

Embryonal Brain Tumours In Children

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Abstract

Brain tumors are the most common solid tumors of childhood and represent a diverse group of neoplasms with varying histology. Despite the enormous improvements in the treatment over the last few decades, brain tumors in childhood remain the greatest challenge in pediatric oncology. Embryonal tumors are the largest group of malignant brain tumors in children. According to the 2007 world health organization (WHO) classification of central nervous system tumors this group includes three main histological entities; medulloblastoma, primitive neuroectodermal tumor and atypical teratoid/rhabdoid tumor. Medulloblastoma constitutes 20% of the primary CNS tumors and 40% of all cerebellar neoplasms; the most common brain tumor among children. On the contrary atypical teratoid/rhabdoid tumor occurs primarily in early childhood and is a rare neoplasm. It behaves in a very aggressive manner and while cure is possible, no standard or effective therapy has been defined for the most patients. Multiple signaling pathways have been associated with tumor formation and growth. Here we present the histological and immunohistochemical features of each neoplasm and try to examine the involvement of these pathways in embryonal tumor malignancy, focusing on their mode of deregulation, prognostic value, functional effects and amplifications for therapy, since a better understanding of the molecular pathways, involved in these tumors formation may allow the discovery of new drugs, which act on specific targets. In addition, there is a major hope for the future, that the incorporation of biological agents, targeting specific signaling pathways will have the potential to act favorably on these diseases, make treatment more effective and also allow a reduction in neurotoxic therapy.

Key Words: embryonal tumor, medulloblastoma, atypical teratoid rhabdoid tumor, prognosis.

Introduction

Central nervous system tumors are the second most common neoplasm in children after leukemia. Embryonal brain tumours account for 20-25% of all brain neoplasms in children and represent the second most frequent group of pediatric brain tumours after astrocytomas¹⁻⁴. Embryonal brain neoplasms can be undifferentiated, whereas others exhibit specific cytoarchitectural or immunophenotypic features that classify them into a specific category. The histogenesis of embryonal brain neoplasms has been a matter of debate. The latest world health organization (WHO) Classification scheme on brain tumours has incorporated some changes in the group of central nervous system (CNS) embryonal neoplasms [Table 1]. Embryonal tumors comprise medulloblastoma, CNS primitive neuroectodermal tumour [PNET] and Atypical Teratoid/Rhabdoid tumour, which correspond to grade IV tumours according to WHO Classification 2,3. The histological and genetic features of the above neoplasms will be analyzed in the following text.

Medulloblastoma

Medulloblastoma (MB) constitutes 40% of all cerebellar neoplasms; the most common brain tumor among children. The annual incidence of MB is approximately 0,5/100.000 children younger than 15 years, with 70% of the tumors occurring in persons less than 16 years of age [1]. The group of MB comprises a) classical b) desmoplastic/nodular c) with extensive nodularity d) anaplastic and d) large cell MB.

In the latest WHO Classification, two new MB variants were recognized a) MB with extensive nodularity and b) the anaplastic MB. On the contrary, medulloblastoma and melanotic MB were considered patterns of differentiation, without any distinct genetic features to warrant designation as variants [5,6]. Therefore, the

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descriptive terms MB with rhabdomyoblastic differentiation and MB with melanotic differentiation are proposed. These tumor usually have a worse prognosis [4].

Histologically, MB belongs to the family of small blue cell tumours with phenotypic resemblance to the primitive neuroectoderm of the embryonal central nervous system [5]. This tumour is composed of densely packed cells with round to elongated hyperchromatic nucleus and a limited rim of cytoplasm. Nuclear size and pleomorphism pattern is variable. Mitotic activity is usually brisk, nevertheless in approximately 25% of the cases mitoses may be infrequent. Glomeruloid vascular hyperplasia and geographic necrosis are rare findings. Invasion of the subarachnoid space may elicit a characteristic desmoplastic reaction, with ribbons and clusters entrapped among collagen and reticular fibers. Spongioblastic features characterized by arrangement of tumour nuclei with their long axes in parallel may be also observed. The predominant neuronal differentiation of the neoplasm is evident by the immunopositivity to neuronal markers, the presence of Homer Wright rosettes in almost 40%, clusters of neurocytic or rare ganglion cells in 5% of the cases and unusual presence of neuropil. Glial differentiation, manifested mainly immunohistochemically in the form of small cell clusters with astrocytic features [5].

Desmoplastic/nodular MB is characterized by reticulin-free nodules [pale islands] surrounded by densely packed highly proliferative cells with hyperchromatic/moderately pleomorphic nuclei with dense reticulin network [2,5]. The pattern may be focal and the nodules differ in the degree of cytological malignancy. The nodules are the manifestation of neuronal differentiation and are composed of neuropil and uniform cells usually neurocytic with low mitotic activity and increased apoptosis. A MB with only increased amount of collagen or reticular fibers without nodules should not be classified as a desmoplastic/nodular MB.

MB with extensive nodularity represents 2% of all MB cases and usually occurs in children less than 2 years of age. This variant was previously designated as cerebellar neuroblastoma, is the most recently described and is composed almost entirely from nodules with or without little desmoplastic internodular tissue [5,7]. The main difference of this variant from the desmoplastic MB is the expanded lobular architecture due to enlargement of reticulin free pale zones of

reduced cellularity. The above zones are composed of neuropil and neurocytic cells with characteristic streaming [5,7]. Following chemotherapy, MB with extensive nodularity may undergo further maturation to tumours composed of ganglion cells.

Anaplastic MB is characterized by marked pleomorphism, nuclear moulding, cell-cell wrapping, brisk mitotic activity with atypical forms and extensive apoptosis [5,8]. Because all MB variants demonstrated some degree of atypia, the presence of the above features only focally is not sufficient to classify the MB as an anaplastic one. Presence of anaplasia does not preclude the presence of Homer Wright rosettes or pale islands. Overtime progression of a non anaplastic MB to an anaplastic one and transition in a single tumour has been observed.

Large cell MB represents 2-4% of all MB and is characterized by monomorphic cells with large vesicular nuclei, a prominent nucleolus and variable eosinophilic cytoplasm [5,9]. This variant is mainly defined by the shape of the nucleus and not necessarily by the cell size. Characteristic features are the loss of cellular cohesion and the abundant mitoses and apoptosis. Large cell and anaplastic MB have a considerable cytological overlap and in some studies a combined category has been proposed [5,8].

MB with myogenic differentiation, previously named medulloblastoma, is not a distinct entity in WHO 2007 classification and describes any variant of MB containing rhabdomyoblastic elements. Spindle cells, scattered or clumped large oval cells or strap cells with cross striation are seen, showing expression of Desmin, Myoglobin, fast myosin, without SMA detection. MB with melanotic differentiation, previously termed melanocytic MB, is not a separate variant in the new WHO classification. Groups of melanotic cells can occur in different variants of MB appearing undifferentiated or epithelial forming tubules, papillae or clusters. Immunohistochemistry reveals variable S-100 expression, while ultrastructurally oculocutaneous melanin with melanosomes is revealed.

Immunohistochemistry

Synaptophysin, NSE, class III tubulin, MAP-2 [microtubule associated protein 2] are detected at least focally in the majority of MB, while Neurofilaments are only rarely detected [2,5]. Homer Wright rosettes, pale islands, areas of neuropil and fibrillar perivascular

rosettes are predominantly immunoreactive with the above markers. In the large cell variant, a dot like expression of Synaptophysin, Neurofilaments and Chromogranin A is observed. Other neuronal markers that can be detected are: nestin, marker of precursor neuroepithelial cells, neural adhesion molecules (CD56/NCAM), a-internexin, peripherin, nerve growth factors and receptors (TRKA, TRKB, TRKC) and low affinity NGFR detected in the internodular areas of desmoplastic MB. GFAP shows variable expression in MB. GFAP is usually detected a) in bona fide neoplastic cells b) in scattered astrocyte-like cells in undifferentiated MB mainly around blood vessels c) in fibrillary cells in the pale islands or in the internodular areas of large cell/anaplastic MB and e) rarely in the neoplastic cells of the large cell MB. INI1 protein expression, the product of the tumour suppressor gene INI1/SMARCB1 which is inactivated in Atypical teratoid/rhabdoid tumours, is retained in the nuclei of all MB.

Proliferation-Apoptosis

The growth fraction of MB, as assessed by Ki-67/MIB-1 immunolabelling, is generally high. Proliferative indices vary between MB types and within the same tumour, being high in large cell MB and extremely low in the pale islands of the desmoplastic/nodular variant [5,10]. Apoptosis indices are similar to mitotic indices. One exception constitute the pale islands of the desmoplastic variant, which show increase apoptotic but low proliferation index. However, no difference exist in the overall apoptotic index between classical and desmoplastic/nodular MB variants. Bcl-2, a well known inhibitor of apoptosis, is expressed in nearly 30% of MB, more frequently in the desmoplastic/nodular variant with a predominant expression in the internodular areas, showing an inverse correlation with neurocytic differentiation [11].

Genetics

MB has been encountered in several familial cancer predisposition syndromes, including patients with TP53 germline mutations [Li Fraumeni syndrome], with PTCH1 mutation [Nevoid basal cell carcinoma syndrome/Gorlin syndrome], with APC mutations [Turcot syndrome type 2]. Based on these observations, several genetic studies using cytogenetics, FISH or CGH revealed various genetic abnormalities in MB. Isochromosome 17q [i17q] is the most common genet-

ic abnormality and is observed in 30-40% of the cases. Loss of 17p, manifests as monosomy 17p is observed in 23-28% of the cases, or as small deletions or recombination on 17p in 38-54% of the cases [2,5,12]. Loss of 17p and i17q are generally associated with the classical MB and are usually associated with adverse prognosis. Candidate genes located at 17 that are involved in MB pathogenesis are the HIC-1, REN, which is a negative regulator of Sonic Hedgehog pathway, and TP-53. Although TP53 mutations are only observed in 5-10 % of MB cases, the P53 pathway can be altered in 21% of the cases due to INK4/ARF deletion [5].

Deletions of 6q, 10q, 11q and 16q can also be found in MB. Two genes located at 10q that are likely to be involved in MB pathogenesis are the PTEN, showing loss or promoter hypermethylation in MB and the DMBT1, showing deletions in MB. MYCC [8q] and MYCN [2p] amplifications have been observed in 4-17% of MB and are associated with the large cell/anaplastic type and with adverse prognosis [12].

Pathways involved in MB pathogenesis

Deregulation of pathways involved in signal transduction and cell proliferation plays a major role in MB pathogenesis [13,14]. Most of these pathways are pivotal for the development of normal brain and include a) the Sonic Hedgehog pathway b) the APC/Wnt (wingless) pathway c) the Notch pathway and d) pathways of neural transcription factors [13,14].

The Sonic Hedgehog pathway

PTCH gene on chromosome 9q22.3, the human homologue of the Drosophila PATCHED gene, is a tumour suppressor gene showing genetic alterations in MB. PTCH is the transmembrane receptor of Sonic Hedgehog [SHH], acting as an inhibitor of Sonic Hedgehog pathway through negative regulation of its co-receptor Smoothed [Smo]. Sonic Hedgehog, the ligand of the pathway, is the main mitogen for the progenitors of the cerebellar external granular layer, having a major role in the cerebellum development. Pathway activation occurs by the binding of SHH to PTCH. This relieves the Smo inhibition from PTCH, leading to translocation of Gli-1 transcription factors to the nucleus and transcription of target genes controlling proliferation and differentiation. Aberrant activation of the pathway, due to loss/inactivation of PTCH or overactivation of SHH, Smo and Gli-1, could lead to MB

development, mainly of the desmoplastic/nodular type. Allelic losses of PTCH have been observed in 10-18% of sporadic MB and inactivating PTCH mutations in 8% of MB, mainly of the desmoplastic variant. Germline mutations of PTCH have been detected in all MB associated with the nevoid basal cell carcinoma syndrome, which are exclusively desmoplastic. Mutations of SHH, Smo or SUFU, another negative regulator of the pathway, are rare in MB. Array-based expression studies proved that Sonic Hedgehog pathway is active and associated with desmoplastic/nodular MB variant [14-16].

APC/Wnt pathway

Germline mutations of the APC gene on 5q cause FAP [Familial Adenomatous Polyposis], a syndrome predisposing to colon cancer. Some FAP patients develop MB in Turcot Syndrome Type 2. APC gene, a tumour suppressor gene, is a negative regulator of the Wnt/wingless pathway. APC forms a complex with glycogen synthetase kinase 3b [GSK3b] and Axin, which regulates b-catenin activity mediating its degradation or stabilization. When Wnt ligands are present, APC/CS3K/Axin complex is activated, allowing b-catenin to enter the nucleus and to induce transcription of pathway targets. APC germline mutations, leading to truncated protein underlie MB in patients of Turcot Syndrome Type 2, while APC mutations are only observed in 3-4% of sporadic MB. Loss or inactivating mutations of b-catenin have been observed in 5-10% of sporadic MB. However, immunohistochemical nuclear expression of b-catenin has been observed in 18-25% of sporadic MB, indicating Wnt pathway activation. Array-based genetic studies demonstrated that 13% of MB were classified into a Wnt subgroup. Wnt activity seems to be associated with non-desmoplastic/non nodular MB, representing the signature of ventricular zone-derived tumours [15-18].

Notch pathway

Notch signaling pathway plays a critical role in neural stem cells regulation and normal brain development. Notch2 is a major mitogen of the cerebellar external granular layer progenitors cells. Notch 2 amplifications are observed in 15% of MB. Many transcription factors that have been implicated in normal brain development are deregulated in MB. PAX5 and PAX6 mRNAs were detected in 70 and 78% of MB respec-

tively, while NeuroD, SOX nerve growth factors, especially SOX4 and REST, a repressor of neural differentiation, are overexpressed in MB [16-18].

The above data resulted in the introduction of a hypothetical model for MB histogenesis, proposed in WHO 2007 Classification. In this view, MB can arise from more than one cell types [5,12,19]. The desmoplastic /nodular MB and MB with extensive nodularity, which are mainly hemispheric or midline tumours, derive from the cerebellar external granular layer mainly through activation of the Sonic Hedgehog pathway [LOH of 9q22]. In contrast, classical MB, primarily midline tumour, derive from the ventricular zone matrix/or midline external granular layer through LOH of 17p and activation of the Wnt pathway. The anaplastic/large cell MB derives through MYC amplification directly from the ventricular zone matrix or from progression of classical MB. This hypothetical model combines the previously proposed theories regarding the histogenesis of MB and PNETs.

Prognostic factors

Although treatment has improved survival in children suffering from MB, with 5 year survival reaching 60-70%, there is still a high risk group of patients with adverse prognosis. Large cell and anaplastic medulloblastomas are associated with a significant poorer prognosis than other MB types, while desmoplastic/nodular MB and MB with extensive nodularity show better prognosis than classical MB [5,9]. Conflicting data exist on the prognostic value of PCNA and Ki67/MIB-1 proliferation indices. MB showing focal apoptosis are associated with a better prognosis compared to MB with diffuse or extensive apoptosis. Expression of mitotic cyclins, cyclin A and B1, as well as EGFR and HER-2 have been correlated with patient's survival [20,21].

Although bcl-2 expression in classical MB has been associated with adverse prognosis, this is not related to an earlier recurrence. Molecular genetic markers, like 17q, loss of 17p, MYCC or MYCN amplification, 6q gain, overexpression of ErbB2, p53 and CDK6 are associated with adverse prognosis. In contrast, 6q deletion, immunohistochemical nuclear expression of b-catenin and TRKC expression have been associated with prolonged survival [19,23].

CNS Primitive Neuroectodermal Tumours [PNET]

CNS PNET constitute a heterogeneous group of tumours occurring predominantly in children and adolescents [24]. CNS PNET are composed of undifferentiated or poorly differentiated cells, which may display divergent differentiation along neuronal, glial or ependymal cell lines. Typical features are the early onset and aggressive biological behaviour. The term CNS PNET includes a) CNS supratentorial PNET, [CNS PNET NOS] embryonal tumours composed of undifferentiated or poorly differentiated neuroepithelial cells that occur at any extracerebellar site B) CNS neuroblastomas, tumours with only neuronal differentiation b) CNS ganglioneuroblastomas, when ganglion cells are present c) medulloepitheliomas, tumours with features of embryonal neural tube and d) ependymoblastoma, tumours with ependymoblastic rosettes. In the WHO 2007 Classification, the general term CNS PNET has been recommended, not only to emphasize the biological differences between embryonal brain tumours in the cerebral hemispheres of young children and young adults and the histologically similar cerebellar MB, but also to incorporate similar neoplasms in other extracerebellar sites, like the brain stem and spinal cord. The prefix CNS was added in order to avoid any confusion with peripheral PNET, which are similar but molecularly different neoplasms arising in soft tissues and peripheral nerves.

Although medulloepithelioma and ependymoblastoma were distinct entities in the previous WHO classification, in the current classification are considered variants of CNS PNET. Moreover, an unusual PNET, called embryonal tumour with abundant neuropil and true rosettes occurring in the cerebrum of young children, is mentioned as a provisional entity. The CNS/supratentorial PNET is an embryonal tumour composed of undifferentiated or poorly differentiated cells with the capacity for or with differentiation along neuronal, astrocytic, ependymal, muscular and melanocytic cell lines. Tumours only with neuronal differentiation are called cerebral neuroblastomas and if ganglion cells are also present then are called cerebral ganglioneuroblastomas. The cerebrum is the most common location of the tumours, while CNS PNET have also been described in the suprasellar region and spinal cord.

CNS PNET are usually solid masses with/or without

cysts or hemorrhages, showing an indistinct or clear-cut demarcation from the adjacent brain tissue and firm consistency when they have a predominant desmoplastic component. Calcifications are observed in 50-70% of cases. In 1/3 of the cases, cerebrospinal dissemination is observed, while bone, lymph node and liver metastases have been reported [24]. Histologically the classical undifferentiated PNET is composed of small round cells with a high nuclear/cytoplasmic ratio [2,24]. Tumours with increasing neuronal differentiation are characterized by a) increased fibrillary background (neuropil) b) neuronal features, like vesicular nuclei with nucleoli c) mature ganglion cells d) rare small round neurocytic cells. Nuclear atypia and mitotic activity are variable.

Variable, occasionally prominent, fibrous stroma can be observed, while increased calcification in areas of necrosis/degeneration and glomeruloid vascular hyperplasia are frequently seen. Immunohistochemistry demonstrates expression of variable markers, according to the line of differentiation. Neuronal markers, like Synaptophysin, class III β -tubulin and Neurofilaments are usually expressed in PNET with neuronal differentiation. Despite the small number of genetic studies, CNS/supratentorial PNET show different genetic alterations compared to MB. This is in contrast to the previously discussed theory of a common histogenesis of these tumours [22,25]. CNS supratentorial PNET usually show no loss of 17p, 11q or PTCH mutations, which are frequent in MB. In contrast, supratentorial PNET express neurogenic transcription factors of the NeuroD family and HASH1, a neurogenic transcription factor, that are not detected in MB [19,23,24]. Children with supratentorial PNET, especially those less than 2 years of age, have a worse overall 5 year survival than children with MB [26].

Medulloepithelioma (ME), is a rare malignant embryonal neoplasm affecting young children, characterized by tubular, papillary and trabecular arrangement of neoplastic cells recapitulating the features of embryonal neural tube. ME is a rare neoplasms affecting children between 6 months to 5 years of age, while half of these tumours occur during the first 2 years of life. Congenital cases and cases occurring beyond the first decade have been reported. The periventricular area is the most common site of occurrence. ME may arise intraventricularly, in the sellar region, cauda equine and presacral area. Outside the CNS, ME arise along the

nerve trunks in the pelvis and in the eye. Intraorbital ME rarely metastasize and has a favourable prognosis, while optic nerve tumours carry an intermediate prognosis between intraorbital and cerebral tumours. Histologically ME recreate the features of embryonal neural tube. The diagnostic feature of ME is the pseudostratified neuroepithelium arranged in papillary and tubular structures composed of cuboidal, and columnar cells with the nuclei perpendicular to the inner/outer surface, showing nucleoli and luminal mitoses. No cilia or blepharoplasts are recognized in the luminal surface, while on the outer surface of the epithelium there is a PAS diastase positivity, Collagen IV immunopositive limiting membrane. Immunohistochemistry reveals in the neuroepithelial component expression of nestin and vimentin. In neuronal areas, variable expression of Synaptophysin, Neurofilaments, EMA and cytokeratins can be observed, while there is no expression of GFAP, S-100 and NSE.

Ependymoblastoma is a rare embryonal neoplasm affecting mainly infants and young children, which is histologically characterized by ependymoblastic (multi-layered) rosettes. These tumors are usually supratentorial–paraventricular, large, and well demarcated. Widespread leptomeningeal invasion and extra neural metastases have been documented [27]. Histologically, ependymoblastoma is a primitive neuroectodermal tumour with increased cellularity and characteristic ependymoblastic rosettes. Immunohistochemistry reveals S-100, vimentin, Cytokeratin, GFAP, carbonic anhydrase isoenzyme II and rarely Neurofilament expression. The differential diagnosis includes a) anaplastic ependymoma, with the characteristic perivascular pseudorosettes b) medulloepithelioma, with the characteristic pseudostratified neuroepithelium forming large long linear tubules and papilla c) embryonal tumour with abundant neuropil and true rosettes (ETANTR) [22,27,28].

Atypical Teratoid Rhabdoid Tumour /Rhabdoid Tumour predisposition syndrome [RTPS]

Rhabdoid Tumour predisposition syndrome [RTPS] is a disorder characterized by an increased risk to develop malignant rhabdoid tumours [MRT] generally due to constitutional loss or inactivation of one allele of INI1/hSNF5/SMARCB1 gene on chromosome 22q11.2 [29,30]. Children with multiple MRT or with affected sib-

lings or with other affected relatives are almost certainly afflicted by the syndrome, while familial cases are rare. Demonstration of a germline mutation of INI1 gene is sufficient for RTPS diagnosis. Patients with germline INI1 mutations can develop a MRT within their first year of life, which can correspond to an isolated Atypical Teratoid Rhabdoid Tumour [AT/RT], or AT/RT plus a synchronous renal or extrarenal MRT in soft tissues. Bilateral renal MRT or MRT in infancy are strongly associated with a germline INI1 mutation.

Atypical Teratoid Rhabdoid tumour, grade IV according to WHO classification, can occur sporadically or as a part of RTPS. AT/RT is a highly malignant CNS tumour predominately in young children, with a male preponderance, typically containing rhabdoid cells often with primitive neuroectodermal cells and divergent differentiation along epithelial, glial, neuronal or mesenchymal-like lines. AT/RT is associated with inactivation of INI1/hSNF5/SMARCB1 gene in almost all cases.

AT/RT can be found supratentorially, especially in cerebral hemispheres, in the suprasellar region and pineal gland. Infratentorially AT/RT can be found in the cerebellar hemispheres, the cerebellopontine angle and brain stem³⁰. Spinal localization is rare, while cerebrospinal fluid and leptomeningeal dissemination at presentation can be seen in 20% and 25% of the cases respectively [30,31].

Histologically the hallmark of AT/RT is the heterogeneity [30]. Presence of rhabdoid cells is the characteristic features, corresponding to cells with eccentric nuclei, containing fine chromatin and a prominent eosinophilic nucleolus and a well-defined abundant eosinophilic cytoplasm with a globular inclusion. Rhabdoid cells are characterized by morphological variation, being large with less atypia and abundant finely granular cytoplasm or cytoplasmic vacuolization. Nests, sheets or a jumbled appearance of rhabdoid cells can be observed. Most neoplasms have variable components with PNET-like, mesenchymal and epithelial features.

In 2/3 of AT/RT cases, a small cell component predominates, while mesenchymal differentiation is less common. Abundant mitoses and geographic necrosis are common features. The differential diagnosis between AT/RT and PNET, choroid plexus carcinomas or germ cell tumours may be difficult on morphological grounds. Immunohistochemistry reveals expression of

various markers reflecting the polyphenotypic differentiation of AT/RT. Immunohistochemical staining for INI1 protein is a sensitive and specific marker for AT/RT, since biallelic inactivation of the INI1 gene results in loss of nuclear expression in the tumours, while normal cells and the other embryonal neoplasms retain nuclear staining [32]. CNS embryonal neoplasms without rhabdoid features with loss of INI1 protein expression represent AT/RT, while choroid plexus carcinomas show no loss of INI1 expression despite the rarely reported but debated INI1 inactivation. Proliferative activity of AT/RT in children is high, as reflected by Ki-67/MIB-1 expression in 50-100% of the cells [33].

Mutation or loss of the INI1 gene locus at 22q11.2 is the genetic hallmark of AT/RT [30,34,35]. INI1 protein

is a component of the mammalian SWI/SNF complex, which functions in a ATP-dependent manner to alter chromatin structure and is recruited to promoters of genes that regulate growth, cell cycle and differentiation [30,35]. Although the precise function of INI1 and its role in malignant transformation are not fully elucidated, it appears to act through p16/Rb/E2F and p-53 pathways. INI1 functions as a tumour suppressor gene, implying that two successive hits are needed for malignant transformation. Loss of the INI1 protein is seen in almost all AT/RT cases and 75% of them have deletions or mutations of the INI1 gene. AT/RT are highly aggressive neoplasms and the overall survival ranges from 11-24 months, while children over 3 years of age are associated with longer survival [30].

Table 1. Embryonal brain neoplasms according to WHO Classification 2007

WHO 2007.

Medulloblastoma

-Classical

-Desmoplastic/nodular

-Medulloblastoma with extensive nodularity

-Large cell medulloblastoma

-Anaplastic medulloblastoma

CNS Primitive neuroectodermal tumours[CNS PNET]

-CNS PNET , NOS

-CNS Neuroblastoma,

-CNS Ganglioneuroblastoma

-Medulloepithelioma

-Ependymoblastoma

Atypical Teratoid Rhabdoid Tumor

Βιβλιογραφία

- Embryonal tumours. Louis D.N, Ohgaki H, Wiestler O.D, Cavenee W.K [eds]: World Health Organization Classification of Tumours of the Central Nervous System IARC Press, Lyon, 2007, pp 132-149.
- Embryonal tumours. Burger P.C and Scheithauer B. Tumors of the central nervous system AFIP Atlas of Tumor Pathology series 4, 2007, pp 251-294.
- Louis DL, Ohgaki H, Wiestler OD et al. The 2007 WHO Classification of tumours of the central nervous system Acta Neuropathol [Berl] 2007; 114:97-109.
- Alexiou GA, Moschovi M, Stefanaki K et al. Epidemiology of pediatric brain tumors in Greece (1991-2008). Experience from the Agia Sofia Children's Hospital. Cen Eur Neurosurg 2011; 72: 1-4.
- Giangaspero F, Eberhart C.G, Haapasalo H, et al. Medulloblastoma. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK [eds]: World Health Organization Classification of Tumours of the Central Nervous System IARC Press, Lyon, 2007, pp 132-140.
- Alexiou G et al. Brain Pathol. 2011
- Giangaspero F, Perilongo G, Fondelli MP et al. Medulloblastoma with extensive nodularity: a variant with favourable prognosis J Neurosurg 1999;91:971-7.
- Von Hoff, Hartmann W, Von Bueren AG et al. Large cell/anaplastic medulloblastoma: outcome according to myc status, histopathological and clinical risk factors. Pediatr Blood Cancer 2010;54: 369-76.

9. Verma S, Tavara C, Gilles F. Histologic features and prognosis in pediatric medulloblastoma. *Pediatr Develop Pathol* 2008; 17:1.
10. Das P, Puri T, Sharma MC, et al. Medulloblastomas: correlative study of MIB-1 proliferation index along with expression of c-MYC, ERBB2 and apoptotic proteins along with histological typing and outcome *Child Nerv Syst* 2009;25:825-835.
11. Schuller U, Schober F, Kretzschmar HA, Herms J. Bcl-2 expression inversely correlates with tumour cell differentiation in medulloblastoma *Neuropathol Appl Neurobiol* 2004; 30:513-2112.
12. Pfister S, Remke M, Benner A et al. Outcome prediction in pediatric medulloblastomas based on DNA copy number aberrations of chromosomes 6q and 17q and MYC and MYCN loci *J Clin Oncol* 2009;27:1627-36.13. Guessous F, Li Y, Abounader R. Signaling pathways in medulloblastoma. *J Cell Physiol* 2008;217:577-83.
14. Baryawno N, Sveinbjörnsson B, Kogner P, et al. Medulloblastoma: a disease with disorganized developmental signaling cascades. *Cell Cycle*. 2010;9:2548-54
15. Ellison DW, Dalton J, Kocak M et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. *Acta Neuropathol*. 2011 Jan 26. [Epub ahead of print]
16. Yoon JW, Gilbertson R, Iannaccone S et al. Defining a role for Sonic Hedgehog pathway activation in desmoplastic medulloblastoma by identifying GLI1 target genes *Int J Cancer* 2009;124:109-19.
17. Fattet S, Haberier C, Legoux P et al. Beta-catenin status in paediatric medulloblastoma: correlation of immunohistochemical expression with mutational status, genetic profiles and clinical characteristics. *J Pathol* 2009;218:86-94.
18. Rogers HA, Miller S, Lowe J et al. An investigation of the Wnt pathway activation and association with survival in central nervous system primitive neuroectodermal tumours [CNS PNET]. *Br J Cancer* 2009;21:1292-302.
19. Northcott PA, Korshunov A, Witt H. Medulloblastoma Comprises Four Distinct Molecular Variants *J Clin Oncol*. 2010 Dec [Epub ahead of print]
20. Moschovi M, Alexiou GA, Patereli A, et al. Prognostic significance of cyclin A and B1 in pediatric embryonal tumors. *J Neurooncol*. 2010 Nov 11.
21. Patereli A, Alexiou G, Stefanaki K, et al. Expression of epidermal growth factor and receptor and HER-2 in pediatric embryonal brain tumors. *Pediatr Neurosurg*. DOI: 10.1159/000316640.
22. Korshunov A, Kool M, Hasselblatt M, et al. Molecular diagnostics of CNS embryonal tumors *Acta Neuropathol* 2010;120:553-66.
23. Stanton BZ, Peng LF. Small-molecule modulators of the Sonic Hedgehog signaling pathway. *Mol Biosyst*. 2010; 6:44-54.
24. McLendon RE, Judkins AR, Eberhart CG, et al. Central nervous system primitive neuroectodermal tumours. Louis D.N, Ohgaki H, Wiestler OD, Cavenee WK [eds]: World Health Organization Classification of Tumours of the Central Nervous System IARC Press, Lyon, 2007, pp 141-146.
25. Gessi M, Giangaspero F, Lauriola L et al. Embryonal tumors with abundant neuropil and true rosettes: a distinctive CNS primitive neuroectodermal tumor *Am J Surg Pathol* 2009;33:211-7.
26. Pfister S, Remke M, Toedt G et al. Supratentorial primitive neuroectodermal tumors of the central nervous system frequently harbour deletions of the CDKN2A locus and other genomic aberrations distinct from medulloblastoma. *Genes Chromosomes Cancer* 2007;46:839-51.
27. Behdad A, Perry A. Central nervous system primitive neuroectodermal tumors: a clinicopathologic and genetic study of 33 cases. *Brain Pathol* 2009;Jun25.
28. Judkins AR, Ellison DW. Ependymoblastoma: Dear, Damned, Distracting Diagnosis. *Farewell Brain Pathol* 2008 Dec 17.
29. Wesseling P, Biegel JA, Eberhart CG, et al. Rhabdoid predisposition syndrome in Louis D.N, Ohgaki H, Wiestler OD, Cavenee WK [eds]: World Health Organization Classification of Tumours of the Central Nervous System IARC Press, Lyon, 2007 pp 234-5.
30. Judkins AR, Eberhart CG, Wesseling P. Atypical teratoid/rhabdoid tumour in Louis DN, Ohgaki H, Wiestler OD, Cavenee WK [eds]: World Health Organization Classification of Tumours of the Central Nervous System IARC Press, Lyon, 2007 pp 147-9.
31. Kordes U, Gesk S, Fruwald MC, et al. Clinical and molecular features in patients with atypical teratoid rhabdoid tumor or malignant rhabdoid tumor. *Genes Chromosomes Cancer* 2010;49:176-181.
32. Ma HI, Kao CL, Lee YY. Differential expression profiling between atypical teratoid/rhabdoid and medulloblastoma tumor in vitro and in vivo using microarray analysis. *Childs Nerv Syst*. 2010;26:293-303.0
33. Judkins AR. Immunohistochemistry of INI1 expression: a new tool for old challenges in CNS and soft tissue pathology *Adv Anat Pathol* 2007;11:335-9
34. Schittenheim J, Nagel C, Meyermann R, et al. Atypical teratoid/rhabdoid tumors may show morphological and immunohistochemical features seen in choroid plexus tumors *Neuropathology* 2011 Jan 30.
35. Eaton KW, Tooke LS, Wainwright LM, et al. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors *Pediatr Blood Cancer*. 2011;56:7-15.
36. Patil S, Perry A, Maccollin H et al. Immunohistochemical analysis supports a role for INI1/SMARCB1 in hereditary forms of schwannomas but not in solitary sporadic schwannomas. *Brain Pathol*. 2008;18:517-519.
37. Bourdeaut F, Lequin D, Brugieres L. Frequent hSNF5/INI1 germline mutations in patients with rhabdoid tumor *Clin Cancer Res*. 2011;17:31-8.