REVISÃO

CYTOGENETICS IN PEDIATRIC MEDULLOBLASTOMAS

A CITOGENÉTICA EM MEDULOBLASTOMAS

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ABSTRACT

Medulloblastoma is a very frequent type of tumor in childhood and adolescence. It is preferentially located in the posterior fossa (also known as the infratentorial compartment) and mainly affects the cerebellum. Although some significant progress has been made in the treatment of these patients, many aspects regarding the biological behavior of this tumor are still unclear. Thus, the study of the genetic events involved in these neoplasias can be considered a valuable tool in the understanding of these tumors, since the biological behavior of a tumor is ultimately determined by its genetic alterations. The most commonly observed alteration in MB is an isochromosome 17, but by itself this aberration does not constitute a prognostic factor; it only reflects an unbridled cell proliferation. Several genes (as, for example, TP53, ABR and HIC-1), seem to be related to the genesis of these tumors, but further studies are necessary to shed

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light on this matter. Advances in the field of molecular cytogenetics have allowed for the identification of an increasing number of chromosome markers connected with the genesis of proliferation processes. Thus this review had the purpose of presenting an updated survey of the literature on medulloblastoma.

Indexing terms: adolescent, analysis cytogenetics, child, medulloblastoma, neoplasms, pediatrics.

RESUMO

A meduloblastoma é um tipo de tumor freqüentemente encontrada na infância e adolescência. É geralmente encontrada na fossa posterior (também conhecida como o compartimento infratentorial) e afeta, principalmente, o cerebelo. Embora um progresso significativo tenha sido alcançado no tratamento destes pacientes, muitos aspetos do comportamento biológico deste tumor ainda estão incertos. Portanto o estudo dos eventos genéticos envolvidos nestas neoplasias poderia ser considerado uma ferramenta útil na compreensão destes tumores, desde que, o comportamento biológico de um tumor passou a ser determinado pelas suas alterações genéticas. Em meduloblastoma, a alteração observada com maior frequência é um isocromossomo 17, mas sozinha esta aberração não constitui um fator prognóstico; apenas reflete uma proliferação celular desenfreada. Vários genes (por exemplo, TP53, ABR e HIC-1) parecem estar relacionados à gênese destes tumores, mas estudos mais aprofundados são necessários para esclarecer o assunto. Os avanços no campo de citogenética molecular tem permitido a identificação de um número crescente de marcadores de cromossomos ligados à gênese de processos de proliferação. Portanto, o objetivo desta revisão é apresentar uma revisão atualizada da literatura sobre meduloblastoma.

***Termos de indexação**: adolescente, análise citogenética, criança, meduloblastoma, neoplasias, pediatria.*

INTRODUCTION

Medulloblastoma (MB) is the most frequent primary tumor of the central nervous system (CNS) in children, although certain authors consider it as the second most commonly seen tumor in children and adolescents, after astrocytomas[1]. MB is preferentially located in the posterior fossa (also known as the infratentorial compartment) and mainly affects the cerebellum. MB, cerebellar astrocytoma and ependymoma are the most frequent tumors and are directly related to the cerebellum[2].

The treatment of MB is predominantly surgical, aiming at a maximal resection of the tumor, followed by chemotherapy and radiotherapy. Under certain conditions, dissemination of the tumor through the cephalorrachidian fluid can occur, up to its implantation in the spinal bone marrow[3]. The use of chemotherapy has improved the survival rates in high-risk patients, besides retarding radiotherapy in children below the age of 3 years old[4].

Though the treatment is extremely aggressive, only 60% of the children treated are cured, so the great majority will present sequelae for a long time after treatment[5,6]. With the purpose of circumventing this gloomy picture, two study groups were set up, the Children's Cancer Group and the International Society of Pediatric Oncology, the task of which has been to discover molecular markers which could be helpful in determining the prognosis[6]. Although a variable number of molecular markers have been proposed for MB, none have been validated for routine clinical use[7,8]. In addition to this approach, other efforts have been made to identify patients who could be cured with less intensive therapy and to develop more effective treatments for children who

are resistant to the treatments currently available[6]. The success of these studies will depend, primarily, on a correct collection method and adequate tumor processing[9].

The aim of this study was to evaluate the cytogenetic aberrations in MB using the data available in the literature as the strategy. Articles that suggest possible marker chromosomes were selected. These results could help in the prognosis and diagnosis of this neoplasia.

Clinical and histological aspects

Histologically, MB has a variable mitotic activity and consists of small cells with hyperchromatic, round or oval, nuclei with little cytoplasm[10]. The clinical picture of the patients is characterized by hydrocephaly with elevated intracranial pressure, besides symptoms like headache, lethargy and morning vomiting. Children whose cranial sutures are not yet fused may present an increased head circumference. Cerebellar invasion results in ataxia and dysmetria[11].

Classification

The classification of brain tumors is based on their location in the brain and their histopathological characteristics. Undifferentiated neuroectodermal tumors of the cerebellum are classically called MB, whereas histologically identical tumors located in the pineal region are diagnosed as pineoblastomas[12]. The nomenclature of pediatric brain tumors is controversial and potentially confusing. Some pathologists advocate the abandonment of classifications based on traditional morphology on behalf of a terminology that depends more extensively on the phenotypic characteristics of the tumor. In the latter system, MB is known as primitive neuroectodermal tumor (PNET) and is further subdivided based on cell differentiation. The most recent classification of the World Health Organization (WHO) for brain tumors maintains the term "medulloblastoma" for undifferentiated tumors of the posterior fossa, describing 3 additional subtypes which include: a) elongated cells, which occur in approximately 4% of cases; b) desmoplastic; and c) rare MB, which is characterized by elevated nodularity and advanced neuronal differentiation[13,14]. The current WHO classification names all tumors which are morphologically similar to medulloblastoma as PNET, including ependymoblastoma and pineoblastoma in this category as well as cerebellar medulloblastoma and supratentorial tumors such as cerebellar neuroblastoma[15]. Although these tumors share similar histological characteristics, recent studies suggest that they represent genetically different groups of tumors[11].

Epidemiology

MB accounts for about 20%-25% of CNS neoplasias in children and constitutes approximately 40% of the tumors observed in the posterior fossa[3]. The mean age of incidence is 7.3 years, with peaks at 3 and 7 years of age. As in all tumors of the CNS, there is a predominance in males, the male/female proportion varying from 1.1:1 to 2.6:1[16,17].

This neoplasm occurs in all regions of the world, not prevailing in any specific subpopulation or racial group[18]. Its annual incidence is lower than 2 cases/million in Central American, South American and Asian countries. In Oceania, North America and Europe, the number of recorded cases is considerably higher (rates of at least 5 cases/million)[19].

Etiologic factors

A possible correlation between CNS tumors and environmental agents has been postulated. Nitrogen compounds and smoking were studied, but no evidence was found that these elements might play a critical role in triggering the tumorigenesis process[20].

Familial aggregation is not clear-cut, although cases have been described in monozygotic twins and in non-twin siblings. The occurrence of MB has also

been observed in patients with Fanconi's anemia[21], neurofibromatosis type 1[22] and Gorlin syndrome[23,24]. As for autosomal recessive diseases, the occurrence of MB has been reported in ataxia-telangiectasia[25] and in Turcot's syndrome[26].

An increasing number of chromosomal abnormalities have been described in brain tumors, particularly in MB[27-29]. The study of these tumors (including histology, epidemiology, etiology, etc.), associated with an understanding of the genetic events involved, could provide important information, since the biological behavior of a tumor is ultimately determined by its genetic alterations[30].

Conventional cytogenetics and MB

The specific chromosomal abnormality most frequently reported in MB is isochromosome 17q [i(17q)], resulting in a loss of heterozygosis ("LOH") of the short arm of chromosome 17[31-33]. The deletion of 17p can be caused by a variety of mechanisms, such as: formation of i(17q), terminal deletions, unbalanced translocations and homologous recombination[34].

Besides being an alteration that is commonly observed in MB, i(17q) is also recurrent in several other types of tumor. Although it has already been suggested that the presence of this anomaly may have a primary effect in triggering the tumor progression process, its actual role and importance are not yet entirely clear[32]. Furthermore, the meaning of the presence of this clonal abnormality as a prognostic factor is still intriguing to many researchers[35-38]. This abnormality may contribute only to the unbridled cell proliferation, whereas other variables, such as the extension of the surgical resection and the time of radiotherapy, should still be considered as the most important prognostic factors[29].

The formation of an isochromosome allows certain genes to be lost and/or added to chromosome 17. Both the loss of tumor suppressor genes and the amplification of oncogenes contribute to the tumorigenesis process through a significant increase in the production of normal or abnormal proteins[39].

Certain authors have reported that in several neoplasias, tumor suppressor *TP53* is a frequently mutated gene, therefore being considered a potential candidate for triggering MB. This assumption bears[40] on the fact that this gene is located on the short arm of chromosome 17. Other authors, however, have postulated that the number of mutations in this suppressor gene is not elevated in MB, it therefore seeming unlikely that the formation of an i(17q) should give the cell any proliferative advantage[41].

Other genes (ABR and HIC-1) located on 17p are also under study. These molecular markers have been described in the literature, and for some of them correlation studies are under way, to better determine the prognosis. An illustrative example of these studies is the finding of a high oncogene c-erbB-2 expression through its product, HER2, in 84% of the MB cases, associated to a poor prognosis[42].

Other, less frequent alterations have been identified, such as a gain in chromosome 1 and deletions of 1p or 1q, 6q, 11 and 16q[43]. Unbalanced translocations of 20q13 and t(8;11) (q11;p11) have also been found[43,44]. Sainati et al.[45] observed deletions in the 1p32-36 region, abnormalities on chromosome 11, such as dup(11)(q13.2q23), del(11)(q23) and a trisomy involving chromosome 8. Bayani et al.[46], reported that chromosomes 3, 6, 7, 10, 14, 17, 18 and 22 were frequently affected, whether by gain, loss or translocation. Chromosomes 6, 7 and 14 were more commonly rearranged (9%), followed by chromosomes 3, 5, 10, 13, 18 and 22 (with a frequency of 7.7%), and finally chromosome 17, with a percentage of 6.4%.

Further cytogenetic studies have reported other abnormalities observed in MB, such as: gain in chromosome 7, loss of chromosomes 10, 22 and the sex chromosomes[47,48], occurrence of *double-minute* chromosomes (dmins) in 20% of the cases[45], t(1;19)(q23;q13)[49] and ins(1:10)(q31;q23q26)29. The role played by the last two chromosome abnormalities in the pathogenesis process of this neoplasia is not yet entirely clear[29,49].

Fluorescent *in situ* hybridization and MB

The success of cytogenetic studies in solid tumors has been limited, due to difficulty in obtaining an adequate number of metaphase cells and the poor quality of the spread and banded chromosomes[50-53]. What helped these studies to progress was the development of cytogenetic techniques in interphase nuclei by *in situ* hybridization. The applicability of the Fluorescent *in situ* Hybridization (FISH) method to interphase cells gives this technique an extraordinary series of advantages as compared to conventional analysis: a greater number of cells can be analyzed for chromosome aberrations; cells are not affected by technical artifacts; and, moreover, it provides important information regarding translocations and gene amplification[54].

Additionally, the use of this technique on paraffin-soaked slides offers further advantages, such as the possibility of analyzing a considerable number of nuclei and of assessing the frequency with which a given chromosome alteration occurs in a certain tumor[39].

Isochromosome 17q [i(7q)] is the chromosome alteration most commonly seen (30-60% of cases) in *in situ* hybridization studies of this kind of tumor[29,38,39,55]. Deletions in the region 22q11.2 were also detected in 16 of the 18 MB cases (89%) studied by this technique[56].

Gilhuis et al.[30] examined 10 MBs and one MB cell line. They detected an amplification site in region 8q24 in the cell line corresponding to gene *MYCC*. Gain of genetic material at the position 2p21-24 was also demonstrated in two tumors; this is the region where the oncogene *MYCN* is located. Amplifications of the oncogenes *MYCC*, epidermal growth factor receptor gene (EGFR) and *MYCN* seem to be closely related to a rapid progression of medulloblastomas[14,57,58].

Comparative Genomic Hybridization and MB

The application of the Comparative Genomic Hybridization (CGH) technique has proven to be a more efficient approach in defining complex structural and numerical abnormalities in tumor studies[59,60]. This technique represents an alternative method that requires specific digital analysis programs and the use of expensive probes[61].

CGH is a rapid and convenient technique for the study of genetic alterations, mainly in solid tumors, because it provides a profile of all genomic alterations that could help understand the molecular basis for the development of the tumor[55]. Specific subchromosomal gains and losses can be accurately detected, without having to use specific probes or have previous knowledge of the chromosomal alterations presented[62,63]. However, balanced alterations like translocations and inversions (which do not involve loss or gain of DNA) cannot be detected by CGH. The localization of regions presenting amplifications or deletions by CGH can subsequently be confirmed by FISH[30].

The capability of this technique to evaluate the entire genome by a simple hybridization process represents a significant advantage over conventional cytogenetic analysis. This becomes particularly evident with solid tumors, in which this analysis is often limited by the poor quality of the slides obtained with traditional banding methods[60].

Using CGH, several chromosomes were identified which seem to contribute to the development of MBs[30,64,65]. Amongst the chromosomes with deletions, the most recurrent were 10q, 8p and Y[30]. The loss of chromosomes 4, 12, 19, 3, 6, 9, 11, 16 and 22 occurred less frequently[46,66]. In a study of 27 MB cases, Reardon et al.[64], found a number of abnormalities, including nonrandom losses in the regions of chromosomes 10q and 8p, which have already been mentioned, besides chromosomes 11, 16q and 17p. Other nonrandom losses were observed in chromosome regions 10q23-qter, 17p, 18q22-qter and 13q14-q22 by Gilhuis et al.[30]. The latter region contains the genes for retinoblastoma 1 (*RB1)*, 'disrupted in B cell malignancy 1' (DBM1) and breast cancer 2 (BRCA2), which are directly associated with the proliferation processes[67].

A high level of gain in genetic material was reported by Eberhart et al.[68]. The chromosome regions involved included: 2q14-22, 3p23, 5p14-pter, 8q24, 9p22-23, 10p12-pter, 12q24, 12p11-12, 17p11-12 and Xp11. Amplifications of chromosome bands 5p15.3 and 11q22.3 were reported by Reardon et al.[64], and nonrandom gains were detected in regions 1p, 2p21-24 and 7q11.2[30]. Tong et al.[69], studied 14 samples by CGH and detected nonrandom losses in regions 8p, 17p, 16q, 8q and 1p, in addition to gains of genetic material on 17q, 12q, 7q and 1p.

Oncogene amplifications are frequently observed in MBs, especially in the regions 8q24 *(MYCC)* and 2p24 (*MYCN*)[43,46,55,70]. These amplifications confirm the findings obtained by FISH, conferring a growth advantage to these tumor cells *in vitro*[43]. The *dmins* are the main karyotype elements showing oncogene amplification[45].

Although there are reports of different numbers of chromosomes and subchromosomal regions involved in the progression process of MBs, most papers highlight the frequency with which chromosomes 7 and 17 are altered[29,30]. The results published show gains on the entire chromosome 7 and/or 17, or part of them, in 60% of the tumor cases[29].

The cytogenetic techniques described in this review have been used at the Pediatrics Laboratory of the FMRP-USP Hospital das Clínicas and at the Human Cytogenetic Laboratory of the Center of Biological Sciences of UFPA, where our research team carries out chromosome studies aimed at diagnosing such neoplasias. With this review, we intend to contribute to the publication of the molecular technological advances developed, starting from the classical methodology, which allow for the identification of the chromosome markers currently used for the study of proliferative processes in Pediatrics.

CONCLUSION

The development of molecular cytogenetic methods has brought an extraordinary number of advantages over conventional analysis. It must be pointed out, however, that the molecular methods, although very useful in identifying chromosome aberrations, should not replace the conventional method, because the latter provides information based on the complete karyotype. This can be exemplified by the cytogenetic study of MBs, in which the most frequent alteration, i(17q), is detected in most cases studied by conventional cytogenetics and FISH, but to a lesser extent by CGH. Several genes, such as *TP53, ABR* and *HIC-1*, located on 17p, are currently under study for having been shown as potential candidates in triggering MBs. Nevertheless, it seems that the detection of an i(17q) by itself, does not represent a prognostic factor in MB.

It is likely that, in the near future, the analyses of an increasing number of cases will allow for the recognition of still unknown chromosome aberrations in MB and its aggressive forms. The advances in molecular technology, starting from the classical cytogenetic methodology will make it possible to identify a greater number of chromosome markers. These markers will in turn provide a better understanding of the genetic events involved in the genesis of proliferation processes in pediatric cancers, and are likely to be crucial for clinical prognosis determination.

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