v. 5, n. 13, 2025

International Journal of Health Science

A COMPREHENSIVE REVIEW OF THE GENETIC COMPONENTS AND CLINICAL MANIFESTATIONS OF TURCOT SYNDROME

Acceptance date: 27/02/2025

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Abstract: Turcot syndrome is a rare genetic disorder characterized by the development of both colorectal polyps and brain tumors. It is caused by mutations in the APC gene, which plays a role in regulating cell growth and division. The two main types of Turcot syndrome are type 1, which is associated with mutations in one of the MMR genes, and type 2, which is related to mutations in the APC gene. Patients with type 2 Turcot syndrome typically develop colorectal polyps and medulloblastoma (a type of brain tumor that arises in the cerebellum). The diagnosis of Turcot syndrome is based on a combination of clinical history, physical examination, image exams, and genetic testing. There is currently no cure for Turcot syndrome, but treatment can help manage the symptoms and improve the quality of life for patients.
Keywords: Turcot Syndrome; Clinical manifestations; Treatment; Genetic.

INTRODUCTION

Turcot syndrome is a rare genetic disorder that is characterized by the development of both colorectal polyps and brain tumors. It is also known as intestinal adenomatous polyposis, multiple polyposis, disseminated polyposis, familial adenomatosis, and familial colonic polyposis. The epidemiology of Turcot syndrome is difficult to describe, as it is a rare disease that has had a variable definition over the years. The syndrome is caused by mutations in the APC gene, which plays a role in regulating cell growth and division and can be inherited in an autosomal recessive or autosomal dominant manner, or also occur sporadically (1;2).

Hereditary nonpolyposis colorectal cancer (HNPCC), which is associated with mutations in mismatch repair (MMR) genes, and familial adenomatous polyposis (FAP), which is associated with a mutation in the APC gene, are the two most well-known types of hereditary colorectal cancer. The presence of a brain tumor in a patient with HNPCC or FAP is considered to be Turcot syndrome 1 (TS1)

DOI https://doi.org/10.22533/at.ed.1595132525021

or Turcot syndrome 2 (TS2), respectively. Patients with FAP have a 92% increased risk of developing medulloblastoma[1].

The clinical manifestations of Turcot syndrome vary depending on the type of mutation that is present. Patients with TS1 typically develop colorectal polyps and glioblastoma multiforme (a type of brain tumor). Patients with type 2 Turcot syndrome typically develop colorectal polyps and medulloblastoma (a type of brain tumor that arises in the cerebellum).

The diagnosis of Turcot syndrome is based on a combination of clinical history, physical examination, image exams, and genetic testing. There is currently no cure for Turcot syndrome, but treatment can help manage the symptoms and improve the quality of life for patients.

This review aimed to provide a comprehensive overview of the genetic components and clinical manifestations of Turcot syndrome. Furthermore, it will discuss the different types of Turcot syndrome, the genes that are involved, the clinical features of the syndrome, and the diagnostic and treatment options.

METHODS

This is a review whose data search strategy included studies obtained through three databases: PubMed, Lilacs, and Scielo. The search was conducted using the descriptive term "síndrome de Turcot" and its English counterpart "Turcot syndrome" for articles published in the last 10 years (2013-2023) in English, Portuguese, and Spanish. The present study included case reports, randomized trials, and systematic reviews that addressed colorectal polyposis associated with central nervous system (CNS) neoplasia in children and adults, without age restrictions, of both sexes, in any region of the world. Moreover, it was excluded book chapters, abstracts, duplicate articles, and articles that did not describe the genetic composition or clinical manifestation. Thus, 38 articles were obtained, 31 in PubMed, 4 in BVS, and 3 in Scielo. We excluded 32 references for the reasons listed in the exclusion criteria. A total of 6 articles met the inclusion criteria. The reference flow is summarized in the study flowchart (Fig. 1).

RESULTS

Table 1 summarizes the genetic mutations and their associated clinical manifestations as reported in the included studies. Dinarvand et al. (2019) identified mutations in the APC gene (codons 697 to 1224) linked to a wide range of symptoms, including gastric fundic gland polyps, duodenal polyps, CHRPE, fibromas, fibromatosis, nasal angiofibromas, thyroid carcinomas, hepatoblastomas, second brain tumors, and pancreatic and biliary tumors. Waller et al. (2016) described germinal mutations in the APC gene on chromosome 5q21 associated with metastatic colorectal cancer and desmoid tumors. Costa et al. (2019) differentiated between Type 1 and Type 2 mutations, where Type 1 (MMR gene) showed symptoms similar to Lynch syndrome, and Type 2 (APC gene) manifested symptoms akin to Multiple Familial Polyposis, including second brain tumors and non-neuroepithelial tumors of the CNS.

Further studies expanded on these findings. Hernández et al. (2018) reported APC gene mutations linked to CNS expansive lesions, digestive bleeding, mucus secretion, rectal tenesmus, and rectal prolapse. Chanis et al. (2014) found germinal mutations in the APC gene (chromosome 5q21-q22) correlated with medulloblastoma, gliomas (Turcot syndrome), thyroid cancer, hepatoblastoma, and gastric carcinoma. Sousa et al. (2012) distinguished between Type 1 mutations in MMR genes, causing various neurological symptoms such as focal deficits, mood and personality changes, seizures, and signs of intracranial hypertension, and Type 2 mutations in the APC gene with similar neurological symptoms. These findings underscore the diverse clinical mani-

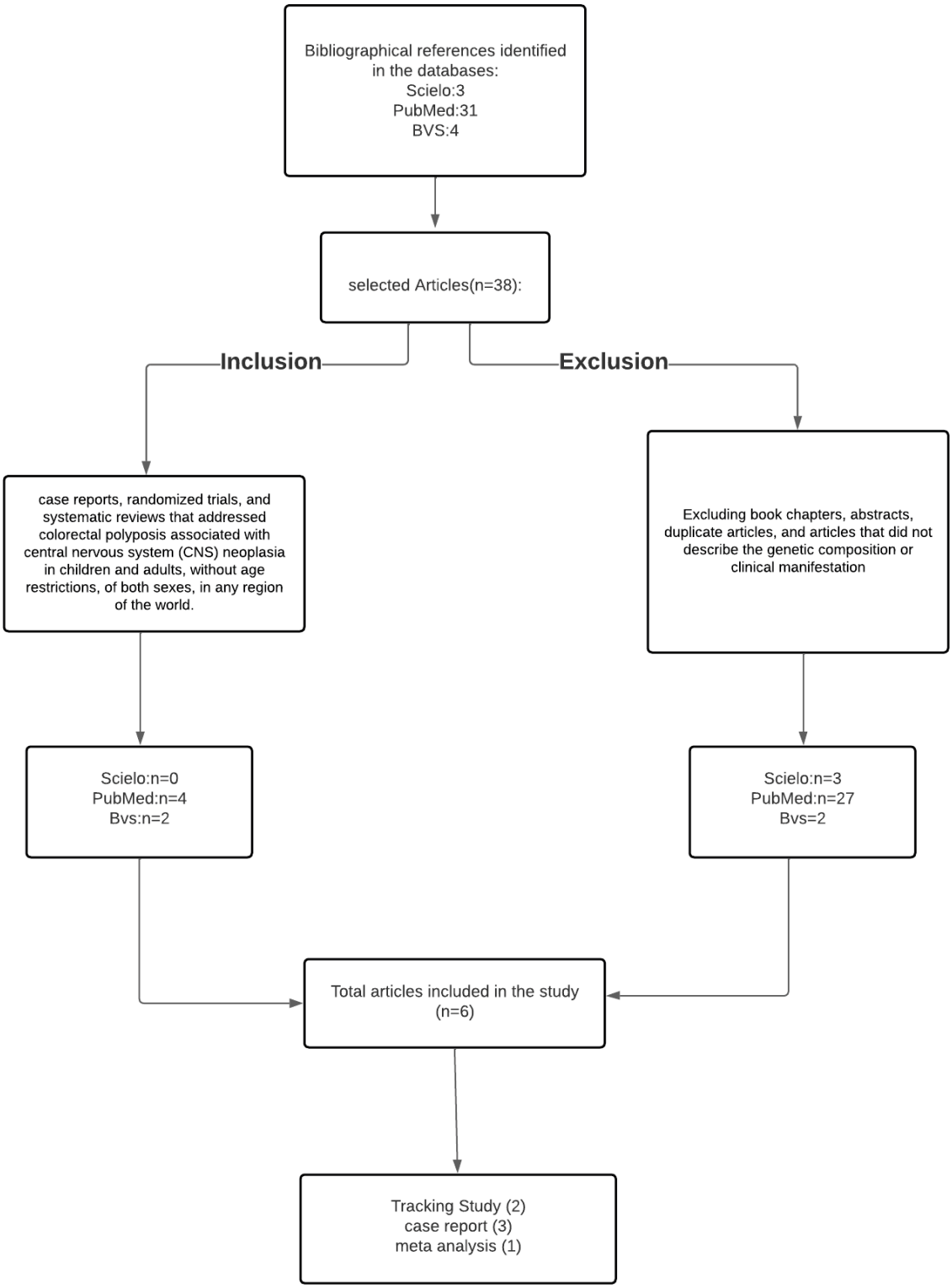

Figure 1 - Flowchart of the study showing the selection process for the review

festations associated with specific genetic mutations, emphasizing the importance of precise genetic identification for accurate diagnosis and treatment planning.

Reference	Genetics	Varying Signs and Symptoms
Dinarvand et al., 2019	Mutations in the *APC* (Adenomatous Polyposis Coli) gene, between codons 697 e 1224	Gastric fundic gland polyps (PGFs), duodenal polyps, congenital hypertrophy of retinal pigment epithelium (CHRPE), fibromas, fibromatosis, nasal angiofibromas, thyroid carcinomas, hepatoblastomas (HBs), second brain tumor, and pancreatic and biliary tumors
Waller et al., 2016	Germinal mutations in the APC gene, located on chromosome 5q21	metastatic colorectal cancer and desmoid tumors
Costa et al., 2019	Type 1, mutation in the MMR (MisMatches Repair) gene Type 2, mutation in the APC gene	Second brain tumor, non-neuroepithelial tumors of the central nervous system, type 1 has a phenotype similar to Lynch syndrome, and type 2 has a phenotype similar to Multiple Familial Polyposis
Hernández et al., 2018	Mutation in the APC gene	Central Nervous System expansive lesion, digestive bleeding, mucus secretion, rectal tenesmus, and rectal prolapse
Chanis et al., 2014	Germinal mutations in the APC gene, located on chromosome 5q21-q22	Medulloblastoma, gliomas (Turcot syndrome), thyroid cancer, hepatoblastoma, and gastric carcinoma
Sousa et al., 2012	Type 1 is caused by mutations in one of the MMR genes; Type 2 is caused by mutations in the APC gene	A variety of neurological symptoms, including focal deficits, mood and personality changes, seizures, and signs of intracranial hypertension

Table 1 - Summary of Genetic Mutations and Associated Signs and Symptoms in Various Studies

DISCUSSION

PAF genetic condition caused by germline mutations in the Adenomatous Polyposis Coli (APC) gene, located in chromosome 5q21-Q22, which plays an important role in regulating intracellular levels of β-catenin, decreasing its concentration in the cytoplasm and stabilizing the tissues. Patients with PAF have an increased risk of developing colorectal cancer. TS is an association of polyposis (PAF) with primary tumors of the central nervous system. Thus, Turcot syndrome is considered an extracolonic manifestation of PAF [3].

The fundamental clinical presentation is colorectal cancer associated with the primary tumor in the CNS. However, due to a wide variety of genes involved and the possibility of overlap, TS has a diverse phenotypic spectrum [1]. More than 800 APC mutations have been described [4]. Turcot syndrome has been clinically and genetically divided into two main types: type 1, with mutations of one of the MMR genes (Mismatch Repair - DNA nucleotide repair) and type 2, with mutations in the APC gene [4]. Type 2 has a higher manifestation of PAF and a higher risk of developing medulloblastoma, while type 1 leads to a greater predisposition to the development of hereditary non-polipid colorectal cancer and GBM (glioblastoma). The most common signs and symptoms of Turcot syndrome include focal neurological deficit, mood and personality changes, seizures and symptoms of intracranial hypertension [5].

Patients with type 1 of TS, in addition to the fundamental clinical presentation, may also present hematological neoplasms, Cafe-au-lait spots and glioblastoma multiforme [1]. Patients with these mutations have fewer colon polyps, although on rare occasions they may have significant polyposis as well [6]. In relation to patients with type 2 of TS, they may present epidermal cysts, tumors in other areas of the body and medulloblastoma due to a mutation of the APC gene [1]. This mutation leads to very significant colon polyposis, with polyps numbering in the thousands.

Patients who expressed the phenotype of colonic polyposis tend to manifest the disease after 17 years-old, and those who did not express the colonic phenotype manifested the disease via brain tumor at 10 years-old [6]. Furthermore, in rare cases patients may also present pituitary adenomas, ependymomas

and astrocytomas [6]. Neurological signs and symptoms are associated with the location and type of tumor.

Children born to inbred parent relationships represent 20% of diagnosed cases of type 1 TS, with no family history of brain tumors or colon cancer. Its clinical presentation is characterized by larger polyps, but in smaller amounts, and is associated with gliomas and skin manifestations, such as Café au lait spots [6]. Type 2 ST is less frequent and typically occurs in descendants of families with PAF grouping. In this type, medulloblastoma is the most common CNS cancer. The occurrence of colorectal cancer occurs later in TS2 than in TS1, and skin lesions, when present, appear more epidermal cysts than coffee spots with milk.

Patients with FAP have a relative risk of developing medulloblastoma, being up to 92% [7]. As a result, an APC mutation is present by default in the PAF. APC mutations are not found in sporadic Medulloblastomas; therefore, it is concluded that medulloblastoma presenting in a patient with an APC mutation is the most likely Turcot syndrome [1]. About 40% of patients with Turcot syndrome develop a medulloblastoma. Approximately 30% of families identified with PAF resulted from new mutations or mosaic inheritance as opposed to autosomal recessive inheritance [8]. Patients are born with the disease but manifest with it in early adulthood or earlier. It is estimated that approximately 75% to 80% of individuals with APC-associated polyposis have an affected parent [9].

The diagnosis of Turcot syndrome is based on a combination of clinical history of multiple adenomatous colon polyposis symptoms and primary neuroepithelial tumors of the central nervous system accompanied by complementary examinations [10]. The hypothesis must be confirmed by imaging and genetic examination. The imaging test of choice for diagnosis is magnetic resonance imaging (MRI). The genetic examination for definitive diagnosis of PAF requires molecular analysis of APC [4] [11]. Therefore, it is proposed that the children of patients with PAF should be screened by genetic testing and start flexible sigmoidoscopy at 10 years of age, with subsequent annual examinations [12].

The therapeutic approach of medulloblastomas is a combination of chemotherapy, surgical resection and radiotherapy [10]. Overall five-year survival with standard treatment is between 70% and 85%. Of the subgroups, classical histology has a 5-year event-free survival of 84%, desmoplastic tumors 77% and large cell anaplastic tumors 57% [10]. MYC and MYCN are factors of poor prognosis and, as such, correlate with the worse prognosis of Group 3 (MYC) and SHH (MYCN) [4].

CONCLUSION

In summary, it is concluded that Turcot syndrome is divided into two main types: type 1, which is associated with mutations in one of the MMR genes; and type 2, related to mutations in the APC gene. In relation to clinical manifestations, there are differences between the two types of TS, with type 2 presenting with PAF more frequently and medulloblastoma development, while type 1 is often associated with hereditary non-polyposis colorectal cancer and glioblastoma. Based on the work presented, it was evidenced that TS of type 2 is less frequent when compared to type 1.

As for the diagnosis, a medical history covering the main clinical manifestations of TS is necessary, associating with complementary examinations, such as MRI and genetic testing. The therapy for Turcot Syndrome involves a combination of chemotherapy, radiation therapy, and surgical approach. The survival of patients undergoing treatment (5 years of therapy) is high, corresponding to between 70% and 85% of those treated.

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