75. Flannery T, Kondziolka D, Lunsford LD. Boost Gamma Knife surgery during multimodality management of medulloblastoma/PNET tumors. In: Hayat M. (eds.) Paediatric Cancer, Volume 3. Springer, Dordrecht; 2012, p.159-71. DOI: 10.1007/978-94-007-4528-5_18.
76. Packer RJ, Goldwein J, Nicholson HS, et al. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study. J Clin Oncol. 1999;17(7):2127-36.
77. Baryawno N, Vseinbjornsson B, Eksborg S, Orrego A, Segerstrom L, Oqvist CO, et al. Tumor-growth-promoting cyclooxygenase-2 prostaglandin E2 pathway provides medulloblastoma therapeutic targets. Neuro Oncol. 2008;10(5):661-74. DOI: 10.1215/15228517-2008-035.

This is an open access article published under the terms and conditions of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License (https://creativecommons.org/licenses/by-nc-nd/4.0/). CC BY-NC-ND 4.0 license requires that reusers give credit to the creator by citing or quoting the original work. It allows reusers to copy, share, read, download, print, redistribute the material in any medium or format, or to link to the full texts of the articles, for non-commercial purposes only. If others remix, adapt, or build upon the material, they may not distribute the modified material.