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Research Article

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The Prevalence of Lymphoid Nodular Hyperplasia in Children and Adolescents with Autism Spectrum Disorder

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Abstract

Lymphoid nodular hyperplasia (LNH) is characterized by diffuse hyperplasia of lymphoid follicles in the gastrointestinal tract, commonly observed in children with abdominal pain, food allergies, and autism. Clinical evaluation, colonoscopy, and anatomopathology are key tools in diagnosing LNH in the terminal ileum, notably associated with autism, inflammatory changes, and eosinophil influx. This study examines the clinical-endoscopic correlation with anatomopathological findings in autistic children and adolescents undergoing ileocolonoscopy to investigate nodosity in the terminal ileum. A total of 100 cases were retrospectively analyzed, including 50 patients with autism spectrum disorder (ASD) and 50 controls without ASD, all under 16 and subjected to ileocolonoscopy at HUAP over the last 20 years. There was a predominance of males in the ASD group ($\chi2 = 10.18$, $p < 0.001$), aged between three and 16 years. The control group showed a balanced gender distribution. No significant age difference was found between the groups. The incidence of LNH was significantly higher in ASD patients ($\chi2 = 36.99$, $p < 0.001$), with moderate LNH more frequent in ASD ($\chi2 = 37.44$, $p < 0.001$) and mild LNH more common in controls ($\chi2 = 39.60$, $p = 0.001$). Clinical complaints did not differ significantly between groups except for abdominal distension, which was more frequent in ASD ($\chi2 = 4.17$, $p = 0.041$), while blood in stool and diarrhea were more common in controls ($\chi2 = 16.88$, $p < 0.001$ and $\chi2 = 5.88$, $p = 0.015$, respectively). Endoscopic features of nodosity in the terminal ileum were reliably diagnosed through biopsy and confirmed by anatomopathological analysis. The study suggests a correlation between digestive and neurological symptoms, indicating a link between the Enteric Nervous System (ENS) and the Central Nervous System (CNS), supporting the "second brain" concept of the gut, and justifying gastrointestinal investigation in autistic patients with digestive symptoms.

Keywords: Ileocolonoscopy, Lymphoid nodular, Hyperplasia, Autism spectrum disorder, Children, Adolescents

1. Introduction

The lymphoid nodular hyperplasia (LNH) is a common finding in children with abdominal pain, food allergy and autism. Clinic, colonoscopy and anatomopathological study are tools for the diagnosis of LNH in the terminal ileum related to autism, inflammatory changes, and eosinophil influx.

The way autism is viewed has changed a lot since the classic description by Kanner in 1968 [1]. What was previously seen as an intractable disease related exclusively to the brain is now considered a dysfunction of the central nervous system (CNS) with disturbances in different organs and systems, such as the immune system and the digestive tract [2]. Gastrointestinal disorders are related to the immune system and the CNS, as they are common in patients with Autism Spectrum Disorder (ASD), being investigated by recommendations of the American Academy of Pediatrics in

the pathophysiology of ASD [3,4].

The interrelationship between the digestive tract and the CNS was first described by Columbia University, with lymphatic in the CNS, having the marrow as the access route [5]. Further study carried out at Johns Hopkins University, additionally demonstrated that irritation in the gastrointestinal system sends signals to the CNS, triggering mood changes and that the activity of the digestive system can affect cognition (thinking and memory skills) functioning as a second brain, making the enteric nervous system, a signaling pathway to the CNS, characterizing the connection of the intestines with the brain [6].

The changes in the digestive tract must be evaluated clinically, by functional anatomical changes and by endoscopy with biopsies looking for LNH, which characterizes the activation of Peyer's patches in response to immunological changes resulting from autism thus proving the interaction and proving the gut-brain interaction [7,8]. Functional gastrointestinal disorders are now classified within the Rome IV framework as disorders of gut–brain interaction [9].

The major prevalence of gastrointestinal symptoms in patients with autism compared to healthy controls has been extensively proved, with a potential secondary impact on children's behaviors. From a physio-pathological point of view, dysbiosis associated to impaired gastrointestinal permeability has been suggested as a potential trigger thus altering the normal nervous system functions. Dietary or pharmacological interventions are often utilized; however, results are still debated. In this uncertain context, the existence of a possible link between gastrointestinal inflammation and neuropsychiatric disorders needs to be clarified in the way to find the right dietetic and pharmacological tools to obtain the best effects on bowel and neurological inflammatory process and for this reason improvement of gastrointestinal and autistic symptoms [10].

Our study confirmed the high prevalence of gastrointestinal symptoms and pathological microscopic histological alterations in more than four hundred patients with autism that underwent upper and lower endoscopy with biopsies in our unit. A significant association between clinical manifestations and histological alterations has been identified with a significant improvement of clinical and neuropsychiatric symptoms after dietetic and pharmacological treatment of the intestinal inflammation. Further controlled prospective studies are required in order to confirm these correlations and permit to treat this category of patients at the very early onset of gastrointestinal symptoms.

2. Methods

2.1 Study design

This is a cross-sectional, retrospective, observational and analytical study of cases of nodosity in the terminal ileum approved by the institution's Research Ethics Committee (CEP) under the Certificate of Presentation for Ethical Assessment (CAAE) of Universidade Federal Fluminense. This research standard is defined in Resolution National Health Commission nº 466 of 2012 and in Operational Standard nº 001 of 2013. All patients' guardians signed the free and informed statement (Consent to Participate declaration). Epidemiological and/or clinical data were obtained from medical requisitions and/or records.

Endoscopy and pathological information were collected from the exam log book and from the database provided by the endoscopy and pathology services of Hospital Universitário Antonio Pedro (HUAP), Universidade Federal Fluminense with a diagnosis of lymphoid nodular hyperplasia confirmed by the results of the histopathological study. Exclusion criteria include cases that did not have material in sufficient quantity and quality for analysis, as well as cases with insufficient information in medical requests and/or medical records.

2.2 Study populations

The study population included one hundred retrospectively selected cases of children and adolescents (<16 years), divided in two groups of 50 patients with ASD and 50 without ASD (control group). Both, complaining of abdominal pain, gastroesophageal reflux, vomiting, diarrhea, blood in the stool, abdominal distension and others gastrointestinal symptoms. All the subjects were submitted to lower digestive endoscopy in the pediatric gastroenterology service under anesthesia, over the past 20 years. According to the service protocol, all patients were admitted to the to the pediatrics department at a Brazilian public hospital. HUAP Pediatric Infirmary the day before their colonoscopy and discharged the same day after the procedure.

2.3 Data collection

All reports of lower digestive endoscopies, including ileocolonoscopies, were reviewed. These reports contained the indications for the examination, endoscopic findings, microscopic annotations, and histopathological results of the biopsies.

The ileocecal valve was intubated and the terminal ileum visualized in all examinations. Biopsies were routinely taken from the terminal ileum, and from any other areas showing significant abnormalities. Each biopsy was properly labeled with the patient's name, medical record number, and biopsy site, preserved in formalin, and sent to the pathology service for the histopathological analysis, including a high-power field eosinophil count. Nodularity in the terminal ileum was diagnosed using established morphological criteria, including assessment for lymphoid nodules and hyperplasia, as well as identification of any other intestinal pathology observed during the procedure.

Descriptive statistics were calculated for the study variables. Means and standard deviations were used for numerical variables, while categorical variables were summarized as percentages.

During colonoscopy, images of ileal nodularity suggestive of hyperplasia were documented and biopsied for analysis at the

Pathology Department Biopsy processing followed standardized technical procedures. Nodularity in the terminal ileum was diagnosed using established morphological criteria, including the assessment of lymphoid nodules, lymphoid hyperplasia, and any other observed intestinal pathology.

2.4 Classification of nodosities according to the endoscopic aspects

Only nodular lesions greater than 2 mm in diameter were included in the study. Endoscopic severity was graded as mild, moderate, or severe (intense). Mild nodularity was defined as sparse lesions of 2 mm or more. Moderate nodularity consisted of clusters of lesions measuring 2mm and 5 mm. Severe (intense) nodularity was characterized by confluent lesions of 5 mm or more.

2.5 Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 20.0. Independent samples t-tests were used to compare mean ages (in months) between groups. Chi-square tests were used to compare categorical variables between the ASD and control groups. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Demographic characterization of study groups

The study included 50 patients with ASD: 41 (82%) males and 9 (18%) females. Ages ranged from 3 years and 1 month to 16 years, with a mean age of 6 years and 5 months. The control group (n=50) consisted of 26 (52%) males and 24 (48%) females, with ages ranging from 2 years and 6 months to 16 years, and a mean age of 6 years and 7 months. A significantly higher proportion of males was observed in the ASD group compared to the control group ($\chi^2 = 10.18$, $p = 0.001$). No significant difference in mean age was found between the groups ($t = 0.28$, $p = 0.779$).

3.2 Clinical Complaints Distribution

The most common gastrointestinal complaints in the ASD group were abdominal pain (60%), followed by abdominal distension (50%), constipation (40%), gastroesophageal reflux (24%), diarrhea (18%), dyspepsia (16%), vomiting (12%), and hematochezia (12%). In the control group, the most frequent gastrointestinal complaint was hematochezia (70%), followed by abdominal pain (50%), diarrhea (40%), abdominal distension (30%), dyspepsia (24%), gastroesophageal reflux (20%), constipation (10%), and vomiting (10%).

No significant differences were found between groups for abdominal pain, gastroesophageal reflux, vomiting, constipation, or dyspepsia (all $p > 0.05$). However, a significantly higher frequency of abdominal distension was observed in the ASD group ($\chi^2 = 4.17$, $p = 0.041$). Further analysis revealed significantly higher frequencies of hematochezia ($\chi^2 = 16.88$, $p < 0.001$) and diarrhea ($\chi^2 = 5.88$, $p = 0.015$) in the control group compared to the ASD group.

3.3 Evaluation of colonoscopy exams

Endoscopic findings showed that all patients in the ASD group exhibited hyperplasia, while the control group showed a significantly lower frequency ($\chi^2 = 36.99$, $p < 0.001$). A significant difference was also observed in the type of lymphoid nodular hyperplasia (LNH) between groups. The ASD group showed a significantly higher frequency of moderate LNH ($\chi^2 = 37.44$, $p < 0.001$), while the control group had a significantly higher frequency of mild LNH ($\chi^2 = 39.60$, $p < 0.001$).

In all cases with severe lymphoid nodular hyperplasia (LNH), in both the ASD and control groups (one case in the control group), immunohistochemistry was performed to rule out lymphoma or other pathologies. Eosinophil counts were performed where indicated; all counts were below 20 eosinophils per high-power field, ruling out ileitis or eosinophilic colitis. In these cases, a clinical diagnosis of food allergy was confirmed. No parasites were detected in any of the 100 cases.

4. Results and Discussion

Global ASD incidence has significantly increased in the last two years. The CDC estimates a prevalence of one ASD case per 54 births; however, this is an average, and reported prevalence varies considerably across studies, with some reporting substantially higher numbers [11].

Diagnostic criteria for ASD, as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association, are primarily clinical, based on observations of the child, parental interviews, and the use of specific assessment tools [12,13]. Diagnostic considerations include deficits in social interaction, preference for objects over people, pronoun reversal, hyperactivity, frustration intolerance, echolalia (repetition of words or phrases), repetitive behaviors, insensitivity to pain, gaze aversion, uneven intellectual abilities, and stereotyped behaviors [14,15].

Routine gastrointestinal evaluations have revealed a higher prevalence of gastrointestinal symptoms, histological abnormalities, and digestive dysfunction in children with autism spectrum disorder (ASD) compared to controls [16] .These gastrointestinal symptoms may overlap with core ASD symptoms through mechanisms involving the gut-brain axis, influencing behavior and cognition. Other pathophysiological mechanisms linking ASD and the gastrointestinal tract involve intestinal inflammation (with or without autoimmunity), and food allergies mediated by IgE or CD4/CD8 pathways [17]. Dysregulation of the gut microbiome may also contribute by affecting intestinal permeability, mucosal immunity, motility, and sensitivity [16].

Complaints related to gastrointestinal tract in patients with ASD are frequent in the world literature, but there is no comparative division between the changes related to colonoscopy findings regarding the following characteristics:

a) gender. In our study, we observed a sex ratio of 4.6:1 males to females among children and adolescents with Autism Spectrum Disorder (ASD). This finding is consistent with previous

literature. For example, a study conducted in Venezuela reported a male predominance, with 71.1% of their ASD cohort being male, resulting in a male-to-female ratio of 2.6:1 among patients undergoing endoscopic investigation for digestive symptoms [18]. In 2016, our research group published findings that indicated a male-to-female ratio of 3.65:1 [19]. Similarly, in 2018, Christensen et al. documented a higher prevalence of males, with ratios ranging from 3.5 to 4: [20,21].

Recent data from the Centers for Disease Control and Prevention (CDC) in the United States, released in 2020, further substantiate these findings, indicating a male predominance with a male-to-female ratio of 4.3:1 among children with ASD [9]. These statistics confirm the ongoing gender disparity observed in ASD prevalence, reinforcing trends noted in the existing literature. Our findings regarding gender distribution align with these documented patterns;

b) age group. In our study, the median age for colonoscopy to investigate digestive symptoms was 6 years old. This finding contrasts with data from a multicenter study conducted in Rio de Janeiro, Caracas, and Washington, which reported a mean age of 1.98 years for the investigation of digestive symptoms using both upper and lower gastrointestinal endoscopy [18]. However, more recent data from the Brazilian experience indicate an average age of 6 years and 2 months for similar procedures [19].

While literature data on this topic exhibit variability, it is essential to consider the context in Brazil. The extended time between the onset of digestive complaints, obtaining medical care, and subsequent referrals for colonoscopy and/or upper endoscopy can be attributed to the limited number of specialized services available for these examinations, which do not adequately meet the increasing demand. This disparity underscores the challenges faced by patients and health care providers in the timely diagnosis and treatment of digestive issues in children and adolescents with Autism Spectrum Disorder;

c) digestive complaints. The digestive complaints observed in our patients with ASD that prompted colonoscopy primarily included abdominal pain (60%), abdominal distension (50%), constipation (40%), diarrhea (18%), and hematochezia (12%). Notably, the prevalence of abdominal pain in our cohort aligns with existing literature, which reports a rate of 58% of patients experiencing such digestive complaints.

Investigating the underlying causes of these digestive symptoms in autistic patients is critically important. Digestive issues may arise from intestinal inflammatory processes, as evidenced by the presence of lymphoid nodular hyperplasia in the terminal ileum [22]. These gastrointestinal symptoms not only contribute to the overall clinical picture in ASD but may also impact the central nervous system through the gut-brain axis, potentially exacerbating ASD symptoms [3, 16, 23-26].

Numerous studies in the literature highlight the significant correlation between gastrointestinal function and the clinical manifestations of ASD [16,27, 28]. This relationship underscores the necessity for comprehensive evaluations of digestive health in this population to enhance both diagnostic and therapeutic strategies.

The gastrointestinal tract alterations are highly prevalent in children with ASD. Common digestive complaints include chronic constipation, which may lead to abdominal distension, as well as diarrhea accompanied by abdominal pain. Unfortunately, these symptoms are often overlooked, as children with ASD may struggle to articulate their discomfort. Consequently, their gastrointestinal issues may be overshadowed by more pronounced behavioral changes that are perceived as more severe. This highlights the need for increased awareness and thorough evaluation of digestive health in children with ASD to ensure that gastrointestinal symptoms are appropriately recognized and addressed;

d) presence of lymphoid follicles and aggregates, characterizing lymphoid nodular hyperplasia. In our study, LNH) in the terminal ileum was identified in 100% of children and adolescents with ASD (Figures 1-3). In contrast, the incidence of LNH in the control group was 46%. Additionally, data from a multicenter study reported the presence of lymphoid nodular hyperplasia in the ileum in patients with ASD, with lymphoid nodules observed in 88% of cases [18]. These findings underscore the significant prevalence of LNH in the gastrointestinal tract of individuals with ASD, suggesting a potential link between these histological changes and the gastrointestinal symptoms frequently reported in this population.

Regarding endoscopic findings, Wakefield et al. (2005) reported the presence of HNL in 83.3% of children exhibiting mucosal abnormalities. These abnormalities included areas of absorptive epithelium, underlying connective tissue, muscle layer, and mucosa. Histopathological examination revealed specific mucosal changes such as increased granulocytes, loss of vascular pattern, and irregular erythema indicative of nonspecific colitis (Figure 4) [29].

In our study, the prevalence of lymphoid nodular hyperplasia was significantly higher in the ileum of children with ASD, with findings of 90% (129/144) in the ASD group compared to 30% (8/27) in the control group. Moreover, the severity of ileal LNH was markedly greater in children with ASD. We observed moderate to severe LNH in 68% of the ASD cases (98 out of 144), as opposed to only 15% (4 out of 27) in the control group [30].

Figure 1: Biopsy of nodosities in the terminal ileum performed by endoscopic visualization

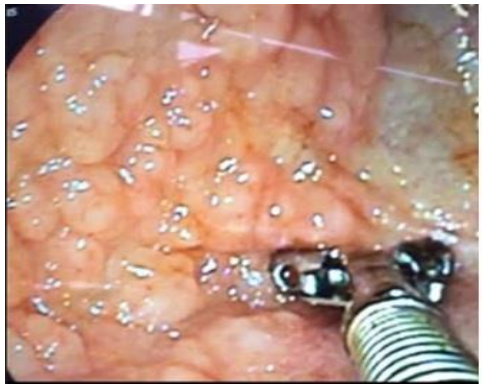

Figure 2: Biopsy of nodosities in the terminal ileum performed by colonoscopy

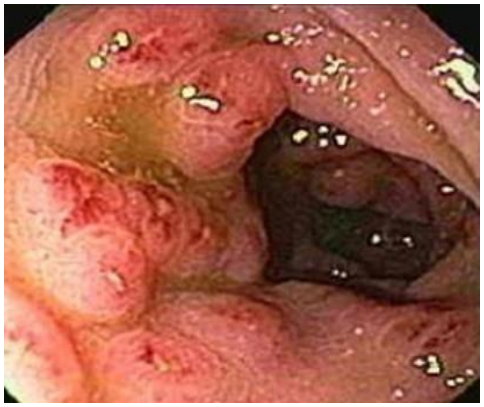

Figure 3: LNH in the terminal ileum with erosions, observed by ileocolonoscopy

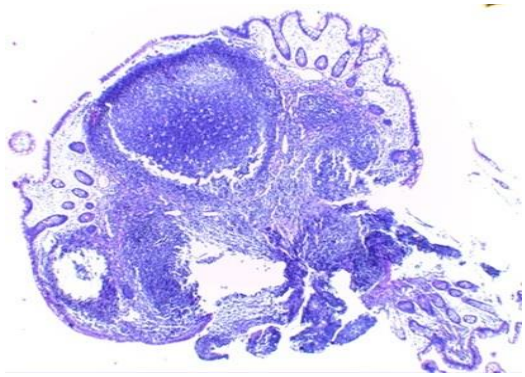

Figure 4: Microscopic examination of polypoid lymphoid nodular hyperplasia, stained by the HE method, 4x magnification.

These findings suggest that LNH in the terminal ileum is a characteristic pathological feature in children with ASD who exhibit gastrointestinal symptoms associated with mucosal inflammation. Our data bolster the hypothesis that HNL represents a significant pathological finding in this population, highlighting its potential relevance to the gastrointestinal issues frequently observed in children with ASD.

There are few publications in the literature on the description of the endoscopic characteristics of the terminal ileum. The endoscopic aspects of this segment, when affected by several diseases, range from an ileum with a normal endoscopic appearance to cases in which the macroscopic examination demonstrates specific characteristics of these diseases [29]. The need for ileum biopsies is confirmed, even in patients with normal ileoscopy, for histopathological study. Indications for upper digestive endoscopy and colonoscopy in children with ASD are well described in various sources in the medical literature, but the histopathological study with the classification remains lacking in updating [3,7,30].

There is a limited number of publications in the literature that specifically describe the endoscopic characteristics of the terminal ileum. The endoscopic presentation of this segment can vary widely, ranging from a normal ileal appearance to macroscopic findings that exhibit specific characteristics associated with various gastrointestinal diseases [31].This variability emphasizes the importance of obtaining ileal biopsies, even in cases where ileoscopy appears normal, to facilitate a comprehensive histopathological evaluation.

While the indications for upper gastrointestinal endoscopy and colonoscopy in children with ASD are well documented in medical literature, there is a notable deficiency in updated histopathological classifications and studies concerning these findings. This gap highlights the pressing need for more in-depth research to enhance our understanding of the endoscopic and histopathological characteristics of the terminal ileum in pediatric patients with ASD. Such research could contribute significantly to improved diagnostic and therapeutic strategies for managing gastrointestinal symptoms in this population [32].

5. Conclusions

Our findings indicating a high incidence of LNH in the terminal ileum of patients with ASD, along with the observed predominance of LNH in males over females, are consistent with existing literature.

The notable prevalence of abdominal pain and distension, in conjunction with the presence of nodular formations in the terminal ileum, characteristic of LNH in all cases of ASD, underscores the importance of conducting both endoscopic and histopathological investigations in patients exhibiting digestive symptoms.

Additionally, the endoscopic characteristics of these nodular formations, which represent the macroscopic manifestation of LNH, can be increasingly identified through ileal biopsies. These findings can be further validated through detailed anatomopathological examination. This approach not only enhances our understanding of the gastrointestinal complications associated with ASD but also supports the need for comprehensive assessment strategies in managing the digestive health of this population.

In children and adolescents from the control group who exhibited digestive symptoms and lymphoid nodular hyperplasia (LNH), it was noted that many of these symptoms were attributable to food allergies.

The correlation between clinical, endoscopic, and anatomopathological findings suggests a potential association between the enteric nervous system (ENS) and the central nervous system (CNS). Inflammatory processes in the ENS may propagate inflammation to the CNS, highlighting the concept of the intestine functioning as a "second brain," as recognized in the global literature. This relationship emphasizes the significance of understanding the gut-brain axis, particularly in the context of gastrointestinal manifestations in pediatric patients, and may inform both diagnostic and therapeutic approaches.

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