Articles

Diagnostic assertiveness of cerebellar pilocytic astrocytoma in the pediatric age

Asertividad diagnóstica de los astrocitomas pilocíticos cerebelosos en la edad pediátrica.

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Abstract: Pilocytic astrocytoma of the cerebellum in the pediatric age is the most frequent benign tumor lesion of the nervous system in children according to the WHO. International literature mentions that being low-grade tumors they have a high curative capacity. If the entire tumor is resected, when it is completely removed, survival increases with a high quality of life for children who presented this pathology and was treated on time. However, the delay in diagnosis and therefore in its treatment could generate the possibility of tumor transformation, the malignant nature of the transformed injuries has a very high morbidity and mortality, without mentioning that the degree of cognitive sequelae greatly affects the quality of life of the survivors. That is why the training of pediatric and non- pediatric first contact doctors imply a great responsibility since it gives the population and patients suffering from this nosology the possibility to improve their future life, as well as reduce the cost of the impact caused by the injuries they suffer. On the other hand, these tumors can transform generating devastating prognoses, without taking into account the economic and social repercussions of patients suffering from a low-grade tumor. When it is detected and treated assertively in a timely manner, it offers them greater opportunities than those who did not have such a timely diagnosis.

Keywords: Astrocytoma, pilocytic astrocytoma, low-grade brain tumors, quality of life, timely treatment..

Resumen: Los astrocitomas pilocíticos del cerebelo en la edad pediátrica son la lesión tumoral benigna del sistema nervioso más frecuente en niños según la OMS, la literatura internacional menciona que al ser tumores de bajo grado tienen una alta capacidad curativa, si se reseca todo el tumor, cuando es removido en su totalidad, la supervivencia aumenta, con una alta calidad de vida para los niños que presentaron esta patología y fueron tratados oportunamente, sin embargo, el retraso en el diagnóstico y por ende en su tratamiento podría generar la posibilidad de transformación tumoral, la naturaleza maligna de las lesiones transformadas tienen una morbilidad y mortalidad muy altas, sin mencionar que el grado de secuelas cognitivas que perjudica en gran medida la calidad de vida de los supervivientes. Es por ello, que la formación de los médicos de primer contacto, pediatras y no pediatras conlleva una gran responsabilidad, pues otorga a la población y a los pacientes que padecen esta nosología,

la posibilidad de mejora en una vida futura, así como, reduce el costo del impacto de las lesiones que sufren, por otra parte estos tumores pueden transformarse, generando pronósticos devastadores, sin tener en cuenta que la repercusión económica y social de los pacientes que padecen un tumor de bajo grado, cuando se detecta y trata asertivamente, en forma oportuna, les brinda mayores oportunidades que aquellos que no tuvieron tal puntualidad diagnóstica.

Palabras clave: Astrocitomas, astrocitomas pilocíticos, tumores cerebrales de bajo grado, calidad de vida, tratamiento oportuno..

INTRODUCTION

Central nervous system tumors are a heterogeneous group of multiple neoplasms that share considerable morbidity and mortality.[1]Central nervous system (CNS) tumors represent 2% of all neoplasms.[2] Being such that they represent a public health problem worldwide,[2] mainly for the age group between 0-14 years.[3] The Central Brain Tumor Registry of the United States (CBTRUS), in the 2020 CBTRUS Statistical Report, CBTRUS presents observed and relative survival, based on the Centers for Disease Control and Prevention (CDC) and the National Program of Cancer Registries (NPCR) data, this dataset provides population-based information for 93.6% of the US population for the years 2001 to 2016 and is a subset of the data used for the incidence calculations presented in the 2020 CBTRUS Statistical Report.[2] In pediatric age, the incidence of presentation is increasing and the essential concern is the morbidity[3] of each sequela that may present, thus reducing the quality of life of patients who suffer from a central nervous system tumor at an early age.[4] Brain tumors deserve a separate consideration from the rest of neoplasic lesions of pediatric age for several reasons, among which are, their anatomical distribution that strongly favors tumor behavior and neurodevelopment of the infant, as well as an immature neurocognitive state.[2,5] Brain tumors are the most common solid tumors in children,[6] and are the leading cause of childhood cancer-related deaths.[7] Low-grade gliomas comprise several subgroups, including pilocytic, pilomyxoid, subependymal giant cell, and diffuse astrocytomas.[6] Low-grade gliomas, specifically astrocytoma, are the most frequent presentation in tumors of the central nervous system,[2,3,7] which is why our main objective will be to denote the clinical information previous to the diagnosis established in the literature about these tumors.

DEFINITION

Pilocytic astrocytoma (PA) is a World Health Organization(WHO) grade 1 tumor,[3] that is the most common primary braintumor in children aged between 5 and 14 years, and the secondmost common brain tumor in children aged from 0 to 4 and 15to 19 years old.[6] It is most often located in the cerebellum, but it can occur in other brain regions.[5-7] In children, PA typicallybehaves indolent and may be surgically curable.[8] Radiationtherapy is generally reserved for patients with recurrent orprogressive tumors in whom additional surgery is not possible.[5-7] Signs and symptoms of raised intracranial pressure maysimulate other disorders and often confuse the clinicalpresentation.[8] Two cancer predisposing syndromes,neurofibromatosis type 1 (NF1) and tuberous sclerosis complex,are associated with an increased frequency of pilocyticastrocytomas and subependymal giant cell astrocytomas,respectively.[9] However, most low-grade gliomas (LGGs) arisesporadically.[9]

CLASSIFICATION

Pilocytic astrocytoma, previously known as cystic cerebellar astrocytoma or juvenile pilocytic astrocytoma,[10] was first described in 1931 by Harvey Cushing, based on a case series of cerebellar astrocytoma; though he never used these terms but rather described a spongioblastoma.[10,11] They are low-grade, and usually well circumscribed tumors, which tend to occur in young patients.[10,11] According to the WHO classification of central nervous system tumors, they are considered grade I gliomas and have a good prognosis.[11,12]. Astrocytic tumors arise from astrocytes and are the most common tumor of glial origin.[2,12] The WHO 2016 categorized these tumors as either "diffuse gliomas" or "other astrocytic tumors".[11-14] Diffuse gliomas include grade II and III diffuse astrocytoma, grade IV glioblastoma, and diffuse gliomas of childhood.[11] The "other astrocytic tumors" group include PA, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, and anaplastic pleomorphic xanthoastrocytoma.[11-14] The classification system described above is histological.[14] It is worth noting that the 2016 WHO classification gives more importance to genetic and molecular markers for categorizing gliomas; however, PA is essentially a histological diagnosis.[11] In the same way the update of the WHO classification system in its 2021 edition, PA is graded as a low-grade glioma or grade 1 to the circumscribed tumor, with a higher incidence in the posterior fossa and with histology compatible with pilocytic astrocytoma.[15]

EPIDEMIOLOGY

In children and adolescents (from 0 to 19 years old), the incidence rate of primary malignant and non-malignant brain and other CNS tumors was 6.[14] per 100,000 between 2013 and 2017.[3] Incidence was higher in females compared to males (6.22 versus 6.07 per 100,000), in Caucasian compared to African Americans (6.36 versus 4.83 per 100,000), and non-Hispanics compared to Hispanics (6.42 versus 5.26 per 100,000).[3,16] Brain and other CNS tumors (both malignant and non-malignant) were the most common cancer site in persons aged 0-14 years,[2] with an average annual age-adjusted incidence rates (AAAIR of) 5.83 per 100,000 population.[3] Brain and other CNS tumors were the most common cancer in both males and females in this age group.[2,3] Incidence rates of pilocytic astrocytoma, germ cell tumors, and embryonal tumors were higher in the younger groups and lower within the older groups.[2,3] The distribution of reported tumors with histologically confirmed diagnosis from 2013 to 2017 is presented by histology and reported WHO grade in 65.2% of tumors had complete WHO grade information, but there was substantial variation by histology.[2,3,16] The histologic types with the highest WHO grade were anaplastic oligodendroglioma (93.7%), anaplastic astrocytoma (95.7%), and oligoastrocytic tumors (94.8%).[2-4,16] This for the WHO graduation in its 2016 edition.[2-4,15,17]Although the overall incidence of primary brain and other CNS tumors was slightly higher in African Americans compared to Caucasians, the incidence of many specific histologies was significantly higher among Caucasians.[15] Incidence rates for glioblastoma ($p<0.0001$), all other astrocytomas ($p <0.0001$), and nerve sheath tumors ($p <0.0001$) were approximately 2 times higher in Caucasians than in African Americans.[3,16] Average annual incidence rates were higher for tumors of neuroepithelial tissue (3.88 per 100,000 population).[2,3,15] Among these tumors, the most common histologies were pilocytic astrocytoma (0.92 per 100,000 population).[2,3] Median survival was not able to be estimated for pilocytic astrocytoma, ependymal tumors, or germ cell tumors as >50% of individuals remained alive during the 15 year follow up period.[2,3] CBTRUS incorporate treatment patterns which may explain differences between these population-level estimates and other published estimates.[2,3]Demographic factors

such as age at diagnosis, sex, race and ethnicity are known to have a significant effect on survival time after diagnosis in primary brain and other CNS tumors.[2,3,15-17] In Mexico, Chico- Ponce de Leon, et al; In 2006 conducted a study in which he reported that, for the Mexican population studied in the Hospital Infantil de México Federico Gómez (HIMFG), the most frequently found brain tumors of the central nervous system were astrocytomas, with 32%, and medulloblastomas, with 19%.[18] Craniopharyngiomas with 11% and ependymomas with 10.24%.[18] The authors did not find a significant difference in incidence by gender.[18] Most statistics report a higher frequency of tumors in the posterior fossa in children, with a frequency of between 60 and 70%.[10,18]

CLINICAL MANIFESTATIONS

The clinical data that causes a tumor lesion of the central nervous system are divided into two groups: focal symptoms and generalized symptoms.[1,2,15] Focal symptoms are related to the location of tumor and its extension[1,18] and generalized symptoms are those that are related to growth and compression generated secondarily, which leads to headache, nausea, papilledema and seizures, among others.[1,3,18] Therefore, it is suggested to approach the clinic from the two points previously mentioned,

a) Manifestations of intracranial hypertension: 1. Headache in 55 to 77% of cases[19-27] 2. Irritability is more frequent the younger the patient.[18,28] 3. "Projectile" vomiting, with a frequency of 39 to 60% in supratentorials, and 73 to 78% in infratentorials.[18-22,29,30] 4. Papilledema present in 37% of supratentorial cases, and in 68-90% of infratentorial cases. [18,25,26,29] 5. Diplopia observed in 8 to 65% of cases.[29,31] 6. Increased head circumference (it is of diagnostic value in children under two or three years of age),[18] and it occurs in 6% to 16% in infratentorial tumors.[18,32,33]

b) Location data (the location data will denote which of the intracranial sites are affected by the tumor lesion and it has been observed that radiotoxicity can develop similar problems in brain targeting)[1,3,18] 1. Cranial nerves,[18,25] 2. Areas of cerebral eloquence (according to Brodmann's areas),[5,18] 3. Brain stem and nuclei of autonomic eloquence (hypothalamic, respiratory, etc.).[1,3,18] 4. Motor and sensory regions.[18]

Similarly, there are two other groups of complementary signs and symptoms and they are: c) Signs of neuronal irritation (epilepsy),[1,18] and d) Behavioral disorders.[1,18]

Other authors conclude that the most common symptoms were headache, vomiting and nausea.[34] That is why epidemiology reports in order of appearance the astrocytomas, being 95% more frequent in the posterior fossa,[2,3,16,18] as first-contact doctors, the commitment is in detecting lesions of the cerebellar hemisphere,[1,18] which cause peripheral ataxia, dysmetria, intention tremor, nystagmus, and dysarthria.[34] Posterior fossa lesions can also cause cranial nerve palsy.[18,33,34] Diplopia can occur due to abducens palsy due to stretching of the nerve.[1,18,34] They may also have blurred vision due to papilledema.[34] Seizures are rare with posterior fossa lesions.[34] Cerebellar location represents 95% of PA in the pediatric age versus 26% of PA in adults.[2,3] At the time of diagnosis, most patients will have clinical signs of cerebellar dysfunction,[1,2,18] especially appendicular dysmetria and truncal unsteadiness,[13,18,34] the papilledema and extraocular movement abnormalities are somewhat more variable.[35] Dysmetria and gait unsteadiness are inconsistent in early presentation and may be confused with photo-phobia or psychological manifestations.[35] Patients tend to develop hydrocephalus later in the course of illness, with associated symptoms of increased intracranial pressure.[18,34,35]

PHYSIOPATHOLOGY

The evolution of medical science in conjunction with molecular advances have given us the ability to demonstrate the alterations generated by many of the pathologies.[34-36] In recent years, giant steps have been taken in oncology in terms of molecular diagnosis, which leads us to understand why and how tumor lesions happen. In this case of pilocytic astrocytoma, a series of molecular analyzes showed that many pilocytic astrocytomas exhibit translocations or, less frequently, activating mutations of the BRAF gene, which can promote the development of tumors.[13,36,37] BRAF-KIAA fusions are common in pilocytic tumors of the cerebellum (pilocytic astrocytoma) and tumors of the optic pathway and cause constitutive activation of the BRAF protein,[36,37] while BRAF mutations are more common in gangliogliomas, pleomorphic xanthoastrocytomas, and astrocytomas cerebellar pilocytic, they infiltrated for what they are not originated in the posterior fossa.[38] Tumors lacking BRAF fusions or mutations often have alterations in other components of the mitogen-activated protein kinase (MAPK) signaling pathway, including NF1 mutations and RAF fusions. This convergence of mutations on a single downstream pathway prompted interest in the targeted inhibition of MAPK signaling as a therapy for these tumors.[36-38] Most PA are thought to be sporadic mutations rather than inherited.[36-38] BRAF gene alterations and MAPK signaling pathway alterations have been found in the majority of PA.[11,39,40] BRAF is an intracellular serine/threonine kinase involved in the activation of the mitogen-activated kinase (MAPK) pathway.[41]BRAF is a proto- oncogene, mutations of which have been found to cause human cancers.[41,42] Oncogene-induced senescence (OIS) is a key biological mechanism that controls tumor growth and behavior.[43,44] Further supporting the idea that these tumors may be subject to OIS.[44,45] Additionally, loss of CDKN2A the MAPK alteration in PA is associated with a worse clinical outcome, suggesting that this pathway is crucial for OIS in these tumors.[46] The most common genetic alteration found in PA is the tandem duplication at 7q34, which produces a fusion between two genes, KIAA1549 and BRAF.[46] This fusion results in loss of the BRAF autoregulatory domain at the amino-terminus and constitutive kinase activity of the Ras/ERK pathway.[46,47] The KIAA1549- BRAF fusion is found in 60–94% of PA, more commonly in those arising in the cerebellum.[35,47]

DIAGNOSIS

Diagnosis is the initial challenge of cerebellar pilocytic astrocytomas, since having a highly variable clinic this can be a watershed for multiple differential diagnoses. Timely diagnosis is of vital importance as it reduces the risk of malignant transformation and reduction of sequelae.[1,3,18] We will divide the diagnosis into the following parts:

Clinical

PA may appear with secondary symptoms to the posterior fossa mass effect.[1,18] This may include obstructive hydrocephalus, with resulting headache, nausea and vomiting, and papilledema.[1,3,18] If hydrocephalus occurs before fusion of the cranial sutures (<18 months of age), then an increase in head circumference is likely.[5] We can encompass the clinical SNOOPY strategy developed by Franco and León in 2018[48] (Table 1), as a starting point in clinical evaluation.

TABLE 1
SNOOPY diagnostic strategy

Table 1. SNOOPY diagnostic strategy

S (Systemic)	Presence of systemic symptoms such as: pain, fever, weight loss, asthenia, vomiting (associated with oncological lesions).
N(Neurologic)	Neurological symptoms such as: paralysis, ataxia, aphasia, paresthesia.
O (Onset)	Of subacute clinical onset (depending on the temporality of neurological and systemic alterations).
O (Other)	Other associated causes such as: neurofibromatosis, tuberous sclerosis complex, tumor lesions or pre-existing hereditary diseases.
P (Progressive)	That the clinical manifestations are progressive (do not limit and increase the signs and symptoms).
Y (Image)	Presence of lesions by neuroimaging studies.

Timing strategy for the diagnosis of childhood brain tumors.

Timing strategy for the diagnosis of childhood brain tumors.

Neuroimaging

The diagnostic approach requires clinical suspicion necessarily combined with neuroimaging evaluation.[2,3] These studies are also essential because they provide information for preoperative planning, as well as the probable etiology, although finally the definitive diagnosis is given by the histopathological study.[1,10,47,49] At computed tomography (CT), most cerebellar and cerebral pilocytic astrocytomas have a well-demarcated appearance with a smaller round or oval shape.[10] At magnetic resonance (MR), pilocytic astrocytoma is typically isointense to hypointense relative to normal (Figure 1), brain with T1- weighted pulse sequences and hyperintense compared with normal brain with T2-weighted pulse sequences.[10] Reports of MR spectroscopy performed on the soft-tissue portions of pilocytic astrocytomas have documented elevation in the choline (Cho) to .-acetylaspartate (NAA) ratio, ranging from 1.80 to 3.40 (comparade with 0.53-0.75 for normal cerebellum).[10]

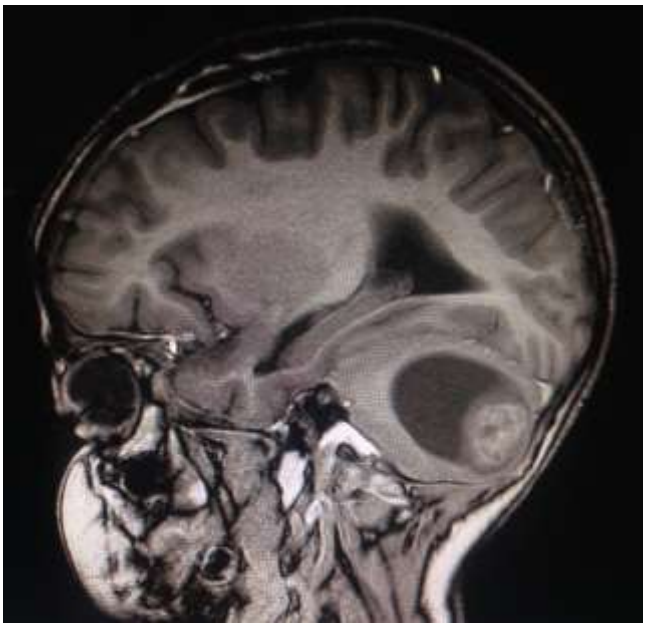

FIGURE 1
Magnetic resonance imaging of the brain with cerebellar pilocytic astrocytoma

Histological

PA are generally circumscribed slow growing cystic tumors.[2,3] Macroscopically, they often present with a solid mural soft gray nodule accompanied by a cyst.[35,50,51] PA are usually macroscopically discrete and displace rather than invade the surrounding brain, although parenchymal infiltration of several centimeters and invasion of the leptomeninges may be seen in cerebellar tumors.[35]Tumors of the visual pathway, including the optic nerve, often have less clear borders;[50-52] they can be followed to a point beyond which they become less cellular without a clear termination.[52] Chronic lesions can contain hemosiderin or calcifications.[35,52] Microscopically, PA consist of a variable proportion of compacted bipolar pyloid cells arranged in bundles associated with characteristic eosinophilic Rosenthal fibers interspersed with loosely textured stellate cells with microcysts and granular bodies.[35,53] Smear preparations show considerable cytological variation.[17,53] The term pilocytic refers to elongated hair-like projections that are similar to reactive astrocytes and show strong glial fibrillar acid protein (GFAP) staining .[35,53]The hair-like process can spread throughout the microscopic field.[53] Characteristically known as "protoplasmic astrocytes" they show a small b cell, eosinophilic granular bodies are globular aggregates within astrocytic processes and show periodic acid reactivity: Schiff, α1-antymotrypsin and α1- antitrypsin.[53] Oligodendroglioma-like cells can be seen in PA, especially at cerebellar sites.[17,35,53,54] The number of mitoses ranges from 0 to an exceptional 4 per 10 high-power fields, and the MIB-1 marking rates from 0 to 3.9%: these latter values overlap with those of grade II astrocytomas and they are not useful for the differential diagnosis between these entities. [54] PA are highly vascular.[35,53] Hyalinization of blood vessels is common.[35] Normal neurons can become entrapped and can cause confusion with gangliogliomas.[13,17,53] The distinction between diffuse fibrillar astrocytoma and PA can sometimes be a matter of debate, although molecular findings may simplify the diagnosis.[35] A closely related tumor is pilomyxoid astrocytoma (classified as WHO grade II), which has an eminently mucoid matrix and an angiocentric arrangement of monomorphic bipolar tumor cells, without Rosenthal fibers or eosinophilic granular bodies/hyaline droplets and less frequently contains cystic components or large tumor cysts.[17,54]

They are mainly located in the hypothalamic region and have a propensity for spreading cerebrospinal fluid and local recurrences.[17] Some PA may show considerable hyperchromasia and pleomorphism, with a diffuse growth pattern, infarct-like necrosis, glomeruloid vasculature, and infiltration of the leptomeninges that can mimic a high-grade diffuse astrocytoma.[35] PA recur mainly locally, especially when they are incompletely removed and/or located in unresectable sites.[55] They can also spread, mainly to the leptomeninges, and this can occur early in the history of the disease.[55] Pathology cannot predict such a propensity to spread.[54] Leptomeningeal deposits are usually slow growing and long-term survival is possible.[7]

TREATMENT

The treatment of PA depends largely on the host (patient) and the tumor itself, the variables that must be considered in the host are: age, pathological, prenatal and perinatal antecedents, inheritance or genetic load for lesions and nutritional status.[5,56] Regarding the variables to be considered for the tumor lesion they are: location, shape (by neuroimaging), degree of infiltration, and histology, also the prognosis and subsequent treatment are also dependent on the integrity of the extirpation.[56]Cerebellar astrocytoma is a surgical entity, and the primary treatment of cerebellar astrocytomas is surgical resection, with the goal of obtaining total tumor removal.[56] In fact, extent of resection is the main predictor of recurrence and survival.[5] Children are usually diagnosed when they already have symptoms as a consequence of increased intracranial pressure.[5] In those cases, in which there is cloudiness or cardiorespiratory instability, immediate intervention with the placement of an external ventricular drain is mandatory.[5] In these cases, the utmost care should be taken to avoid excessive drainage, which can result in an upward herniation.[5,55,56] Preoperative placement of an external ventricular drain in non-emergency cases is a matter of preference of the surgeon, but in the practice the surgeon prefers to avoid it and start with dexamethasone (0.25 to 0.5 mg / kg per day), which generally relieves symptoms in 6 to12 hours.[2-5] The surgical approach will be the indication formedical management to address this injury.[1-3,5,55]The surgicalapproach will be determined by the location of the tumor, thegeneral condition and the age of the patient.[5,53-57] The mainstayof treatment is surgical excision with the aim of completing theresection margins while achieving minimal neurologicalinjury.[5,58] Complete resection is considered curative of thedisease.[58] However, involvement of the brain stem or cranialnerves can prevent complete resection.[5] Resection of the nodule only and not of the cyst wall is recommended.[58,59] However,tumors with a thick cyst wall can be considered part of the noduleand therefore excised.[58] Conventional radiation therapy is notrequired; instead, serial imaging is more appropriate.[60] Radiationtherapy, particularly in this region of the brain, has significantsequelae.[60] If there is a recurrence, additional surgical resectionis usually adopted.[60] Radiation therapy may be appropriate if itis surgically unresectable or if there is malignant histology.[61] Insome studies, stereotactic radiosurgery (SRS) gave excellentresults for residual and recurrent tumors.[50,61] Although, there hasbeen criticism regarding the length of follow-up in thesestudies.[62] There is some concern that SRS may promoteanaplastic transformation.[62]

The complete management for a correct diagnosis and subsequent treatment of astrocytomas, should contain a comprehensive protocol in which to evaluate: representative clinical data, neuroimaging studies, surgical approach and histological study of the tumor,[1,5] as shown in Figure 2.

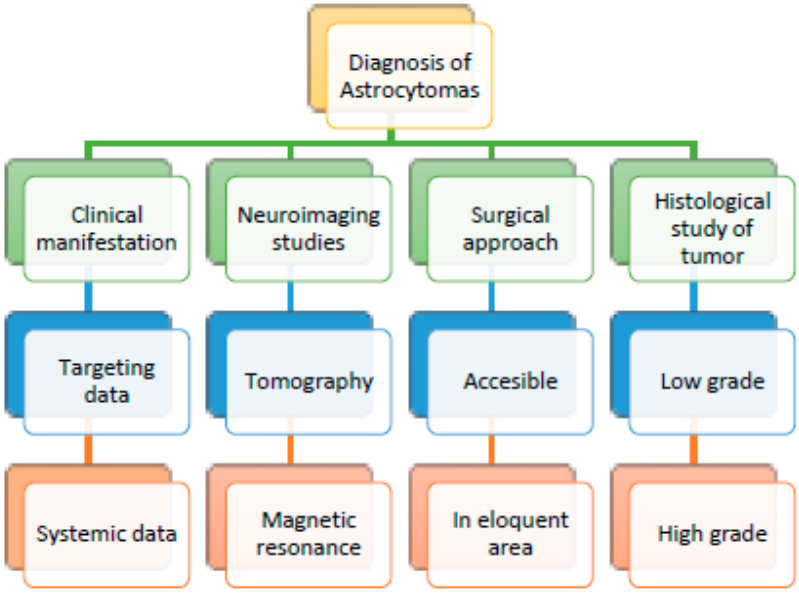

Figure 2. Comprehensive diagnosis of astrocytomas.[1,5]

FIGURE 2
Comprehensive diagnosis of astrocytomas
1, 5

PREVENTION

There are no modifiable risk factors for PA.[58] Some genetic conditions such as NF1 predispose families to PA, and therefore genetic testing and counseling may be appropriate. However, most PA are due to sporadic mutations.[60-62] Epigenetic variations depend to a large extent on genetic inheritance and the environmental development to which they are exposed; however, in the case of pilocytic astrocytoma, the ideal is timely detection with immediate strategies and low cost of the first contact doctor[1,38] (Table 1).

PROGNOSIS

After complete resection, recurrence occurs in less than 5% of patients compared with up to 50% of those with residual disease.[56] The 10-year survival rate is nearly 100%. [57] Even after partial resections, patients can be observed and reoperation or other forms of treatment can be reserved for those with progressive disease.[35] Overall, the prognosis for patients with pilocytic astrocytoma is excellent, with a survival rate of 10 years of up to 94% and a 20-year survival rate of 79% .[10]

CONCLUSION

What is analyzed and documented in this article gives us a better overview of the importance of timely diagnosis, because by having assertiveness, the health of an infant can allow optimal neurodevelopment or a poor state with sequelae that decrease the quality of life of the child patient. Educating the first contact doctor allows the improvement of vulnerable populations.

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