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Medical conditions mimicking the acute surgical abdomen in children

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Background We present our experience with children landing up in our pediatric surgery emergency with potentially confounding medical conditions that evade diagnosis. It is imperative to apply sound clinical judgement in the evaluation of these patients so that an unnecessary laparotomy can be avoided but, at the same time, a lifesaving intervention is not denied.

Patients and methods This is a retrospective descriptive analysis pertaining to all patients who were admitted in our department from 1 January 2014 to 31 July 2017. A total of 27 867 patients presented to our out-patient department of these, 3034 were admitted to our ward. A total of 1531 surgeries were performed, of which 288 were for various abdominal surgical conditions. A total of 16 patients, representing 0.5 % of the admissions, were eventually found to have an acute abdomen secondary to a medical cause.

Results Out of the above 16 patients, 10 had to undergo exploratory laparotomy (62.5%). Eight patients of the 10 operated had a negative laparotomy. Two of the 10 operated were found to have a surgically correctable cause, one with ovarian torsion and one with severe colonic edema secondary to Kawasaki's disease causing intestinal obstruction.

Conclusion Although eight patients with negative laparotomy result constitute only 0.5% of all the surgeries and 2.7% of all the laparotomies, it still forms the bulk (i.e. 8/16=50%) of the patients with underlying medical cause of the surgical abdomen. There were two deaths, representing a mortality of 12.5% (2/16=12.5%), with one in the operated group and one in the nonoperated group. This is why we want to stress the importance of caution and sound clinical judgement in evaluating this subset of patients. Ann Pediatr Surg 14:165–170 © 2018 Annals of Pediatric Surgery.

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Introduction

A significant number of patients presenting with acute abdominal pain experience nonsurgical conditions. Failure by the examining physician to recognize important clinical clues may lead to unnecessary and often harmful surgical intervention. At the same time, it should be kept in mind that there may be instances where surgery is clearly indicated. So it is imperative to apply sound clinical judgement in the evaluation of these patients so that an unnecessary laparotomy can be avoided but, at the same time, a lifesaving intervention is not denied. The differential diagnosis of the acute abdomen has been well documented in medical literature [1–3]. This discussion will be limited to those clinical signposts which should alert the clinician to a possible medical etiology while encountering a pediatric patient with clinical features mimicking an acute surgical abdomen. This study aims to emphasize the timely recognition of these potentially fatal but treatable medical issues in children whose clinical picture is confused with an acute abdomen leading to a delay in possibly lifesaving medical intervention.

Patients and methods

This is a retrospective analysis of all patients who were admitted in the Department of Pediatric Surgery, Jawaharlal Nehru Medical College, Aligarh Muslim University, from 1 January 2014 to 31 July 2017 (3 years

and 7 months). During this time period, 27 867 patients presented to our out-patient department for various conditions. Of these, 3034 patients required admission. A total of 1531 surgeries were performed, of which 288 were for various surgical conditions of the abdomen. A total of 16 children, representing 0.5% of the admissions, were eventually found to have an acute abdomen secondary to a medical cause.

Results

Although 16 children were admitted for acute abdomen that was eventually found to be secondary to a medical cause, 10 of these 16 underwent an exploratory laparotomy (10/16 = 62.5%). Of the 10 operated patients, nine had a negative laparotomy result, and two patients had a clearly identifiable surgically correctable cause, that is, one with ovarian torsion and one with severe colonic edema secondary to Kawasaki disease causing intestinal obstruction. Although eight patients with negative laparotomy result constitute only 0.5% of all the surgeries and 2.7% of all the laparotomies, it still forms the bulk (i.e. 8/16 = 50%) of the patients with underlying medical cause of the surgical abdomen. There were two deaths, representing a mortality of 12.5% (2/16 = 12.5%), with one in the operated group and one in the nonoperated group. This is why we want to stress the importance of caution and sound clinical

judgement in evaluating this subset of patients. We present our experience with such patients and highlight the important clinical clues that can help us make a good clinical decision.

Familial metabolic

(1) Acute intermittent porphyria (Patient no. 1 in Table 1).

Endocrine disorders

- (1) Diabetic ketoacidosis (Patient no. 2 and 3 in Table 1).
- (2) Hypothyroidism (Van Wyk-Grumbach syndrome) (Patient no. 4 in Table 1).
- (3) Hyperparathyroidism (Patient no. 5 in Table 1).
- (4) Congenital adrenal hyperplasia (CAH) (Patient no. 6 in Table 1).

Inflammatory (noninfectious)

- (1) Celiac disease (Patient no. 7 in Table 1).
- (2) Nonspecific colitis (Patient no. 8 in Table 1).

Inflammatory (infectious)

- (1) Neutrophilic typhlitis (Patient no. 9 in Table 1).
- (2) Spontaneous bacterial peritonitis (nephrotic syndrome) (Patient no. 10 in Table 1).
- (3) Congenital cytomegalovirus hepatitis (Patient no. 11 in Table 1).
- (4) Congenital listerial infection (Patient no. 12 in Table 1).
- (5) Dengue (Patient no. 13 in Table 1).

Vasculitis/collagen hypersensitivity

- (1) Kawasaki disease (Patient no. 14 in Table 1).
- (2) Henoch-Schonlein purpura (Patient no. 15 in Table 1).

Drug/toxin

(1) Lead poisoning (Patient no. 16 in Table 1).

Discussion

Diagnostic telltale symptoms in history Present history

Although a complete description of the patient's abdominal symptoms should be obtained, this alone is seldom helpful in identifying a medical cause. Attention should be paid to events surrounding the onset of pain, including possible relationship to physical exertion, trauma, sexual abuse, battered baby, self-medication, or onset and pattern of menarche. Factors affecting the pain, such as relation to respiration or position, should be noted, as should extraabdominal (shoulder or testicular) radiation. Sudden severe pain will have an abrupt and noticeable beginning as in perforation of hollow viscus, passage of renal stone, etc., and some of the examples in this category may require immediate surgery. However, an abdominal vascular accident, that is, mesenteric occlusion or leaking aneurysm, may appear with catastrophic onset without much localizing signs,

though it is rare in children [1,2]. Similarly location of pain, radiation, aggravating or alleviating factors, and associated symptoms may all provide some valuable clues. Pain is associated with vomiting in most cases, but the onset, persistence, and severity of vomiting are much greater with intestinal obstruction than any primary inflammatory disorder. An important point to remember here is that pain nearly always precedes vomiting with surgical problems; however, the opposite sequence is commonly observed with nonspecific abdominal disorders (e.g. gastroenteritis) [3–5].

Even greater attention should be paid to systemic features accompanying the abdominal complaints. Unusually high fever, chills, or profuse diarrhea should alert the physician to an underlying medical condition. Active joint symptoms occurring with an acute abdomen, or skin eruptions appearing at the onset of symptoms, should cast immediate doubt on a surgical diagnosis. Other clinical features that should arouse suspicion of a nonsurgical condition include unexplained dyspnea, pleuritic chest pain, urethral or vaginal discharge, bloody or unusually dark urine, and concurrent neurological symptoms [3–5].

Past history

A history of recurring and intermittent episodes of acute abdominal distress suggests a medical diagnosis. This is especially true if there is a family history of such occurrences. A patient with a history of recurrent joint, pleuritic, or unusual dermatologic complaints should also be approached with this clinical suspicion in mind. An often overlooked clue is a past history of passage of renal calculi or gravel. A detailed inquiry into possible foreign body ingestion or aspiration and picophagia must not be neglected. A number of acute abdominal manifestations are caused by drug abuse, especially lead toxicity, resulting from a myriad of prevalent environmental exposures. Finally, the physician should be alert to a history of recent travel to geographical areas endemic for illnesses with gastrointestinal manifestations.

An exhaustive antenatal history, including maternal drug intake, maternal systemic illnesses, radiation exposure, toxoplasma other infections rubella cytomegalovirus herpes simplex and other maternal infections is clearly warranted.

Immunization history is important as mesenteric lymphadenopathy and intussusception have been linked to certain vaccines, particularly the rotavirus vaccine [6].

A detailed family history can provide important clinical clues as certain medical conditions masquerading the surgical abdomen run in families like thalassemias and idiopathic thrombocytopenic purpura [7].

Diagnostic telltale signs in examination

While examining the patient with an acute abdomen for a possible medical condition, careful search should be made for purpuric or petechial rash; nodular lesions or other skin eruptions; tender, swollen, or inflamed joints; and conjunctivitis. When the patient's distress is severe and out of proportion compared with abdominal symptoms, the physician should suspect an underlying medical cause. Always auscultate the heart for any murmur or additional

Table 1 Specific medical conditions accompanied by acute abdomen : our experience

Patient no.	Age (years)	Sex	Relevant clinical features accompanying abdominal pain	Investigations	Treatment received	Surgery E/L (exploratory laparotomy)	Outcome	Final diagnosis
1	5	Male	Fever, rash, shock, and dark urine	TLC 70 000 with no immature cells (leukemoid reaction)	Medical management	No	Improved, on follow-up	Acute intermittent porphyria
2	13	Male	Fever, intractable nonbilious vomiting, and polyuria despite dehydration	Raised urinary ketones, elevated plasma and urinary glucose, severe metabolic acidosis, and Widal positive result	Management of systemic infection and parenteral regular insulin	No	Improved on follow-up	Insulin-dependent diabetes mellitus with diabetic ketoacidosis (precipitated by septicemia owing to enteric fever)
3	9	Female	Fever, intractable nonbilious vomiting, and polyuria despite dehydration	Raised urinary ketones, elevated plasma and urinary glucose level, and severe metabolic acidosis	ů .	No	Expired	Insulin-dependent diabetes mellitus with diabetic ketoacidosis
ı	12	Female	Abdominal distention, short stature, precocious puberty, obesity, and dysmorphic features (Cretinism)	Abdominal mass (ovarian cyst on USG); TSH was highly elevated but detected after surgery; FSH and LH were normal	Operated	E/L with excision of right ovarian cyst with torsion	Improved after surgery and thyroxine (general well-being and decreasing trend of serum TSH), on follow up, intermittent pain due to cysts in left ovary also	Hypothyroidism (Van Wyk-Grumbach syndrome)
5	11	Male	Polyuria and intermittent colicky abdominal pain	Bilateral nephrolithiasis with CKD (on USG), elevated ionized serum calcium and phosphate with increased abnormally radiopaque bones on skeletal radiographies	Medical management, steroids, and diuretics	No	Improved with medical management	Primary hyperparathyroism
6	7 days	Male	Full-term normal delivery and ambiguous genitalia	Nonbilious vomiting, poor feeding, raised CRP, hypothermia, hyperkalemia, hyponatremia, metabolic acidosis, and could not afford karyotyping and hormonal work up	Responded to fluid resuscitation and steroids	No	Improved with medical management	Congenital adrenal hyperplasia
,	6	Male	Alternating diarrhea and constipation since 1 year, fever, absolute abdominal distension, and constipation for 4 days; child also had short stature and iron-deficiency anemia	Multiple air fluid levels on AXR, tissue transglutaminase was raised 30 folds, upper GI endoscopy with duodenal biopsy revealed villous atrophy suggestive of celiac disease	Once celiac disease was confirmed after detailed evaluation, the patient was put on gluten-free diet once the acute attack subsided with conservative management after negative laparotomy finding	Patient had to be operated in emergency for features of acute intestinal obstruction but no mechanical cause of obstruction could be seen	Improved with gluten-free diet	Celiac disease
3	9	Male	Presented with only mild abdominal pain but had a 1-day history of rectal bleeding which was altered but red in color	USG was suggestive of large bowel edema (ileocecal intussusceptions); CT abdomen revealed diffuse large bowel wall edema; rectosigmoidoscopy could not be done as patient had developed anal stenosis (operated somewhere in neonatal period for low anorectal malformation)	Patient received multiple blood transfusions, and ultimately decision was taken to explore the abdomen as the bleeding did not stop even after 48 h and tachycardia was slowly increasing	Entire bowel was healthy on exploration		Nonspecific colitis
)	10	Male	Fever and vomiting	Neutrophilia; USG of abdomen showed right iliac fossa probe tenderness with moderate ascitic fluid; Typhi Dot IgM did not reveal substantial titers to suggest a diagnosis of enteric fever		Operated with a diagnosis of acute appendicitis in mind. No appendicitis or appendicolith was found, terminal ileum and cecum were found to be edematous. Appendix was, however, excised and sent for HPE	Improved	Neutrophilic typhlitis
10	13	Male	Fever and generalized body swelling for 1 week, and diffuse abdominal tenderness and distension	Urine for albumin 4+ and no red blood cells. USG was suggestive of ascites and sluggish bowel peristalsis, ascitic tap showed polymorphocytosis, ascitic fluid culture showed <i>E. coli</i> , and renal biopsy	IV fluids and antibiotics, and steroids were started once acute episode was controlled	No	Improved with antibiotics initially and steroids in the long term	Spontaneous bacterial peritonitis secondary to nephrotic syndrome

was suggestive of minimal change disease

Table 1 (continued)

Patient no.	Age (years)	Sex	Relevant clinical features accompanying abdominal pain	Investigations	Treatment received	Surgery E/L (exploratory laparotomy)	Outcome	Final diagnosis
11	2 months	Male	Jaundice, abdominal distention, and constipation	AXR-AF levels, leucopenia, thrombocytopenia, and IgM and IgG reactive for CMV on TORCH serology	Treated on the lines of congenital CMV infection with sepsis after negative laparotomy and positive CMV serology findings	Operated but no mechanical cause of intestinal obstruction could be demonstrated	Expired within 14 days of admission	Congenital CMV hepatitis
12	15 days	Female	3-day baby with poor feeding and profuse watery diarrhea along with streaks of fresh blood, hypothermia, and neck retraction, and the mother had a history of diarrhea of 10-day duration in her last trimester which resolved with some overthe-counter drugs	Sepsis screen of the neonate was suggestive of systemic infection. CSF examination revealed neutrophilia and elevated proteins for age indicative of meningitis. Blood culture revealed growth of Listeria monocytogenes sensitive to ampicillin and amikacin, and USG suggestive of ileocolic intussusception	Treated with systemic antibiotics as per blood culture results	Operated but no obstruction or intussusception found	Improved	Congenital Listerial infection transmitted vertically
13	7	Male	High-grade fever, severe abdominal pain and constipation for 5 days, shock, and also history of polyarthralgia	USG showed pericholecystic fluid, ascites, and bilateral pleural effusion; air fluid levels on AXR; leucopenia with normal platelet counts and clumping without any hemoparasites; NS1 antigen for dengue along with reactive IgM; and platelet counts showed a decreasing trend over the course of admission	Treated with appropriate IV fluids and antibiotics, platelet transfusions, and other symptomatic therapy	Operated for intestinal obstruction but no mechanical cause of obstruction was found	Improved	Dengue
14	3	Male	Fever for 5 days; vomiting, abdominal pain and distension for 2 days; and conjunctivitis, skin desquamation following abdominal symptoms	Air fluid levels on AXR, and USG suggestive of ileocolic intussusception	Abdominal symptoms were relieved after ileostomy but the skin rash began to appear and worsen postoperatively; cardiac echocardiography revealed transient coronary ectasia; and a diagnosis of Kawasaki disease was made. Patient was started on aspirin and began to improve slowly	allowing ileal contents to be easily milked across, ileostomy was made with multiple biopsies from enlarged	6 months later after distal cologram confirmed normal passage of bowel contents across distal bowel; follow-up	Kawasaki disease
15	4	Male	Fever for 5 days; vomiting for 2 days; moderate diffuse abdominal pain, few erythematous rashes noted 2 days later over lower limbs and buttocks, and the rashes were palpable and nonblanchable, with no similar past history	Normal blood counts, USG was suspicious for ileocolic intussusception	Following recovery from surgery, symptomatic treatment in the form of IV fluid, antibiotics, and analgesia was given; no steroids were required	Operated but no intussusceptions found, few enlarged mesenteric lymph	Improved	Henoch-Schonlein purpura
16	7	Female	Chronic abdominal pain, progressive pallor, picophagia, now presented with 1-day history of sudden-onset abdominal pain, vomiting and constipation with blood in stools	Leukocytosis; AXR showed multiple air fluid levels, serum, microcytosis, tear drop cells, serum ferritin and serum iron levels were low, raised serum and urine lead levels	Once chronic lead toxicity with acute exacerbation was diagnosed, chelation therapy was started	Operated but no significant abnormality found	Improved	Lead poisoning

AXR, abdominal x-ray; CKD, chronic kidney disease; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; CSF, cerebrospinal fluid; FSH, follicle-stimulating hormone; GI, gastrointestinal tract; HPE, histopathological examination; IgM, immunoglobulin M; IV, intravenous; LH, luteinizing hormone; TLC, total leukocyte count; TORCH, toxoplasma other infections rubella cytomegalovirus herpes simplex; TSH, thyroid-stimulating hormone; USG, ultrasonography.

heart sounds as well as look for other signs of sinister cardiac disease. Splinter hemorrhages, Osler's nodes, Janeway lesions, and Roth spots are the peripheral stigmata of endocarditis one should look for. Other findings suggestive of a medical condition include extensive lymphadenopathy, pallor with or without hepatospleenomegaly, and gross neurological deficits. If the diagnosis is not clear after the initial evaluation, repeated physical examination by the same physician often is useful. A detailed history and examination may reveal a previously indolent clinical feature presenting now with sudden acute symptoms, like previously small lymph nodes now turning acutely inflamed. This may reveal diseases like tuberculosis, AIDS, and other chronic diseases presenting for the first time in a neonate or a child.

Investigations/diagnostic imaging

A plain radiography of the abdomen in supine and erect position and/or lateral decubitus films may be ordered. Plain radiographs of chest may be obtained in most cases. Ultrasonography of the abdomen may be very helpful in acute abdominal conditions related to hepatobiliary tract, solid visceral tumor, and pelvic pathologies. Recent advances in computed tomography (CT) helped include thinner slices, faster scan time, and higher spatial resolution allowing for more accurate evaluation. Spiral CT eliminates respiratory motion artifacts and decreases the required amount of intravenous contrast. The newest generation spiral CT scanner has multiple detectors and can scan the entire abdomen and pelvis in very short time. CT scan in patients with acute abdominal pain has considerable diagnostic and therapeutic effect [8].

Important inferences/conclusions

A simple clinical examination or investigation can usually help us differentiate a medical cause from a surgical cause in patients with an acute abdomen, but it is worth mentioning that sometimes even a relatively straightforward diagnosis may seem confusing and be missed. Listed below are some helpful points for a diagnostician confronting the problem of a child with acute abdominal pain:

- (1) Acute disease of the chest may closely mimic primary diseases of abdomen. Pneumonia, empyema, congenital cardiac diseases, and congestive heart failure should always be considered. Most patients of emetogenic rupture of the esophagus have abdominal and not chest pain.
- (2) Quite often the exact etiology cannot be decided on initial examination, that is, appendicitis may present initially with just vomiting or mild periumbilical pain which can be confusing, whereas the characteristic right iliac fossa tenderness that helps clinch the diagnosis appears much later, and some cases of intestinal obstruction may resolve whereas some go on to worsen and require laparotomy. So it is prudent to observe the patient closely for 12–24 h, reassess frequently, and if the patient's condition deteriorates, previous judgment should be suspended and exploration carried out.
- (3) Acute pancreatitis is a diagnosis of exclusion (except exceptionally high serum amylase and lipase). Even

- after the diagnosis of presumed pancreatitis, if the patient's abdominal signs worsen, exploratory laparotomy should be done without any fear of deleterious effects on the course of pancreatitis.
- (4) Acute pyelonephritis occasionally produces abdominal pain out of proportion to dysuria and can sometimes mimic acute appendicitis, cholecystitis or intestinal obstruction. Urinalysis and urine specific gravity can reveal this relatively straightforward.
- (5) Though peptic ulcer disease is uncommon in children, it can present with atypical signs and symptoms. We had one such case where a 7-year-old male child presented with acute abdomen but no free gas under diaphragm. On exploration, he had a perforated duodenal ulcer which was repaired. On the contrary, over the course of the present study, we have operated two neonates who had grossly detectable free intraperitoneal gas on abdominal x-ray, but no bowel perforation could be found anywhere on exploration. Both neonates underwent peritoneal lavage and improved postoperatively.
- (6) Some diseases involving small-sized and mediumsized vessels may produce acute abdomen-like picture. There have been case reports of such patients with colonic or small bowel edema presenting with clinical features of intestinal obstruction making an exploratory laparotomy mandatory [9]. In our case (Table 1, case number 14), a patient presented with clinical features of acute obstruction and air fluid levels on erect abdominal radiography. On exploration, the cause of obstruction was found to be because of diffuse large bowel edema, especially at the ileocecal junction. Histopathology of bowel specimen confirmed it to be secondary to small and medium vessel vasculitis. Clinically, the appearance of rash, fever, coronary ectasia on echocardiography and nonpurulent conjunctivitis in the postoperative period made the diagnosis of Kawasaki disease evident. Upon retrospective analysis of the case and relevant literature [9], it was clear that Kawasaki disease can rarely present with abdominal complaints, and it is difficult to diagnose these cases because the gastrointestinal manifestations precede and mask the characteristic rash and the mucocutaneous and cardiac manifestations of the disease.
- (7) One of the most important, though rare, causes of acute abdominal pain is acute porphyria. Because of its wide range of unspecific symptoms and signs, acute porphyria is rarely considered as a differential diagnosis of acute abdomen. Some patients have undergone unnecessary surgery. In a study from Taiwan, 32 patients with porphyria visited emergency room in 13 years, 10 were diagnosed first time in the emergency department itself [10]. All these patients presented with abdominal pain but without fever, dermatological symptoms, or neurological symptoms. On an average most of them attended emergency room repeatedly (at least four times) before being diagnosed properly and were treated with different kind of analgesics including narcotic analgesia. This study leads one to believe that when

- a patient attends emergency room repeatedly with severe abdominal pain, acute porphyria should be taken into consideration.
- (8) Diabetic ketoacidosis is another cause of abdominal pain in accident and emergency department. The chief presenting complaints are nonspecific, and patient may present with acute abdominal pain, vomiting, and reduced consciousness.
- (9) Hypothyroidism is another rare cause of acute abdomen [11]. It is known to cause bilateral ovarian cysts which can present as abdominal lump. In our case, a 12-year-old female patient presented with abdominal distention and exquisite tenderness with urine specific gravity suggestive of bilateral ovarian masses with and suspicious of torsion on the right side. On exploration, bilateral ovarian cysts were found with gangrenous right ovary owing to torsion of ovarian cyst. Unilateral salpingo-oophorectomy was done on the right side. Patient improved postoperatively. But the child continued to look puffy, myxedematous, and irritable. On evaluation, she was found to have normal β-human chorionic gonadotropin, lactate dehydrogenase, and CA125. The serum thyroid-stimulating hormone was highly elevated suggestive of hypothyroidism. She was started on oral thyroxine therapy and put on follow up. Within 6 weeks, her serum thyroid-stimulating hormone decreased to normal range, and within 3 months of treatment, her myxedematous features normalized. She began to show improvement in overall well-being, became more sociable, and demonstrated good weight gain. Hence, in a child with bilateral ovarian cysts, always look for features of hypothyroidism.
- (10) Certain infections can also present as acute abdominal pain. In a study from China, 14 patients with dengue hemorrhagic fever/dengue shock syndrome (out of 382 patients) presented as having acute abdomen. Patients who underwent invasive procedures had prolonged time in the hospital (11 vs. 7 days, P = 0.015) [12].
- (11) Worm infestation is an endemic disease in tropical region. Ascariasis is a helminthic infection very commonly seen in this region especially in communities of low socioeconomic status. Rarely it may present as acute abdomen where most of the modern and sophisticated means of investigative techniques (ultrasound, CT scan, radionuclide study or MRI/MRA) would fail. In a case report from New Jersey, USA, after the unsuccessful attempt to diagnose a case of acute abdomen with all the possible investigative measures, a small bowel series was suggested. The diagnosis of ascariasis leading to obstruction was confirmed and was treated medically successfully [13]. Such diagnosis is more important and should be legitimately thought among immigrant communities in developed countries. Other infections,

- that is, strongyloides, amebiasis, and giardiasis, may also present as acute abdomen. These diagnoses should be kept in mind, especially when the patient gives an associated history of diarrhea [14]. Eosinophilic jejunitis/eosinophilic gastroenteritis, though a rare disorder, may be a cause of acute abdomen [15,16].
- (12) Many patients presenting in emergency room have a symptom model (a friend or relative with a similar complaint), multiple other complaints with somatization, a history of physical abuse at the hand of parent or relative, and sign of guilt or penance may be carefully sought. However, the presence of these features does not exclude the possibility of an organic source of the pain. Their management should always be planned in the background of their previous history, and more reliance on signs rather than symptoms should be given. Consultation with psychiatrist should benefit these patients.

Conflicts of interest

There are no conflicts of interest.

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