Turcot Syndrome. A Rare Case and Literature Review


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Turcot syndrome is a rare disorder characterized by combination of brain and colon tumors. About 150 such cases have been described in the world literature. Our own observation and the literature review are provided in this article.

Keywords: Turcot syndrome, brain tumor, colon tumor, glioblastoma.

J. Turcot [26] described 2 cases of combination of colon polyposis with a brain tumor in two sick relatives, brother and sister in 1959. In the first case polyposis and adenocarcinoma of the sigmoid colon were combined with medulloblastoma; in the second case — with glioblastoma and pituitary adenoma. Three years later, combination of primary brain tumors and colorectal polyposis was called Turcot syndrome by McKusick, who also suggested an autosomal recessive inheritance mode of the disease. Since then, researchers have begun to pay attention to this rare disorder, and the number of observations has started to grow rapidly. The paper by H. Crail [7] describing the case of polyposis colon cancer, medulloblastoma, and thyroid carcinoma (published in 1949) was found retrospectively.

Over 150 cases of patients with the Turcot syndrome have been reported in literature [12, 22]. It became apparent that this is a heterogeneous group of patients having different clinical manifestations of the cancer and heterogeneous genetic changes.

Our own observation is presented below.

A 12-year-old boy T. was sick for 2 years (since 2009), when the rare episodes of headache and nausea appeared. Since spring 2011, the emergence of bright red blood in the stool was noted. Left-sided hemiparesis accompanied by aggravated headache appeared since December 2011. A cystic tumor in the right parietal region was revealed by CT. The surgery aimed at removing the tumor in the right parietal region was performed at a local hospital of his residence in January 2012. The tumor was considered as glioblastoma. Radiation therapy (TFD ~46 Gy) was applied to the tumor bed during the next two months. The blood emergence in the stool was noted again when the patient was subjected to radiation therapy. Sigmoid colon polyp was revealed with rectromanoscopy and a biopsy was performed. Histological diagnosis was the proliferating tubular adenoma.

A recurrent tumor in the right parietal region was revealed with the control CT in April 2012. The child was admitted to the Federal Scientific and Clinical Centre of Pediatric Hematology, Oncology and Immunology named after D. Rogachev in May 2012 for further examination and treatment.

The family history had no data on the incidence of brain or colon tumors. No marriages between close relatives occurred.

The clinical presentation upon admission included left-sided hemiparesis (up to 3 points) and blood in the stool. MRI showed a cystic tumor in the right parietal region and intensive accumulation of the contrast agent by tumor walls (Fig. 1).

The repeated colonoscopy revealed a giant polyp that completely overlapped the lumen of the sigmoid colon, with loose, uneven mucosa with the areas of contact...
bleeding (Fig. 2). The polyp was captured with a loop within the healthy mucosa and removed by monocoagulation. Histological diagnosis was tubular adenoma without signs of malignization. The mucous membrane of the examined parts of the colon was pink. The vascular pattern was clearly defined and uniform. The folds were elastic. The intestinal lumen was not deformed. Polypoid formations (3–15 mm in size, total number of several dozens) were defined throughout the sigmoid.

The second stage of the surgery was the removal of the tumor in the right parietal region. All visible portions of the tumor were removed. Histological diagnosis was pleomorphic astrocytoma (glioblastoma). No tumor remnants were found by the control contrast-enhanced MRI conducted in the first day after surgery. The postoperative period was uncomplicated. The boy was discharged from the Center in satisfactory condition for dynamic follow-up in location of his residence.

Discussion

Terminology. Turcot syndrome is also known in modern literature as the brain tumor polyposis syndrome (BTPS) [22, 26, 27]. It is believed that this term better describes the essence of the disease.

Classification. There are two types of BTPS. BTPS type I is characterized by a combination of hereditary nonpolyposis colon cancer (hereditary nonpolyposis colorectal cancer syndrome — HNPCC), also known as Lynch syndrome, with brain glial tumors (more commonly, glioblastoma) [2, 14, 22, 26, 27]. For reasons not understood, this condition is also called “true Turcot syndrome.” BTPS type II is characterized by a combination of familial adenomatous polyposis (FAP) with medulloblastoma. BTPS type II is sometimes called Crail’s syndrome [2, 12, 14, 26, 27]. It should also be noted that this division has a probabilistic rather than absolute nature, and there is no clear distinction between the syndrome types.

Frequency of occurrence. Population frequency, sexual and racial predisposition are unknown. The disease most often manifests in a young age (10–30 years) [1, 22, 26, 27]. about a total of ~150 cases of Turcot syndrome have been reported in the literature.

Clinical presentation. The clinical presentation of BTPS is nonspecific. Sometimes the disease has symptoms of colon tumors (abdominal pain, blood in the stool) or the presentation of a brain tumor (headache, nausea, vomiting, symptomatic epilepsy, etc.). Presence of BTPS type I in parents or the older generation is uncommon, although it is frequent among siblings. Close or immediate relationship between parents (which is typical of autosomal recessive inheritance) is often described. The number of polyps in the colon of patients with BTPS type I is small (less than 100); however, the risk of colorectal carcinoma exceeds 50%. CNS tumors are gliomas almost without exception (most commonly, glioblastomas; although grade II—III gliomas have also been described) [10, 12, 19, 20, 22, 27].

BTPS type II may manifest in several generations of a family; however, the marriages between close relatives are rare. Patients have a typical pattern of familial adenomatous polyposis; the number of polyps in the colon of such patients reaches several hundreds or thousands. Colorectal carcinomas occur in about 20% of cases. In the brain, medulloblastoma is detected in 60% of cases; however, gliomas, ependymomas, and pineoblastomas have also been described [10, 12, 19, 20, 22, 27].

The skin manifestations, such as café-au-lait (“coffee with milk”), pigmented nevi, basal cell carcinoma, etc. are frequently observed in patients with BTPS [22, 27].

Several cases of combination of colon tumors with brain tumors of non-neuroectodermal nature (lymphomas, meningiomas, pituitary adenomas, craniopharyngiomas) have also been reported. However, such combinations are currently considered as coincidence and do not belong to BTPS [12, 19, 20, 22, 27].

Diagnosing patients with Turcot syndrome has no specific features. Colonoscopy is routinely performed to detect colon tumors, while CT and MRI of the brain are done to diagnose tumors of the central nervous system.

Histology of colon and the brain tumors has no specific features as compared to these tumors in patients without Turcot syndrome [17, 23, 25, 27].

Genetics. Autosomal recessive inheritance is typical of BTPS type I, the autosomal dominant inheritance is common for BTPS type II. Molecular genetic studies have shown that BTPS type I has genetic defects characteristic of hereditary nonpolyposis colon cancer, while genetic features of BTPS type II are common for familial adenomatous polyposis [3, 16, 22, 24, 27].

Hereditary nonpolyposis colon cancer arises from mutations in one of the mismatch repair genes (MMR). They are responsible for the accuracy of DNA replication. The MMR genes include MSH2, MLH1, MSH6, PMS1, PMS2, MSH3, and EXO1 genes. Mutations are
most commonly identified in \textit{MSH2}, \textit{MLH1} and \textit{PMS2} genes. Microsatellite instability is noted in 90\% of the HNPCC cases \cite{8, 9, 13, 15, 24, 27}.

Familial adenomatous polyposis arises from mutations in the \textit{APC} gene on the chromosome 5q21. \textit{APC} belongs to the group of tumor suppressor genes. Protein \textit{APC} suppresses cell proliferation by inhibiting \(b\)-catenin transcriptional activity \cite{2,11, 14, 18, 25}. Mutations in the aforementioned genes are often detected in patients with BPTS.

The above data are summarized in \textit{table}.

Genetic counseling of a patient and his/her family members is an important component of care at BPTS. Counseling for families with confirmed cases of adenomatous polyposis of the colon is especially important and relevant. Diagnosis of BPTS type II is typically made on the basis of clinical data. Genetic analysis of the \textit{APC} gene is carried out in cases where it can provide important information for other family members of the patient. An annual sigmoidoscopy aimed at identifying polyps colon is recommended to family members who have a mutant allele of \textit{APC} gene (starting from the age of 10–12 years) \cite{21}. This approach also extends to the families in which no mutations in the \textit{APC} gene have been identified, but the diagnosis of adenomatous polyposis colon was made on the basis of clear clinical data.

Treatment of patients with the Turcot syndrome employs the same principles as that of patients with sporadic forms of polyposis/carcinoma of the colon or brain tumors. This is a sequence of surgeries to remove tumors, radiation and chemotherapy in various combinations.

An important aspect of the management of patients with BPTS is the prevention of colorectal cancer. A preventive proctocolectomy is recommended for patients with BPTS type II associated with mutations in the \textit{APC} gene and with the presence of colon polyps \cite{4}. Indications for surgery include the detection of colon polyps. Effectiveness of preventive operations in patients with BPTS type I is not so obvious. Common practice is to perform diagnostic colonoscopy every 1–2 years. It has been shown that this approach allows one to identify colorectal cancer at an earlier stage.

Currently, attempts are being made to identify drugs capable of preventing malignization of colon polypos. A randomized trial CAPP2 showed that aspirin in comparison with placebo provides a statistically significant decline in the incidence of colorectal cancer in patients with mutation in mismatch repair genes \cite{6}. A similar study in the patients with adenomatous colon polyposis showed no preventive benefits of aspirin \cite{5}.

Prognosis in patients with BPTS is determined by the malignancy degree of intestinal and brain neoplasms. It is particularly remarkable that the survival among the “syndromic” patients with glioblastoma is substantially higher than that in the sporadic cases \cite{22, 27}.

In our observation, we see a combination of the glial brain tumor of low-grade malignancy with the benign colon polyps. This case is more consistent with Turcot syndrome type I. The materials of brain tumor biopsies obtained at a local hospital of patient’s residence and during the surgery at the Federal Scientific and Clinical Centre of Pediatric Hematology, Oncology and Immunology were carefully analyzed at the Laboratory of Pathomorphology. In fact, glioblastoma was confirmed for the first case, while the diagnosis “pleomorphic xanthoastrocytoma” was correct for the second surgery. We cannot explain this discrepancy in histological diagnosis. The probability of transformation of glioblastoma to a benign tumor is very doubtful. On the other hand, primary glioblastoma is rarely a cystic neoplasm; it is more typical of astrocytomas. We had suggested that the material from the first biopsies might

\begin{table}[h]
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\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Signs} & \textbf{BPTS type I} & \textbf{BPTS type II} & \textbf{Non-syndrome combination of CNS tumors and polyposis of colon} \\
\hline
Colon polyps & Less than 100, large size (>3cm), nonhereditary polyposis; colorectal cancer at a young age (> 50\%) & Multiple (> 100) small polyps, hereditary polyposis, colorectal cancer (20\%) & Different amounts, sometimes occurs in FAP \\
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Tumors of the central nervous system (CNS) & Astrocytoma or glioblastoma at a young age (under 20 years) & Often medulloblastoma & Non-neuroectodermal tumors of the CNS (lymphomas, meningiomas, pituitary adenomas, etc.) \\
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Cutaneous manifestations & Occur frequently (50\%), café au lait spots are most common (40\%) & Various skin manifestations (20\%) & No \\
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Heredity & Often in siblings. No intestine polyposis or CNS tumors in relatives of older generations & Familial polyposis & No familial cases of CNS tumors, but in patients with FAP \\
\hline
Marriages of close relatives & Often (20\%) & No & No \\
\hline
Type of inheritance & Autosomal recessive & Autosomal dominant \textit{APC} gene & Same \\
Genetic defect & \textit{MSH2}, \textit{MLH1} and \textit{PMS2} genes & Familial adenomatous polyposis (FAP) , Gardner’s syndrome & Not identified \\
\hline
Related hereditary diseases & Hereditary nonpolyposis colorectal cancer (HNPCC) & & No \\
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\end{tabular}
\caption{Clinical manifestations of BPTS (Turcot syndrome)}
\end{table}
belong to another patient; however, there is no evidence for this. At the moment the child is under follow-up. He received no adjuvant therapy with regard to the benign nature of formations in his brain and intestine.

**REFERENCES**


**Commentary**

Turcot syndrome, or brain tumor polyposis syndrome (BTPS) is a rare disease that requires further study and attention from neuro-oncologists.

Turcot syndrome, or syndrome of brain tumors and polyposis colon, is a rare hereditary disease. I found no description of this syndrome in Russian-language neurosurgical literature, including the most recent textbooks. Therefore, the publication of this clinical observation and literature review is certainly relevant.

A small clarification on terminology is needed. In English-language biochemical literature, the terms "Constitutional mismatch repair-deficiency syndrome" (CMMR-D) and "Mismatch repair cancer syndrome" (MMRCS) are used more commonly than Turcot syndrome. However, it seems to me that the term "Turcot syndrome" is more appropriate.

Let me say briefly about the molecular basis of the biological processes. During the cell division, at DNA replication the daughter copy may normally contain errors that occur during transcription. The complex system of proteins recognizes defective copies of DNA and cuts them along with the adjacent areas; DNA polymerase then restores the correct sequence of nucleotides in the damage zone. Disturbance of the process of the errors correction leads to genomic instability and uncontrolled growth of cells. The damage at Turcot syndrome is biallelic, which means that symmetrical parts of both DNA strands are damaged. The molecular biological mechanism of Lynch syndrome mentioned by the authors is somewhat different, because only one of a pair of DNA molecules is damaged. Furthermore, brain tumors are not covered by Lynch syndrome (only osteomas may belong to it).

People interested in the problem may be referred to the publication: K. Wimmer, J. Etzler. Constitutional mismatch repair deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet 2008; 124: 2: 105–122.

Once again, I congratulate the authors on an interesting observation and the deep analysis of it.

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