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Original Article

Prevalence and Significance of Mesenteric Lymphadenopathy in Children with Functional Abdominal Pain Disorder - Not Otherwise Specified: A Novel Ultrasonography based Retrospective Case Control Study

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ABSTRACT

Background and Aim: Functional abdominal pain disorder-not otherwise specified is one of the sub-types of functional gastrointestinal disorders, as per the ROME IV criteria. The aim of the present study was to determine the prevalence and assess the significance of mesenteric lymphadenopathy in children with this disorder.
Materials and Methods: This was a retrospective study conducted at a multi-speciality hospital including children, aged 2 to 16 years, with functional abdominal pain disorder – not otherwise specified, who underwent abdominal ultrasonography. The control group consisted of children who underwent abdominal ultrasonography for reasons other than abdominal pain. Pearson's chi-square test was used to compare the significance of the presence of mesenteric lymphadenopathy in the study groups. A p-value of <0.05 was considered as statistically significant.
Results: A total of 200 children were included in the study, with 100 children meeting the ROME IV criteria for functional abdominal pain disorder– not otherwise specified and an equal number of age- and sex-matched controls. On ultrasonography, when the size cut-off for significant mesenteric lymphnodes was 5 mm or more and 8 mm or more in maximum short-axis diameter (MSAD), the difference between the case and control groups was statistically significant. However, when the cut off was 10 mm or more, the association was not significant.
Conclusion: There is a statistically significant association between the presence of mesenteric lymphadenopathy in children and functional abdominal pain disorder – not otherwise specified as compared to the control group.

KEYWORDS: Mesenteric lymphadenopathy, Paediatric, Functional abdominal pain, Ultrasonography, ROME criteria.

Introduction

Functional gastrointestinal disorders (FGIDs), now renamed as disorders of the gut-brain axis, have been classified in detail according to the ROME IV criteria. Functional abdominal pain disorder, one of the subtypes, includes further subtypes such as abdominal pain related to irritable bowel syndrome [IBS], functional dyspepsia, abdominal migraine and functional abdominal pain-not otherwise specified (NOS). Detailed criteria have been laid down for such patients, which, for functional abdominal pain- NOS include recurrent abdominal pain with atleast four episodes per month for two consecutive months.[1]

The presence of mesenteric lymphnodes on ultrasonography is a commonly detected incidental finding. The presence of mesenteric lymphnodes may not always warrant any further investigation, however, there are a large number of diseases that may cause mesenteric lymphadenopathy including malignancies, inflammatory disorders and infective etiologies.[2]

The presence and the significance of mesenteric lymphadenopathy in children with functional abdominal pain disorders has not been studied previously. The aim of the present study was to determine the prevalence of mesenteric lymphadenopathy in children diagnosed with functional abdominal pain disorder– NOS as per ROME IV criteria and assess its significance. The size criteria for enlarged mesenteric lymphnodes most commonly used in radiology, is the presence of three or more lymphnodes with a size of 5 mm or more in maximum short-axis diameter (MSAD).[3,4] However, some studies have reported that this criterion yields a higher false-positive rate.[4-6] The secondary objective of our study was to assess the frequency of enlarged mesenteric lymphnodes using varying size criteria and analyze the differences.

Materials and Methods

This was a retrospective study conducted at a multi-speciality hospital from June 2019 to August 2020. Institutional ethical committee approval was obtained for this study and the need to obtain informed consent was waived off. Consecutive children, aged 2-16 years, reporting to the Radiology department with clinical features of chronic/recurrent functional abdominal pain and meeting the ROME IV criteria for functional abdominal pain disorder– NOS were included in the study. The children were referred after evaluation by a paediatrician with nine years of experience and by a physician with six years of experience. Consecutive children reporting for abdominal ultrasonography for reasons other than abdominal pain were included in the control group. Children with known organic causes for mesenteric lymphadenopathy, such as, pancreatitis, abdominal tuberculosis, appendicitis, malignancy etc., and children with haematological tests suggestive of infection, such as raised leukocyte count (> 11000/mm^3), raised C-reactive protein levels, or raised erythrocyte sedimentation rate, were excluded from cases as well as the controls.

Clinical data and physical examination findings of the study subjects were obtained from the institution's database. The abdominal ultrasonography images were reviewed retrospectively by a single radiologist with four years of experience, from the archives of the radiology department. USG of the abdomen was performed with GE LOGIQ3 PRO machine by using both 6-10 MHz linear probe and 4-6 MHz curvilinear probe.The clinical details and ultrasonography (USG) findings including presence of enlarged mesenteric lymph nodes, their number, size of the largest lymphnode, location of the lymphnodes and any other findings were recorded on a proforma. Each lymph node was measured in maximum short-axis diameter (MSAD) as shown in **Figure 1**. Mesenteric lymph nodes were considered significant when at least three or more were present with a size greater than or equal to 5 mm (MSAD).

Statistical analysis was performed using STATA 11.2 (College Station TX USA) and MS Excel (2018). Age distribution was expressed as mean ± standard deviation (SD). Gender distribution was expressed as frequency and percentage. The prevalence of mesenteric lymphadenopathy was expressed as frequency and percentage. Student's t-test was used to compare the two study groups with respect to age. Pearson's chi-square test was used to compare the two study groups with respect to gender. Pearson's chi-square test was used to measure the association of gender with the presence of mesenteric lymphadenopathy and to assess the significance of

presence of mesenteric lymphadenopathy in the study groups. A p- value of <0.05 was considered as statistically significant.

Results

A total of 200 children were included in the study, with 100 children meeting the ROME IV criteria for functional abdominal pain disorder– NOS, and an equal number of age and sex-matched controls. The controls were primarily referred for ultrasonography follow-up due to renal/ureteric calculus or hydronephrosis, urinary tract infection or lower urinary tract symptoms, gastritis or with recent trauma to the abdomen.

The mean age of the children in the case group was 9.35 ± 3.76 years, ranging from 2-16 years, while in the control group, it was 10.02 ± 3.88 years. A student's t-test was used to compare the two study groups with respect to age, with no significant difference, t(99) = -1.24 (p= 0.108). Of the cases, 53% children were males and 47% were females. In the control group, 54% were males and 46% were females. A chi-square test of independence showed that there was no significant difference between gender among the two groups with a p-value of 0.887. The findings are summarised in **Table 1**.

On USG, when the size cut-off for significant mesenteric lymphnodes was taken as 5 mm or more (MSAD), mesenteric lymphadenopathy was detected in 42% (n=42) of the cases and in 12 % (n=12) of the controls. The difference in the presence of mesenteric lymphadenopathy between the two groups was analysed using Pearson's chi-square test, and the results were statistically significant (p <0.0001).

When the size cut-off was taken as 8 mm or more (MSAD) and 10 mm or more (MSAD), mesenteric lymphadenopathy was detected in 25% (n=25) of cases, 9% (n=9) of controls and 5% (n=5) of cases, 2% (n=2) of controls, respectively. The difference between the two groups was again analysed using Pearson's chi-square test, and the results were statistically significant (p = 0.003), when cut-off was 8 mm or more (MSAD). However, when the cut-off was 10 mm or more (MSAD), the association was not significant (p- = 0.248). The frequency of mesenteric lymphadenopathy with varying size criteria is summarised in **Figure 2**.

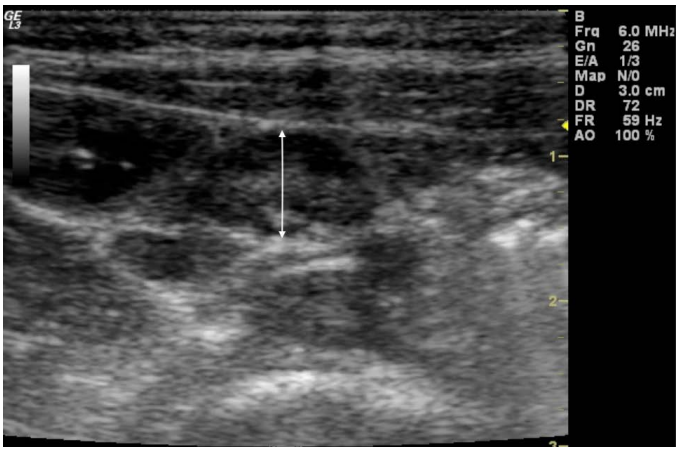

Figure 1: Ultrasound abdomen in axial plane in a subject demonstrating the technique of measuring the size of lymphnode in Maximum short axis diameter (white double sided arrow).

Table 1: Summary of findings in cases and controls (n=100 each).

	Cases (n)	Controls (n)
Males	53	54
Females	47	46
Mean age (years)	9.35 ± 3.76	10.02 ± 3.88
Mean size of mesenteric lymph nodes (mm)	4.14 ± 3.84	1.32 ± 2.79
Mean number of mesenteric lymph nodes	2.82 ± 3.10	0.72± 1.60

When the cut-off was 5 mm or more (MSAD), 42% cases had significant mesenteric lymphnodes, and the mean number of lymphnodes noted was 5.9 ± 2.51 with a mean size of 7.88 ± 2.05 mm (MSAD). On the other hand, of the 12% controls with significant mesenteric lymphnodes, the mean number of lymphnodes noted was 4.33 ± 1.61 with a mean size of 8 ± 1.59 mm (MSAD). Mesenteric lymphnodes were absent in 38% of the cases and in 79% of the controls (**Table 2**).

Of the cases with significant mesenteric lymphnodes, when cut-off was 5 mm or more (MSAD), males comprised 52.4% (n=22) while females comprised 47.6% (n=20). In the control group with significant mesenteric lymphnodes, males and females comprised 50% (n=6) each. Gender was not found to be

significantly associated with the presence of mesenteric lymphadenopathy with a p-value of 0.776.

Out of 42% cases with significant mesenteric lymphnodes, 100% (n=42) cases had mesenteric lymphnodes which were oval in shape. In 95% cases (n=40) with significant mesenteric lymphnodes, fatty hilum was maintained, however, in 5% (n=2) lymph nodes, fatty hilum was lost. Of the controls with mesenteric lymphadenopathy, all cases had oval lymphnodes with maintained fatty hilum. Of the cases and controls with significant mesenteric lymphnodes, there were no other foci of enlarged lymphnodes, apart from mesenteric lymphnodes.

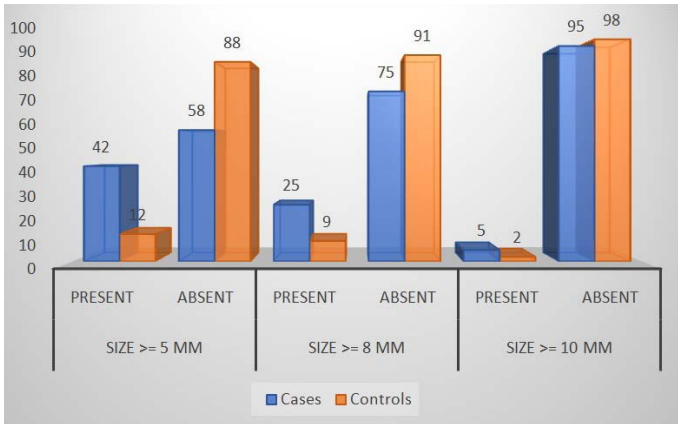

Figure 2: Column chart displaying Frequency of Mesenteric lymphnodes as per varying size criteria.

Table 2: Number of cases and controls with absent mesenteric lymphnodes.

Cases (n=100)	38
Controls (n=100)	79

Table 3: Diagnostic criteria for Functional abdominal pain – Not otherwise specified.
All criteria should be fulfilled for at least four times per month for two consecutive months.

1. Episodic or continuous abdominal pain which does not occur solely during physiologic events.
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine.
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition.

Discussion

FGIDs, also known as disorders of gut-brain interaction, are a group of disorders characterised by the presence of gastro-intestinal symptoms related to motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut micro-organisms, altered central nervous system (CNS) processing or any combination of the above features. There are 33 adult and 20 paediatric FGIDs described in Rome IV criteria.[7]

Among these, functional abdominal pain (FAP) disorder is a commonly encountered subtype in clinical practice that includes abdominal pain related to irritable bowel syndrome (IBS), functional dyspepsia (FD), abdominal migraine and for those children not meeting criteria for IBS, functional dyspepsia, or abdominal migraine, functional abdominal pain- not otherwise specified (NOS). The diagnostic criteria for functional abdominal pain– NOS are summarised in **Table 3**.[1,7]

The term chronic functional abdominal pain is used interchangeably with recurrent abdominal pain and chronic abdominal pain in clinical practice. Chronic abdominal pain is prevalent in children, with rates reaching upto 10%.[8,9] The reported pooled prevalence for functional abdominal pain disorders ranges widely, ranging from 1.6% to 41.2%, with most studies based in Europe, Asia (excluding the Indian subcontinent), Middle East, North and South America.[10] There is currently a lack of prevalence data from the Indian subcontinent.

Abdominal ultrasonography is one of the most commonly performed diagnostic tests in children presenting with pain abdomen to look for an underlying organic pathology. Mesenteric lymphadenopathy in the paediatric age group is commonly associated with several pathological conditions including appendicitis, diverticulitis, cholecystitis, pancreatitis, intussusception[11]; infective processes including those with *Yersinia enterocolitica*, tuberculosis, *Tropheryma whippelii*, HIV; malignancies including lymphoma[2] and connective tissue diseases including systemic lupus erythematosus, systemic sclerosis and rheumatoid arthritis.[12-14] Mesenteric lymphnodes are also commonly noted as an incidental finding on ultrasound in otherwise asymptomatic children.[15,16]

There is currently no universally standardised

definition of enlarged mesenteric lymph nodes, with the most commonly used criteria being the presence of three or more lymph nodes with maximum short-axis diameter (MSAD) of 5 mm or more.[3,4] However, the size of mesenteric lymph nodes is only one of the factors which determines their significance. Other factors, such as appearance, presence of necrosis, and shape also play a role. Even with these characteristics, the size cut-off for mesenteric lymphnodes in asymptomatic children remains debatable. Limited data is available on the evaluation of mesenteric lymph nodes in asymptomatic children, with one study reporting enlarged mesenteric lymphnodes in 28.3-29.1% of asymptomatic children.[3] Additionally, there are very few existing studies on the prevalence and significance of mesenteric lymphadenopathy on ultrasonography in children with chronic abdominal pain.

In our study group, when a cut-off of 5mm or more (MSAD) for enlarged mesenteric lymph nodes was used, 42% of the children had mesenteric lymphadenopathy as compared to 25% when the cut-off was 8 mm or more (MSAD) and 5% when the cut-off was 10 mm or more (MSAD). Some studies have recommended using a higher size criteria for mesenteric lymphadenopathy in children to reduce false positive rate.[4-6] Further prospective studies are needed to validate whether a more standardised definition with a redefined size criteria is necessary, as it could save unnecessary workup of the patients, while also conserving time and resources. The shape and presence of fatty hilum of mesenteric lymph nodes was also noted in our study, and these findings did not show any significant deviation from results obtained in previous studies.

There are currently no studies in the scientific literature on the prevalence or significance of mesenteric lymphadenopathy in children with FAP– NOS. In our study, we found a significant association between the presence of mesenteric lymphadenopathy in children with FAP– NOS and those without abdominal pain/other organic pathology causing mesenteric lymphadenopathy. Whether the presence of mesenteric lymphadenopathy in such patients precludes inclusion in the functional abdominal pain disorder group is a question that needs to be contemplated upon. However, the implication of this finding in such cases should be investigated further through prospective studies with larger datasets and appropriate follow-up of patients. Our study was limited by its retrospective nature.

In our study, gender was not found to be significantly associated with mesenteric lymphadenopathy. There have been varying results reported previously in the literature, with some studies reporting mesenteric lymphadenopathy to be more common in females[17] while others reporting it to be more common in males.[18] The sizes of the enlarged lymphnodes noted in our study are similar to the sizes of enlarged mesenteric lymphnodes as noted in other studies[19] of mesenteric lymphnodes in children with chronic abdominal pain.

Another limitation in our study was the lack of use of cross-sectional imaging to confirm the findings of USG, which is an operator dependent modality.

Conclusion

Our single-centre retrospective study demonstrates a significant association between the presence of mesenteric lymphadenopathy and functional abdominal pain disorder – NOS in children with functional abdominal pain dosorder - NOS, when compared to children without abdominal pain or other organic pathology. Additionally, the diagnosis of mesenteric lymphadenopathy in FAP– NOS being significantly associated with the varying size criteria for the mesenteric lymphnode sizes demands a re-evaluation of the radiologically accepted size criteria for mesenteric lymphadenopathy in children.

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