Gastroenterology and Hepatology From Bed to Bench

EDITORIAL

Gastrointestinal disorders in Down syndrome

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John Langdon Down, an English physician, first described Down syndrome in 1866 but it was not until 1959 that Dr Jerome Lejeune from Paris showed an association with chromosome 21. Down syndrome is the most common chromosomal abnormality occurring in humans and is caused by the presence of all or part of a third copy of chromosome 21. Recent exciting research has shown that trisomy silencing may offer new treatment possibilities (1). Down syndrome presents with typical physical features particularly of the face, and varying degrees of hypotonia and intellectual disability (2). Most children are born to mothers under the age of 35 years but the incidence of Down syndrome increases with maternal age. The condition is encountered worldwide with an incidence of 1 in 650-1000 live births (3). It is associated with a number of conditions including heart and spinal defects, endocrine disorders particularly a high frequency of Hashimoto's thyroiditis and to a lesser extent Graves disease (4), and respiratory and eye problems. In recent years with more enlightened attitudes to disability, the development of surgical techniques to correct defects and improved general care, the survival of infants and life expectancy for Down syndrome have risen dramatically. About sixty years ago in Birmingham, England only 45% of infants survived the first year and only 40% were alive at 5 years (5). Fifty years later in a study also from England, 78% of infants with Down syndrome and a congenital heart defect survived for 1 year and 96% of those without anomalies (6) . An Australian report showed that life expectancy has risen dramatically through the years and by the end of 2002 the median was 60 years (3, 7). It is likely that this increase in survival will continue. With proper management particularly in dedicated clinics (8) those with Down syndrome can go on to lead fulfilled, productive lives with some moving into higher education and employment. This brief review is concerned only with gastrointestinal associations.

Children and adults with Down syndrome will exhibit gastrointestinal symptoms from time to time such as vomiting, diarrhoea, constipation, abdominal pain and discomfort that resolve with minimal or no intervention much as in others. However, they may develop structural and functional disorders of the gastrointestinal tract and related structures more commonly. Estimates of how commonly these occur have often been derived from selected populations such as those attending special clinics for Down syndrome when about 10% of children and teenagers will be affected (9). Over three quarters of neonates attending clinics may have gastrointestinal problems including feeding difficulties or developmental anomalies (10). However, using a registry of congenital malformations covering an area of France for the years 1979 to 1996 when 398 new cases of Down syndrome were identified, 6% were found to have intestinal atresias (11). Medical records for all live born children with Down syndrome born between 1973 and 1980 in northern Sweden were analysed and 7.3% were found to have gastrointestinal malformations (12).

Structural problems may affect the gastrointestinal tract from the mouth to the anus but many conditions will occur in Down syndrome with similar frequency to other children. However, oesophageal, duodenal, and small bowel atresia or stenosis, annular pancreas causing small bowel obstruction, imperforate anus and Hirschsprung disease may be more common than in the general population (13).

Obstruction in the gastrointestinal tract may be detected before birth by imaging techniques and so allow for planned intervention early after birth. If diagnosis is not made pre-birth no bowel actions, vomiting and a distressed baby indicating abdominal pain will suggest bowel obstruction and the need for urgent surgical intervention. Imperforate anus either total or partial may also occur and require surgery. Hirschsprung disease affects about 2% of those with Down syndrome and manifests as a distended abdomen, poor weight gain, vomiting and constipation. Short segment disease can be difficult to diagnose.

Gastro-oesophageal reflux should be suspected in a child who appears uncomfortable during or after feeding. Down children are prone to this because they spend less time in the sitting position and muscle tone in the lower oesophageal sphincter may be reduced thus allowing reflux. It is possible that developmental abnormalities in the enteric nervous system also have a role to play here and also perhaps in other functional disturbances (14, 15). Too liquid feeds may contribute to the problem. Aspiration pneumonia may be a presenting feature of reflux and early evaluation of oesophageal function should be undertaken in children with chronic cough or recurrent pneumonia. Reflux can easily be misdiagnosed as asthma and so remain untreated.

Adults with Down syndrome are also prone to a wide range of gastrointestinal problems including reflux, obesity, constipation and diarrhoea. Infection with *H.pylori* appears to be more common but the implications are not clear (16). Non-immunity to hepatitis A and B can be high and indicates the need for immunisation (16).

Coeliac disease (CD) that is associated with Down syndrome can present at any age. Symptoms in children and adults are protean and include growth failure, malaise, vomiting, abdominal distension, diarrhoea and constipation. Unexplained anaemia, iron and calcium deficiency, point to the diagnosis.

Screening studies have shown a prevalence of CD in Down syndrome of about 5% and because of this strong association some have advocated screening all subjects using human tissue transglutaminase (htTG) and/or endomysial antibodies (EMA) antibodies (17). Screening should begin at the age of 3 years and be repeated every 2-3 years since a single negative test will not rule out CD for life (18). By establishing the HLA status of individuals and excluding those from the programme who do not carry HLA-DQ2 or HLA-DQ8, markers that are necessary for CD to develop, the number of screening tests can be reduced by 60% (18, 19) . Screening has the potential to diagnose all cases irrespective of symptoms. Whether this is an effective approach is still not clear because those with minimal or no symptoms may not be persuaded to undergo a small bowel biopsy to confirm the diagnosis or adhere to a gluten free diet.

A second approach to make the diagnosis of CD in Down syndrome is a case-finding strategy that targets only those with clinical features consistent with the diagnosis e.g. symptoms, unexplained anaemia, hypertransaminasemia, family history. If the diagnosis is suspected, CD specific antibodies should be looked for and if positive a small bowel biopsy advised to confirm the diagnosis. Antibody negative CD occurs and may be due to a false negative test or IgA deficiency in which case IgG based tests are available. If the diagnosis of CD is strongly suspected a duodenal biopsy should be advised even in the absence of antibodies.

Some patients with high levels of tTG (>10 times the upper limit of normal) may not require biopsy to establish the diagnosis of CD because this

accompanies diagnostic histology. This has already been acknowledged in paediatric guidelines (20) which also require endomyseal antibody positivity and the presence of the markers HLA-DQ2 or DQ8 to establish the diagnosis. It is likely these criteria will soon be applied in adult practice. Not having to biopsy some with Down syndrome would be advantageous.

If CD is diagnosed a gluten free diet should be offered and the opportunity to see a dietician experienced in managing the diet. Carers and where possible patients should be involved at all stages of the diagnostic and management process.

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