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The content of serotonin cells in duodenal biopsies of autistic patients

Zawartość serotoniny w błonie śluzowej dwunastnicy pacjentów autystycznych

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- ECH cells – enterochromaffin cells
- ECH 5-HT cells – enterochromaffin serotonin cells
- SERT – serotonin transporter
- 5HT – serotonin
- GI – gastrointestinal

ABSTRACT

Introduction: Autistic spectrum disorders (ASD) don't have the same etiology. Platelet hyperserotonemia remain the most common neurochemical abnormality in these patients. The main producer and storage of peripheral serotonin are enteric enterochromaffin cells – serotonin cells. Platelet hyperserotonemia may result from disorders in the synthesis and/or release of enteric serotonin. An increased number of people with ASD have gastrointestinal disorders. Some of them have a serotonergic background. **Aim:** The aim was to assess the serotonin cells in the duodenal mucosa of patients with ASD. **Material and methods:** Study group: 30 children with ASD, including 73% with *duodenitis chronica*. Control group (patients without ASD): 45 patients, 56% with *duodenitis chronica*. Immunohistochemical assessment of the number of serotonin cells was performed.' **Results:** Children with ASD and *duodenitis* have fewer serotonin cells than autistic children with a normal picture of the duodenum. Children with ASD and *chronic duodenitis* have fewer serotonin cells than patients from the control group. Patients from the control group, suffering from *chronic duodenitis* have an increased number of serotonin cells in relation to children without inflammatory lesions in the duodenum. **Conclusions:** The serotonergic profiles of the GI tract of autistic patients and their peers without autistic symptoms are different. In the course of *chronic duodenitis* in patients with ASD the number of serotonin cells falls while in persons without autistic features it increases significantly. *Chronic duodenitis* contributes to an increase in the number of serotonin cells in persons without autistic features while decreasing it in patients with ASD.

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Introduction

Serotonergic disorders in ASD were pronounced after the conduction of the following examinations: biochemical, pharmacological, behavioural analyses, molecular biology concerning serotonin receptor and transporter, serological and neuroimaging diagnosis (positron emission tomography, PET; functional MRI, fMRI) [1–6]. Estimations of the level of 5HT in peripheral blood in autistic patients in the developmental age indicate prepubescent platelet hyperserotoninemia [7, 8]. In adult patients with ASD, lower than the control values with a decrease in platelet serotonin reuptake have been observed [9]. Simultaneously conducted neuroimaging, pharmacological (SSRI) and behavioural profile examinations suggest central hyposerotoninemia [10]. So far the significance of platelet (PLT) hyperserotoninemia has not been established. The serotonergic profile changes as it grows (function of receptor/neurotransmitter systems, types of 5HT receptors, their activity, number, location, serotonin level). In autistic persons this process is probably disturbed from the neurogenesis [8, 10].

In postnatal life, due to the blood–brain barrier, peripheral and central 5HT are two different deposits. The main producer and a storeroom for the peripheral 5HT are the intestinal enterochromaffin cells (ECH), and specifically their subgroup referred to as serotonin cells (ECH 5HT). 2% of 5HT in our bodies is stored in the CNS, 95% in the intestines (90% in ECH and 10% in the enteric nervous system – ENS), the remaining part is in blood PLT [11]. 5HT is mainly secreted paracrinely from ECH 5HT onto the gastrointestinal (GI) mucosa. It penetrates into the intestinal lamina propria (it impinges on the peripheral nerves' endings and affects the enteric immune system) and diffuses into the peripheral blood. Small amounts can be found in intestinal lumen (trace amount detected in faeces) [12]. 5HT secreted from ECH is subject to active SETR-mediated reuptake. Molecularly identical SERT is present on blood PLT, cells of the mucosa of the intestines and lungs, and in the central, peripheral and enteric nervous system. It has been suspected that it is SERT that is responsible for serotonergic disorders in autistic persons. Conducted molecular analyses do not confirm the above theory [13]. Free 5HT in peripheral blood is subject to first pass metabolism in the liver and to a lower degree in the lungs. It is only the 5HT, hidden in blood PLT that avoids the metabolism [12]. Due to the few-day half-life ($T_{1/2}$) of 5HT and the short time of life of PLT, the PLT level of 5HT reflects the current availability of 5HT for PLT. It should be accepted that PLT 5HT is a reflection of the intestinal production [11]. 5HT is broken down in the body by MAO – A into 5-hydroxyindoleacetic acid (5HIAA), which is subsequently extracted from urine. An indirect proof of an increased serotonin turnover is increased extraction of 5-HIAA [14].

Recently an increased number in ASD patients suffering from problems relating to the GI tract in comparison to the population of persons without the autistic features has been observed. The most common disorders include abdominal pains, disorders in gastrointestinal motor activity and nutritional problems. Both endoscopic and histopathological examinations have confirmed on several occasions an increased number of patients with autistic disorders, suffering from chronic inflammation of the abdomen, the duodenum and the colon [15–18]. Moreover, autistic patients present the signs of microbiological gut dysbiosis [19, 20].

Serotonin is one of the GI transmitters (signaling molecule), which plays a vital role in the perception, motor activity and secretion of the GI tract. The role of 5HT in the ailments (dyspepsia), motor activity disorders (vomiting, diarrhoea, constipation) and gastrointestinal disorders (mainly functional GI disorders, irritable bowel syndrome = IBS) has been proven [21, 22]. The clinical picture of serotonergic disorders corresponds with GI problems of the patients with ASD.

Janusonis conducted a theoretical analysis of biological parameters related to the serotonin system. Using a mathematical model he proved that the content of 5HT in blood platelets depends on the PLT reuptake of serotonin, the amount of free plasma serotonin subject to the first pass metabolism in the liver and lungs, intestinal production of serotonin and the volume of the enteric wall [7]. Because, theoretically, the cause of platelet hyperserotoninemia may be a disorder of the synthesis of serotonin and/or of the release of the enteric serotonin, we made an attempt to assess the proportion of the ECH 5HT cells in the duodenal mucosa.

Material and methods

Characteristics of the study and control group: The total of 75 patients were included in the retrospective analysis: 30 children with autistic spectrum disorders (ASD) and 45 of their peers without the symptoms of ASD (not – ASD). The study was retrospective. The study followed the permission of the Bioethic Committee of the SMU in Katowice (number of the consent L.dz.NN-013-42/03).

The children were patients of the Department of Gastroenterology of the Clinic of Paediatrics of the SMU in Katowice between 2004 and 2006. During clinically indicated hospitalisation, the upper GI endoscopy and the collection of specimens of the mucosa in the descending part of the duodenum were performed. The study group (ASD) and the control group (non-ASD) are homogenous in terms of sex and age.

Study group: a total number of 30 persons (16 AD/14 AA); males $n = 19$, females $n = 11$; age between 3 and 13 years old; average age of 8 years; in 8/30 persons a normal picture of the mucosa was reported (ASD-SN) and in 22/30 of persons were presented with symptoms indicating an inflammation (chronic duodenal inflammation in 9 patients, chronic duodenal inflammation with infiltration of eosinophiles in 13 persons; ASD-Dch).

Control group: a total number of 45 persons; males $n = 28$, females $n = 17$; age between 3 and 13 years; average age of 8 years; the patients from the control group were selected retrospectively based on the relevant medical documentation; they were patients without ASD, where a histopathological examination revealed a normal picture of the duodenal mucosa, corresponding with the picture obtained from