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REVIEW

Treating acid reflux disease in patients with Down syndrome: pharmacological and physiological approaches

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Abstract: Down syndrome (DS) is often accompanied by gastrointestinal disease, occurring mainly in early infancy and frequently requiring therapy. Among motility disorders, the most frequent is gastroesophageal reflux disease (GERD), which may often be misdiagnosed because of its atypical manifestations. Early diagnosis of esophageal functional disorders is essential to prevent respiratory problems, growth retardation in children, weight loss in adults, and to establish the correct type of surgery if needed. Furthermore, the involvement of the enteric nervous system in the pathophysiology of GERD in DS is not yet completely understood but seems supported by much evidence. In fact DS is often associated with motor disorders and this evidence must be considered in the choice of therapy: in particular all options available to improve motility seem to be effective in these patients. The effectiveness of therapy is strictly related to the rate of mental impairment, so that modulating therapy is essential, especially in view of the severity of the neurological status.

Keywords: gastro-esophageal reflux disease, chromosome 21, Down syndrome

Introduction

Down syndrome (DS) is often accompanied by gastrointestinal disease, mainly occurring in early infancy and frequently requiring therapy. Gastrointestinal diseases and feeding difficulties represent a frequent cause of hospital admission (19%) in DS.[1] The most common in DS are congenital gastrointestinal diseases, requiring surgery, in particular esophageal atresia, duodenal obstructions, ano-rectal malformations (ARM), and Hirschsprung's disease (HSCR). Among motility disorders, the most frequent is gastroesophageal reflux disease (GERD).[2] Nevertheless, few data on its diagnosis and management in DS patients have been published.

Gastrointestinal diseases in DS

The association between gastrointestinal disease and DS is well known: as many as 77% of DS newborns have or will develop gastrointestinal problems.[3] These conditions can be classified into mechanical or functional disorders and may be primary or secondary.

In particular, the literature reports about a 300-fold increased risk for annular pancreas and duodenal atresia and about a 100-fold increased risk for HSCR, esophageal, anal, and small bowel atresia.[4] The most common congenital structural defects which result in a mechanical neonatal intestinal obstruction include tracheo-esophageal fistula, duodenal stenosis/atresia, pyloric stenosis, anular pancreas, and ARM.[5,6]

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Functional gastrointestinal obstruction, on the other hand, is most frequently due to achalasia, GERD, HSCR, and constipation.[3] The involvement of the enteric nervous system (ENS) in these associations is not yet completely understood but it seems evident by the fact that some of the most common gastrointestinal symptoms reported by DS patients are functional ones, such as dysphagia, vomiting, and heartburn as well as other esophageal dysmotility symptoms.[7]

As regards the physiopathological basis of the association between DS and gastrointestinal disease, it is generally accepted that the pathological changes in the nervous system of patients with DS probably underlie the physiological and neurological features of the associated anomalies of the gastrointestinal tract. Developmental defects within the ENS are also likely to be the cause of significant functional disorders. There is some evidence that the decrease in normal development of the nervous system in DS may be due either to the basis of decreased neuronal migration or to a failure of the normal dendritic development within nervous system.[8] In addition, in DS patients there may also be an ongoing loss of neural cells in the ENS, similar to that occurring in the brain.[9]

GERD and DS

GERD remains one of the most frequent causes of esophageal symptomatology in DS but runs the risk of being underestimated.[10] Previous studies report a 43% occurrence of serious complications arising from GERD in DS patients. In addition, oropharingeal aspiration may be associated with pneumonia and aspiration syndromes in dysphagic neurological patients, such as DS.[11]

According to the Montreal Definition and Classification of GERD,[12] GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. The same definition is actually adopted in pediatric age, in which some peculiar characteristics are evident: symptoms vary by age and are troublesome when they have an adverse effect on the well-being of children; reflux symptoms that are not troublesome should not be diagnosed as GERD; bilious vomiting should not be diagnosed as GERD; pediatric patients with central nervous system impairment have an increased risk of GERD; typical reflux symptoms are not sufficient to diagnose GERD in children who lack the cognitive ability to report symptoms; atypical and/or respiratory symptoms may be the unique manifestations of GERD in neurologically impaired children; esophageal complications of GERD are esophagitis, hemorrhage, stricture, Barrett's esophagus and, rarely, adenocarcinoma.[13]

GERD is widely known to have a high incidence in neurologically impaired children,[14] who often show atypical symptoms of this condition, however, a high index of suspicion is required to discover GERD and its complications.[15–17]

No single investigation can definitely diagnose GERD. Therefore the choice is based on the clinical context. A 24-hour pH-metry remains the gold standard in diagnosing GERD. Radiography and pulmonary scintiscan may be useful in identifying the presence of aspiration. The barium contrast upper gastrointestinal study is also helpful in identifying the presence of hiatus hernia, strictures, swallowing disturbances, the motility of esophagus and stomach and to rule out anatomical anomalies. Gastroscopy is helpful in detecting reflux esophagitis and biopsies are taken to assess its severity. Esophageal manometry is useful to detect motor esophageal disorders (especially in neurologically impaired patients) and the competence of the lower esophageal sphincter.[18]

In addition, DS seems to be associated with primary and secondary esophageal motility disorders, for unknown causes. Thus, patients with either frequent esophageal symptoms and/or atypical manifestations such as food rejection, frequent vomiting, coughing, and failure to thrive should be evaluated for esophageal function. Early diagnosis of esophageal functional disorders is essential to prevent respiratory problems, growth retardation in children, weight loss in adults, and to establish the correct type of surgery if needed.[7]

Treatment of GERD in DS

The rationale in the treatment of GERD is focused on decreasing the symptoms, the frequency and duration of reflux events, healing the injured mucosa and preventing complications.[19]

The treatment of GERD in DS is based on the protocols of treatment of GERD in the normal pediatric population. Two fundamental aspects must be kept in mind. First, DS is often associated with motor disorders and this evidence has to be considered in the choice of therapy: in particular all the options available to improve motility seem to be effective in these patients. Second, the effectiveness of therapy is strictly related to the rate of mental impairment, so that modulating therapy is mandatory especially in view of the severity of the neurological status.

GERD therapy consists of a combination of the following options:

Conservative treatment

Frequent small feeds of thickened formula or food minimize gastric distension and reduce GERD. Elevation of the upper body at 60°, maintained for 24 hours a day, aids esophageal clearance and effectively reduces symptoms of reflux in two-thirds of infants while awake and during sleep.[20]

Medical treatment

If conservative measures do not improve symptoms, medical therapy is recommended. Pharmacological therapies are aimed at the various steps in the pathophysiology of GERD. These include the use of antacids, hydrogen ion-blocking drugs, proton pump inhibitors (PPI) and prokinetics agents.[21] Antacids work by neutralizing gastric acids. Prokinetics work by increasing esophageal peristalsis, increasing the lower esophageal sphincter pressure, and enhancing gastric emptying, even if their effectiveness has not yet been universally accepted.[22] H2-blockers and PPIs work by decreasing the secretion of gastric acids.[23] The advent of PPI in particular has strongly influenced the treatment of GERD, especially in neurologically impaired children.[24]

Surgical treatment

Surgery for GERD is one of the most common major operations in children. The primary indication in performing an anti-reflux operation is the control of intractable or life-threatening GERD: surgical treatment is usually performed after unsuccessful trials of prolonged medical therapy, in patients with severe complications of reflux, such as aspiration, failure to thrive or esophagitis with strictures or Barrett's esophagus.[25] The major objectives of operative repair are to increase the high pressure zone in the lower esophagus by accentuating the angle of His and increasing the length of the abdominal esophagus. The most widely used fundoplication procedure was originally described by Nissen and Rossetti, and consists of the intra-abdominal positioning of the distal esophagus, hiatus hernia repair, and a 360° fundal wrap.[26] The technique has been developed and we now have the option of partial fundoplication wrapping techniques, which refer to any wrap less than 360°. Laparoscopic fundoplication can be also performed safely and with equivalent results in neurologically impaired children.[27] Anti-reflux surgery is characterized by high grade morbidity, however, so that a correct indication for surgery is essential. Problems with anti-reflux surgery occur especially in children with neurological impairment.[28] In this context, esophageal dysmotility has been shown to complicate the postoperative course following surgical corrective procedures.[29] Alternatives to fundoplication, especially in children with neurodevelopmental disorders, include insertion of a gastrojejunal tube or jejunostomy.[30] These procedures are less invasive but do not treat GERD, thus necessitating long-term medical treatment, and require continuous jejunal feeding. An alternative operation has recently been proposed for children with severe neurological conditions and consists of total esophagogastric disconnection.[31] The procedure aims to prevent GERD while allowing at the same time bolus feeds via the gastrostomy. Nevertheless, the technique has a very high complication, failure and mortality rate.[32] So that it must be limited in very few carefully selected patients.[14]

Conclusion

GERD is frequent in DS, and its severity is strictly related to the severity of neurological impairment. Therapy has to be chosen according to the underlying causes of GERD and to the severity of its complications.

Disclosure

The authors declare no conflicts of interest.

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