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Review Article

Hereditary Syndromes Associated with Brain Tumors. Literature Review.

Enrique Marcos Sierra Benítez MD[1*], Maatla Shatho Yolanda Sithole MD[2], Potlako Picasso Ntabe MD[3], Morulaganyi Mogae MD[4], Tshielo Nature Otsogile MD[2], Kevin Kwenkim Petelo MD[5], Ndapiwa Precious Lebalang MD[6], Unami Gwendoline Badubi MD[7] and Friday Edoh MD[2]

[1] First degree specialist in Internal Medicine, Instructor Professor, University of Medical Sciences of Matanzas, Internal Medicine Team, Nyangabgwe Referral Hospital, Botswana.

[2] Medical Office, Neurosurgery Team, Nyangabgwe Referral Hospital, Botswana.

[3] Medical Resident, Orthopedics and Traumatology, University of Zambia, Zambia.

[4] Medical Resident, Neurosurgery Team, Nyangabgwe Referral Hospital, Botswana.

[5] Medical Office, Emergency Team, Nyangabgwe Referral Hospital, Botswana.

[6] Medical Resident, Orthopedics and Traumatology, Kenyatta National Hospital, Kenya.

[7] Medical Resident, ENT, University of Nairobi, Kenya.

[8] First degree specialist in Neurosurgery, Assistant Professor, University of Medical Sciences of Matanzas, Neurosurgery Team, Nyangabgwe Referral Hospital, Botswana.

***Corresponding Author:** Enrique Marcos Sierra Benítez, MD, First degree specialist in Neurosurgery, Assistant Professor, University of Medical Sciences of Matanzas, Neurosurgery Team, Nyangabgwe Referral Hospital, Botswana.*

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Abstract

Tumors of the central nervous system (CNS) represent 2% of all neoplasms. Low-prevalence hereditary syndromes constitute only a small proportion of all cases of primary tumors of the central nervous system. Most of these syndromes have autosomal-dominant inheritance, except in the case of Turcot syndrome type 1 which has an autosomal recessive inheritance pattern. It is important in daily neurosurgical practice to be able to recognize these hereditary syndromes in order to apply the best therapeutic alternative in these patients.

***Keywords:** Hereditary Syndromes, Brain tumors*

Introduction

Tumors of the central nervous system (CNS) represent 2% of all neoplasms. They seem to be increasingly frequent, not so much due to a true increase in their incidence, but rather due to the increase in life expectancy of the population in general and technological advances that allow a more timely diagnosis. Currently, the overall incidence rate of primary CNS tumors is 10.82 per 100,000 people per year.[1]

Low-prevalence hereditary syndromes constitute only a small proportion of all cases of primary tumors of the central nervous system. Most of these syndromes have autosomal-dominant inheritance, except in the case of Turcot syndrome type 1 which has an autosomal recessive inheritance pattern. Their clinical and genetic characteristics are summarized in Table 1.[2]

Table 1. Genetic and clinical characteristics of hereditary syndromes.

SYNDROME	AFFECTED GENE	TYPE OF INHERITANCE	CLINICAL FEATURES	ASSOCIATED CNS TUMORS
Neurofibromatosis type 1	NF-1 (17q11.2)	Dominant	Café au lait spots, Neurofibroma, Schwanomas	Astrocytoma, Optic Nerve Glioma
Neurofibromatosis type 2	NF-2 (22q12.2)	Dominant	Meningiomas, vestibular schwanomas, ocular lesions	Ependymomas, Meningiomas, Bilateral vestibular schwanomas
Tuberous Sclerosis	TSC1, TSC2 (9q34) y (14)	Dominant	Benign multisystem tumors	Subependymal giant cell astrocytomas
Li-Fraumeni síndrome	TP53 (17p13.1)	Dominant	Breast, brain and soft tissue cáncer	Glioblastoma, Astrocytoma, Medulloblastoma, Choroid Plexus Carcinoma
Turcot syndrome type 1 and 2	1 (APC), 2 (MMR)	1 (recessive), 2 (dominant)	Adenomatous polyposis and glioblastoma	(Type 1) Anaplastic astrocytoma, (Type 2) Medulloblastoma
Cowden syndrome	PTEN	Dominant	Multiple hamartomas	Dysplastic gangliocytoma of the cerebellum
Lynch síndrome	MSH2, MLH1	Dominant	Gastrointestinal cancer, Endometrial cáncer	Glioblastoma
Gorlin síndrome	PCTH	Dominant	Carcinomas basocelulares, calcificaciones intracraneales	Medulloblastoma
Von-Hippel-Lindau disease	VHL (3p25-26)	Dominant	Hemangioblastoma, pheochromocytoma, neuroendocrine disorders of the páncreas	Hemangiomas of the CNS and Retina

Materials and Methods

An in-depth review was carried out of the main articles published in English and Spanish in relation to various hereditary syndromes, emphasizing these as a cause of tumors of the nervous system.

In this review, aspects related to the molecular characteristics of the hereditary syndromes treated, as well as their clinical and imaging characteristics, are discussed. Given the extensive and complex nature of the topic, we aim to be as specific as possible.

References of articles retrieved by the electronic search were searched for other potentially eligible articles.

Development

Neurofibromatosis type 1.

Neurofibromatosis type 1 (NF1) was first described in 1882 by von Recklinghausen. It is the most common neurocutaneous syndrome, with an approximate incidence of one in every 3,000 to 3,500 live births.[3] It presents autosomal dominant transmission with high penetrance and great variability in its clinical expression. In 30-50% of cases they correspond to de novo mutations. In 1990, the gene responsible for the disease was identified on the long arm of chromosome 17, as well as the protein produced by it, neurofibromin.[4]

Patients with neurofibromatosis characteristically have multiple, cutaneous or plexiform neurofibromas (benign tumors formed by Schwann cells and fibroblasts), café-au-lait spots (abnormal growth of melanocytes) and Lisch nodules (iris hamartomas), as well as a high incidence of malignant neurofibrosarcomas (derived from benign neurofibromas), pheochromocytomas (derived from adrenal medulla) and optic gliomas (derived from glial cells), in addition to pilocytic tumors bone abnormalities , mental retardation and learning difficulties.[5]

The diagnosis of NF1 is based on the presence of at least 2 of the criteria established by the National Institute of Health Consensus Development Conference in 1988, in addition to the clinical and neuroradiological characteristics of said disease, although currently the diagnosis is established by identifying the mutation in the NF1 gene, which is found in 95% of cases. (Table 2)[6]

Table 2. Diagnostic criteria for Neurofibromatosis type 1. The presence of 2 or more of the following criteria is required.

Six or more café au lait spots, of the following diameter: ≥ 5 mm before puberty ≥ 15 mm after puberty
Two or more neurofibromas of any type or one Plexiform Neurofibroma
Axillary or inguinal freckles (Cowden's sign)
Optic tract glioma
Two or more Lisch nodules (benign iris hamartomas)
Typical bone injuries: Sphenoid dysplasia Dysplasia or thinning of the cortex of the long bone (pseudoarthrosis)
First degree relative with NF1

Neurofibromatosis type 2

Neurofibromatosis type 2 is a disabling disease that is inherited in an autosomal dominant manner. It has often been confused with neurofibromatosis type 1, although they are different pathologies. All subjects who inherit a mutation in the neurofibromatosis type 2 (NF2) gene will develop this disease, characterized by the growth of schwannomas, usually vestibular and bilateral, as well as meningiomas or other benign tumors of the central nervous system, before of 30 years of age. Currently, we can identify the NF2 mutation in the majority of affected families. Up to 20% of patients affected by NF2 without a family history, apparently sporadic cases, are actually individuals with mosaicism for that mutation. The morbidity of these tumors is largely due to their treatment, which is mainly surgical. When small, vestibular schwannomas can be completely resected with preservation of both auditory and facial function. In the case of large tumors, a cochlear or brainstem implant can be placed during the same surgical procedure. The main prognostic factors are: the average age at diagnosis, the presence of intracranial meningiomas and whether or not the patient was treated in a specialized center.[7]

Turcot syndrome

Turcot syndrome was first described in 1959 at the Hôtel-Dieu Hospital in Québec, Canada, by doctors Jacqes Turcot, Jean Paul Després and François St. Pierre.[8, 9] It is also a variant of Familial Adenomatous Polyposis that associates tumors of the central nervous system as an extraintestinal manifestation, mainly medulloblastoma and glioma.[10] Currently, only around 120 cases comprising various findings, with various histological types of central nervous system tumors, have been reported worldwide.[11]

The etiology of the syndrome is associated with genetic damage that occurs in two groups of genes; those genes responsible for DNA mismatch correction mechanisms (Type 1), and the APC gene responsible for Familial Adenomatous Polyposis (type 2)[12, 13]. From a molecular point of view, Turcot syndrome is classified into two types. Type 1 is caused by alterations in genes responsible for repairing DNA mismatches. The genes that may be involved in this damage are: MSH2 (2p21), MSH6 (2p16.3), MLH1 (3p22.2) and PMS2 (7p22.1). Type 2 is caused by an alteration in the APC gene (5q22.2), a gene that encodes a tumor suppressor protein. Whatever the etiology, it is recommended to characterize, for diagnostic typing, both the peripheral blood lymphocytes and the DNA of the tumor mass.[14]

The diagnosis is made with rectosigmoidoscopy, colon enema with double contrast and/or colonoscopy to obtain a polyp and thus achieve its histopathological study. It is important to perform a panendoscopy, in search of gastric and especially duodenal polyps, given the high frequency of periampullary carcinoma in them, multiple bilateral spots may also occur due to congenital hypertrophy of the retinal epithelium. The risk of developing carcinoma if the disease is left untreated is 100%. Remembering that Turcot syndrome was initially described as the association of familial colic polyposis and tumors of the central nervous system (medulloblastoma, glioblastomas) and since there were clinical manifestations in the case presented compatible with an expansive lesion of the central nervous system , the authors decided to perform neuroimaging studies, especially simple and contrast-enhanced head CT and nuclear magnetic resonance.[15]

Recent research has described the presence of germline mutations in both the APC gene and a gene responsible for DNA repair. Thus, tumors of the central nervous system should be included, according to Weitz J et al, among the lesions associated with familial colic polyposis and hereditary colorectal cancer not linked to polyposis.[16]

The complex diagnosis of this disease requires that specialists take into account some diagnostic keys to differentiate it from other digestive and/or neoplastic disorders. Examination of the fundus of the eye in search of congenital hypertrophy of the pigment epithelium is of great diagnostic utility. Which, if present, has a specificity close to 100% in patients with Turcot Syndrome, unlike patients with FAP, where it is only present in 70-80% of patients, thus helping to confirm the diagnosis. However, it is not ruled out that pathologists take into account concomitant cases of CNS tumors along with tumors of the digestive tract, to help with diagnostic accuracy, and their typology.[17]

Cowden syndrome

Cowden syndrome was described in 1963 by Loyds and Dennis in a 20-year-old woman named Cowden, from whom the disease takes its name. It is an autosomal dominant disease with variable penetrance and incomplete expressivity characterized by the development of multiple hamartomas. The Cowden Syndrome gene locus has been chromosomally mapped, being on chromosome 10q22-23 where the PTEN (Phosphatase and tensin Homologue) gene is located. PTEN dually encodes a protein and a lipid phosphatase that regulates the phosphoinositol-3-kinase/akt signaling pathway which may result in cell cycle arrest in the G1 phase and apoptosis.[18, 19]

It is essentially characterized by its pathognomonic mucocutaneous signs that are sometimes isolated or accompanied by visceral manifestations. Skin signs are found in 99% of patients, which may be the first lesion of the syndrome. The typical skin lesions consist of facial papules of 1 to 4 mm in diameter, commonly found on the forehead, nose, around the mouth, sometimes in the ear, nasal mucosa, rectal mucosa, oral mucosa. The second most common lesions are papillomas, which have the same topography but are larger in size. Acral keratosis is also characteristic and consists of keratotic papules with a rough surface of 1 to 4 mm, existing on the back parts of the forearm, hands and feet. Non-typical skin lesions may also appear as benign tumors: angiomas, dermal fibromas, lipomas, neurinomas, neurofibromas, xanthomas, xanthelasmas or malignant tumors: melanomas, basal cell carcinoma, squamous cell carcinoma and Merkel carcinomas. At the brain level, macrocephaly, Lhermitte Duclos Disease can develop with a predisposition to the formation of dysplastic cerebral gangliocytomas, Meningiomas.[20]

The diagnosis is made when the patient shows the presence of:

1. Pathognomonic lesions (six or more papules on the face, where three or more must be trichelimomas; facial papules and papillomatosis in the oral mucosa and acral keratosis; six or more palmoplantar keratotic lesions)

2. Presence of two major criteria, one of which has to be macrocephaly or Lhermitte-Duclos Disease.

3. Presence of a major and 3 minor criteria.

4. Presence of 4 minor criteria.[20]

Tuberous sclerosis

Tuberous sclerosis (TS) is a multisystem neurocutaneous syndrome. The observed alterations result from a dysfunction of cell differentiation, proliferation and migration in the early stages of fetal development. ET has an autosomal dominant inheritance, with an incidence of approximately one in every 5,000 to 10,000 births. Currently, mutations have been identified in 2 genes involved in the genesis of the disease: TSC1 (chromosome 9q34) and TSC2 (chromosome 16p13.3). Only 7-37% have a positive family history, with the majority (65-75%) corresponding to de novo mutations.[21, 22]

The diagnosis is defined solely by clinical criteria (Table 3). It is classified as definitive ET if 2 major criteria or one major and 2 minor criteria are present; Probable ET if one major and one minor are recorded, and possible ET when one major or 2 or more minors are observed, without major criteria. Neurological symptoms, present in 85% of cases, are the main cause of morbidity and mortality. Epilepsy and cognitive delay are commonly associated with brain lesions, including glioneuronal hamartomas (also called tuberomas), white matter lesions, and subependymal giant cell astrocytomas.[23] The number and, in particular, the total volume occupied by glioneuronal hamartomas are related to the presence of severe brain dysfunction. The association between the degree of severity of epilepsy and the presence of cortical tuberomas with a cystic appearance has also been demonstrated.[24, 25]

Table 3. Diagnostic criteria for ET.

Major criteria	Minor Criteria
Fascial angiomas/fibrous plaque	Skin lesions in confetti
Shagreen plates	Gingival fibromas
≥ 3 hypopigmented spots	Dental enamel injuries
Periungeal or nail fibromas	Hamartomatous rectal polyps
Lymphangiomyomatosis	Multiple kidney cysts
Renal angiomyolipoma	Non-renal hamartomas
cardiac rhabdomyoma	bone cysts
Multiple retinal nodular hamartomas	retinal hamartoma
Cortical tuberomas	Radial migration lines of white matter
Subependymal nodules	
Subependymal giant cell astrocytomas	

Lhermitte-duclos disease

Lhermitte-Duclos disease (LDD) or dysplastic gangliocytoma of the cerebellum is a rare entity. It presents as a very slow-growing tumor of the cerebellar cortex, which produces a mass effect in the posterior fossa, causing symptoms of hydrocephalus, intracranial hypertension, and cranial nerve dysfunction. Because of this, it is usually diagnosed around the third and fourth decade of life. The WHO included it in grade I of its classification of tumors of the central nervous system (CNS). This entity can occur in isolation or in association with Cowden syndrome (or multiple neoplasia and hamartomas syndrome). It is included within the spectrum of phacomatosis. There are approximately 220 published cases of Lhermitte-Duclos in total.[26]

First described by French neurologists Jacques Lhermitte and P. Duclos in 1920 and named after them. Bulschowsky and Simon also maintained the congenital origin of this lesion and called it hamartoma. In 1933, Foerster and Gagel postulated that the cause of this neoplasia was the Purkinje cell and a decade later, Duncan and Snodgrass established that the neoformation came from hypertrophy of the granular layer. Due to this historical evolution, the entity can be known and found in the literature under various names, some of them are cerebellar dysplastic gangliocytoma, granular cell hypertrophy, diffuse hypertrophy of the cerebellar cortex, Purkinjeoma, ganglioneuroma, gangliomatosis, neurocystic blastoma, hamartomoblastoma or hamartoma of the cerebellum, among others.[27, 28]

The disease is inherited in an autosomal dominant manner and is caused by a mutation of the phosphatase and tensin homologs (PTEN) gene on chromosome 10q 23. Approximately 90% of patients with ELD have a mutation in this gene or its promoters. The PTEN gene was first identified as a tumor suppressor in glioma; when mutated, it results in excessive growth of the tissue.[29] Associations of ELD have been reported with other developmental disorders such as megalencephaly, polydactyly, syndactyly, facial asymmetry, heterotopias, multiple hemangiomas, microgyria, hydromyelia, macroglossia and bone leontiasis, as well as with some syndromes such as neurofibromatosis type I and tuberous sclerosis, among others. MRI usually reveals an intra-axial cerebellar mass with a typical striated pattern, or a tiger stripe pattern (tabby, lamellar or lamellar pattern, characteristic of the lesion). These are seen as hyper- and isointense bands in relation to the matter. gray on T2-weighted images, and iso- and hypointense on T1-weighted images. Findings of calcification and contrast enhancement are rare as in our case, however, cases have been reported where contrast is enhanced and it is probably due to the presence of anomalous veins. Mass effect is common, with compression of the IV ventricle and effacement of the cerebellopontine angle cistern, causing obstructive hydrocephalus. Syringo-hydromyelia can also be secondary to tonsil displacement.[30]

Before recent advances in neuroimaging and microneurosurgery, Lhermitte-Duclos disease tumors were associated with very poor prognosis, and approximately one-third of patients died from mass effect resulting from tumor spread within the posterior fossa. In 1937, Christensen reported the first successful surgery for a dysplastic gangliocytoma of the right cerebellar hemisphere. In general, surgical excision is the mainstay of treatment, complete excision of the hypertrophied lesion is the treatment of choice since recurrence or malignant transformation has been reported after subtotal resection of the lesion. Many authors have recommended total extraction in young adults, even in the absence of symptoms. However, complete excision is not always possible because the lesion often blends with normal cerebellar tissue and is therefore difficult to distinguish. Additionally, the risks of extensive resection include neurological deficits such as cerebellar mutism.[30]

Li-fraumeni syndrome

Li-Fraumeni syndrome, also known as SBLA (Sarcoma, Breast, Leukemia, and Adrenal gland, SBLA) syndrome, was described in 1969 by Li and Fraumeni.[31] It is characterized by the appearance of tumors in multiple organs, generally at an early age, among which soft tissue sarcomas, osteosarcomas, breast cancer in premenopausal women, brain tumors, acute leukemias and breast cancer. the adrenal cortex, are the most common. This rare genetic condition is inherited in an autosomal dominant pattern and has a penetrance of 70% in men and almost 100% in women. 70% of patients with a clinical diagnosis of Li-Fraumeni syndrome have a germline mutation in the TP53 gene and those who meet the Chompret criteria (Table 4) have a 20% chance of having an identifiable mutation in this gene.[32]

Table 4. Diagnostic criteria for Li-Fraumeni Syndrome.

Classic criteria
All of the following criteria must be met: Diagnosis of sarcoma before age 45 First-degree relative diagnosed with cancer before age 45 First or second degree relative with any cancer and age of onset under 45 years or sarcoma at any age
Birch criteria
Proven case of cancer in childhood, or sarcoma, brain tumor or cortico-adrenal carcinoma that appears in a person under 45 years of age and a first or second degree relative with a cancer associated with Li-Fraumeni Syndrome (sarcoma, breast cancer, brain tumor, adrenal-cortical carcinoma or leukemia) detected before 60 years of age
Eales criteria
Two first- or second-degree relatives with Li-Fraumeni Syndrome-related tumors (sarcoma, breast cancer, brain tumor, adrenal cortico-adrenal carcinoma, leukemia, or bronchoalveolar lung cancer) at any age

Chompret criteria
Proven case of a tumor related to Li-Fraumeni Syndrome (sarcoma, breast cancer, brain tumor, cortico -adrenal carcinoma, leukemia or broncho-alveolar lung cancer) in a person under 46 years of age and at least one primary relative. or second degree with a Li-Fraumeni Syndrome-related tumor (except breast cancer if the proven case person has it) detected before age 56, or with multiple primary cancers at any age. Or a proven case with multiple tumors (except multiple breast cancer), two of which are related to Li-Fraumeni Syndrome and the first has appeared before the age of 46. Case with diagnosis of cortico-adrenal tumor or choroid plexus carcinoma, regardless of family history.

Conclusions

Brain tumors constitute a large heterogeneous group of lesions in which a small percentage are secondary to genetic anomalies with hereditary transmission patterns; it is extremely important to be able to recognize them in daily neurosurgical practice.

Conflict of Interest

The authors declare no conflict of interest.

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