

## **GASTROINTESTINAL DISORDERS IN PEOPLE WITH DOWN'S SYNDROME: AN OVERVIEW**

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This presentation is on gastrointestinal (GI) disorders in people with Down's syndrome (DS). I will be looking at both children and adults and a lot of problems crossover between the two. I am going to classify the GI conditions that have an increased incidence in Down's syndrome, describe the pattern of symptoms that they present and the management plan for each, and then explain the background to you. I also want to look specifically at screening in this group, particularly for coeliac disease, and my feeling, looking at the literature, is that we should reject routine screening for coeliac disease in children with DS. However, for research purposes there may be a value in knowing more about this area. That is my opinion, so see what you think at the end of this presentation.

The GI associations of DS can be roughly grouped into three problem areas:

- Embryological and structural
  - Anorectal (imperforate or stenosis)
  - Duodenal or jejunal (stenosis or atresia)
  - Hirschprung disease
- Motility and co-ordination
  - Feeding difficulties
  - Gastro-oesophageal reflux (GOR)
  - Toddler diarrhoea
  - Constipation
  - Gall stones
- Autoimmune
  - Coeliac disease

- Hepatitis.

### **Embryological and structural**

There is an incidence of about 10% of anorectal and duodenal atresia or stenosis and around 2% incidence of Hirschprung disease in children with DS. These figures are much higher than in other children so it is very important for us to be aware of these conditions and to be active about diagnosis so that we can recognise them early and thereby achieve better treatment.

The duodenal and jejunal atresias and stenoses tend to present with bile-stained vomiting which means obstruction, until proved otherwise. Other presenting symptoms are a lot of regurgitation, diarrhoea, or abdominal pain. These children usually do extremely well after straightforward surgery.

Any baby born with Down's syndrome should be examined for an imperforate anus in the delivery room to absolutely exclude it. Midwives and doctors also need to be very active in observing when meconium is first passed. Late passage at more than 24 hours in a child with DS I think warrants consideration of Hirschprung disease. Later presenting features are constipation in the first few months, or constipation with failure to thrive (FTT) in the first year.

### *Hirschprung disease*

Hirschprung disease is due to failure of migration of the ganglion cells to the submucosal and myenteric plexuses of the large bowel. The ganglia seem to be working their way down, but don't get right to the bottom and so you've an area where there are no ganglia present and that segment, right at the bottom, will remain contracted. That segment can be any length from very short to much longer and it will remain contracted. A very important point is that this area has a risk of stasis, infection, enterocolitis and perforation. One of the reasons to pick up this condition early is that the children who develop Hirschprung disease are at risk of enterocolitis early on, getting a perforation and serious morbidity or death. Although we talk about Hirschprung disease presenting early,

50% will present after one month of age in the children with DS. So, even if you see a child at home you can't just say, 'Oh well, they don't have Hirschprung disease'; they're still at risk.

Figure 1 shows a barium enema; the rectum is constricted, and the sigmoid colon dilated. The challenge is always to remember the fact that it is the 'normal' diameter bowel which is actually abnormal and constricted, and that the rather dilated bowel has got the ganglia in it. In biopsies we can show little pockets where there should be ganglia and they are absent, and we can show little pockets where you can see the nerve cells and you can go further and use specialist stains to show the actual ganglia.

The diagnosis of Hirschprung disease involves a suction rectal biopsy which can be done on the ward as it doesn't need any anaesthetic. It is a very simple straightforward test to do, however, it has to be done in conjunction with the laboratory as they will need the samples to be fresh and they would usually do frozen sections and other tests which need to be prearranged. If the diagnosis of Hirschprung disease is confirmed the most typical management has two-stages – a defunctioning colostomy to remove the cause of obstruction, followed by resection of the abnormal aganglionic segment and a pull through of the normal bowel to the anus. One very important point that applies to all children with Hirschprung disease is that even after the operation these children have a risk of enterocolitis. It's not often clear absolutely why, but it seems that after the operation there's still some likelihood of a moderate obstruction and they actually get an illness a bit like obstructive enterocolitis. So, if a child with Hirschprung disease presents with blood in its stool remember that they may have enterocolitis and these children are at risk as they get older of getting septicaemia, perforation and serious morbidity.

Looking at theses and studies in Hirschprung disease, one of the bigger series to have been published comes from Dublin. Of 135 children with Hirschprung disease, 17 had Down's syndrome as well.<sup>1</sup> Of the nine children less than 1 month old, five presented with obstruction, two with enterocolitis and two with perforation. In keeping with what I said earlier, nearly 50% (8) of the children with DS were over 1 month old at

presentation, all with constipation and 5 with enterocolitis as well. In those presenting early, a significant number had enterocolitis or a perforation and these really are things that can be avoided by making midwives more aware of the need to watch for meconium or signs of enterocolitis, particularly in babies with DS. The outcome in Hirschprung disease is, to be perfectly honest, quite tricky anyway, but the outcome in Down's syndrome is a bit less satisfactory. A follow-up study when the children were about 8 years old showed that two had stomas (where they had tried a pull through and it hadn't worked) and there were two deaths, one was cardiac-related and the other was from enterocolitis.

**Audience:** I've been involved in toilet training in children with special needs and when you are doing this with a child with Hirschprung disease, even taking into account they have Down's syndrome, they are one of the most difficult to toilet train. By the time I get involved it is very complex and they've had it for years and I don't want to give the parents false hopes.

I think that's a very important observation and I think the prognosis of continence in children with Down's syndrome is poor. The question is whether there is anything we can do or any ways in which we could be helping parents to see the problem coming and avoid it?

**Audience:** I wonder if it would have made any difference if they had been diagnosed earlier? I was just thinking that for us is it something that we should be asking when we visit newborn babies.

### **Motility**

When considering the children with motility problems the various things we look at are feeding difficulties, gastro-oesophageal reflux, toddler diarrhoea, constipation and gall stones.

### *Constipation*

Constipation is an area that seems very common in children with DS. The child can be thriving and growing very well, but have a major problem with constipation. Obviously it's worthwhile, particularly in Down's syndrome, excluding hypothyroidism, but it does seem that maybe mobility is one of the issues. Certainly, we speak to mothers and they often say that when the baby started to move around, the constipation problem eased.

One of the challenges I find with mothers of constipated babies is that you see a case that is referred by a GP and the child has been constipated since early childhood. You prescribe lactulose and the mother starts her child on 5ml twice a day and they then come back to you and say, 'It's no use doctor, this lactulose is no use'. The problem, of course, is that they stay at 5ml twice a day. One of the challenges in management motivation, whatever the situation, is to try and direct the treatment to an endpoint. When we give antihypertensive treatments – we measure the blood pressure, so with constipation, I think we should be looking at the stools and urging the mothers to look at the stools. They can be given a target stool consistency to aim for with advice to increase the medicines stepwise until it is achieved.

The information in Table 1 was developed Dr Heaton in Bristol for patients with irritable bowel syndrome,<sup>2</sup> but I think it is extremely useful for dealing with children because we can give them a very simple chart and say this is what you have got to look for. The actual chart is illustrated (Figure 2) and provided free by Movicol (iso-osmotic laxative, Norigen, Harefield, UK) representatives. They've funded the production of the chart and it is worth getting hold of copies as it is an extremely useful agent for education and certainly for trying to develop a protocol. One of the issues is to try and involve this type of aid for the parents which will give them the permission to increase the medicines. The parents often need that permission.

I've also encountered two other very useful leaflets (Figure 3):

- *Childhood Soiling* published by Eric (*unclear*).<sup>3</sup>

It's quite expensive and quite wordy too. One section that I really recommend would

be the one concerning the child who will only go to the toilet with their nappy on.

There is the most excellent description of it here for parents and this is a really useful thing to give to parents so that they can understand how this comes about and a stepwise plan to improve it.

- *Drugs and Therapeutics Bulletin* leaflet.<sup>4</sup>

This is very good. There are no diagrams which is a shame, but its language is very straightforward and the wording is good.

Information of this type is one of the things I'd like to be more accessible for parents and for children in this area whether or not they have DS and, as children with Down's syndrome do have more constipation than average, we should certainly be using more leaflets and information.

#### *Toddler diarrhoea*

Toddler diarrhoea is a common problem which presents with a thriving child with undigested vegetable matter and, one of the biggest challenges I found is excluding constipation in this group. Lots of children will have undigested vegetables, but they might well have constipation rather than the toddler diarrhoea. It is more tricky and a good examination of the abdomen is appropriate. I don't do abdominal x-rays because I feel that usually from a good history and the examination, I can get all the information I need. In cases where access to x-rays is restricted or slow, you've got to make a decision based on your clinical judgement.

In my own practice, as far as management is concerned, the dietitian is very much involved with these patients. The number of patients that we find that have too much fruit juice is incredible. I've been referred cases where they've been drinking so much fruit juice that changing that alone has actually sorted out the problem. So that is something we should always think about in children with DS, particularly as fruit juice may be given in an attempt to overcome constipation. Some of these children present with abdominal pain which disappears when fruit juice is taken out of the diet. I don't think it's just the

quantity which matters, I think there may be unusual sugars in these juices that are going to cause the children problems as well.

Then there is the question of bulk-producing elements. A treatment not often used in the community and one I have used on a significant number of patients, is to lower the amount of roughage. A study by Miller and co-workers has shown that we can improve what is in fact toddler diarrhoea if we reduce the roughage a little.<sup>5</sup> Another method is to give Calogen (SHS International, Liverpool, UK), peanut oil that has been processed to remove antigen, and we find that this reduces the amount of stooling in a significant number of children. There are some children for whom it has no effect, but if it does work it does so quite fast. We prescribe it quite a lot. It's available from hospital supplies and is quite palatable – it comes in strawberry or a neutral flavour.

In toddler diarrhoea, if you can avoid doing anything I think that's the ideal and reassuring parents that there is no underlying medical problem is key. However, the common problem area is toilet training and if you can intervene and help them just a little bit then it may be enough to help relieve the problem.

#### *Gastro-oesophageal reflux*

Another group we need to be aware of are those with gastro-oesophageal reflux. These children have milk vomiting, but are often well and thriving. However they should be watched carefully for signs of complications and the development of what we call gastro-oesophageal reflux disease (blood in the vomit and failure to thrive). One particular area which I always note is that when you've got gastro-oesophageal reflux it's well worth considering the mental state of the mother because often it can occur when the mother is depressed. There's work showing that in a group of children who had significant vomiting, when they had the pH monitored it was normal. When the researchers questioned the mothers more closely a significant number were depressed and therefore were sort of over-interpreting the symptoms. (*Note to Dr Charlton. Is there a reference for this?*) Has anyone come across that before?

**Audience:** It must be something to do with the way it's being interpreted because when you look at some of the people who complain about reflux and vomiting, they are not experiencing the amount of vomiting that others accept as being completely normal. These people just spend their lives with a cloth over their shoulder and don't believe they have anything to complain about.

If the child is well I would really try and avoid intervention because often I think that's most reassuring to the parents. If it's a socially unacceptable problem – a number of babies can vomit five times in the car coming to the clinic and so you can imagine what it is like at home – and if the parents want treatment then methods of reducing fluid intake should be considered. There are thickeners such as Carobel Instant (Cow & Gate, Nutricia, Trowbridge, UK) and one that I think that's worth considering in younger children is Enfamil AR (Mead Johnson Nutritionals, Bristol Myers Squibb, Hounslow, UK). Enfamil AR is a thickener which is a normal digestible made from rice and when it comes into contact with an acid it thickens; it's thin in the bottle but thick in the stomach. It's well worth considering in the group who are bottle fed. I have seen patients where it's worked and I think that it's worth thinking about. It can be bought over the counter and I think it can now also be prescribed.

If, however, as mentioned before, there are signs and symptoms of actual gastro-oesophageal reflux disease (blood in the vomit, failure to thrive or difficulty feeding) then this needs investigation, but I would tend not to investigate otherwise. Sometimes you just feel you should treat pragmatically if they've got symptoms, but I think it's important to establish what you're dealing with.

**Audience:** I know there are many children with DS with reflux and vomiting, but I'm always worried that we're going miss a minor upper GI problem, such as a degree of narrowing, and it has been reported in the literature although not very often. We recently investigated a case that we had accepted as reflux; a child who vomited continually and whose parents weren't overly concerned and

now he's five and still doing it – you are worried that you are missing something. There's a case of adult who has been picked up as having a narrowing that wasn't picked up earlier.

I think if there's bile-stained vomiting, certainly with the Down's syndrome, it would be well worthwhile considering a narrowing because of the increased structural problems they have.

**Audience:** If they have significant gastro-oesophageal reflux would you expect them to have respiratory symptoms as well if it was severe?

There is a group who definitely have respiratory problems and I think that if a child with Down's syndrome is having breathing problems it may be that you need to consider silent reflux. The consequence of silent reflux is that the milk doesn't come out, but it can spill over into the airways.

#### *Gall stones and abdominal pain*

Abdominal pain is very common and it's more likely to be recurrent abdominal pain of childhood. However it is worthwhile considering that it could be a dyspeptic kind of pain and, although evidence is scarce to support the practice, most people think that the features that help us distinguish it are whether it is night pain or pain after fatty meals.

Gall stones have been found in a number of children with Down's syndrome – I've had several present to me for advice with gall stones. When you look at the literature it advises that if there are no symptoms you can leave them alone; that's what we have done so far and everything has gone well. It's always challenging because there has been a big push to take gall stones out in the past, so if you see gall stones just reassure the parents. The gall stones tend to be found by chance and I'm not sure how common they are. It would be interesting to ask a radiologist because any of the radiologists who do a lot of renal scans could have been tempted to look at gall bladders and then you would have some sort of population.

## Autoimmune problems

### *Coeliac disease*

Coeliac disease can present with diarrhoea, failure to thrive, general misery, abdominal distension and iron deficiency anaemia. I make it my practice always to exclude giardia in this group. In this country it is thought that there is a 1–2% risk of coeliac disease in DS. If you look at the series from Italy and other countries it is much greater and that's for two reasons – there is increased incidence of genetic predisposition and the intake of gluten is much greater. An important point which, obviously, is relevant to adults is that this risk is lifelong, moreover we're finding in the general population that there are now more people presenting later with coeliac disease so we are not getting so much of the traditional bump. The other group we're diagnosing are children with definite, but what I would describe as minimal, GI symptoms which have been recognised as secondary symptoms.

### *Screening for coeliac disease*

The antibody screening tests have definitely uncovered children who can be better once they're recognized but having symptoms is the key thing. You need to have symptoms to have these tests so they are screening tests of a symptomatic population, they are not screening tests of the general population. To make a diagnosis we need to show positive markers. There should definitely be increasing changes in the small intestine and a response to a gluten-free diet. If the child is under two years, there is a chance that they may have transient enteropathy. Therefore, I offer all children who are diagnosed under two years a later challenge and biopsy to ensure they've definitely got coeliac disease. I usually rechallenge before they go to school, so it's usually around the fifth year. You need to leave it long enough for them to be well before you do it again.

Several markers can be used:

- Gliadin antibodies – IgG and IgA

IgA is more sensitive, so in cases of coeliac disease more will have IgA positive.

However, in children there is a problem of a high level of IgA deficiency, particularly

in the early phase where some children have a late switch on of IgA. Children can be IgA deficient for the first five or so years of life (the laboratory at Nottingham allows up to 10 years), so if IgA is deficient IgG gliadin antibody needs to be checked as well. The IgG gliadin antibody should be positive you would hope even if you are IgG inefficient. In Down's syndrome we have to remember that IgA insufficiency is increased, so if you are diagnosing coeliac disease and you have negative markers, check your IgA levels and a child with a low IgA needs a biopsy. Remember that these are only screening tests so if you have symptoms and negative tests I would still consider a biopsy. *(Note for Dr Charlton. Please check that the above is correct as the tape was unclear.)*

- Endomysial antibodies (EMA)

This test is done from the fluorescence and it is the most sensitive and specific test. About 95% of patients diagnosed with coeliac disease will actually have a positive test and if you're taking the population that has symptoms you'll only pick up about 5% who don't have coeliac disease. The reason you have to have symptoms is that some people have a positive result before developing the symptoms of coeliac disease. The antibodies are tested on monkey oesophagus. The serum is poured onto monkey oesophagus, washed off and an antibody with a fluorescent dye is added to the serum which shows up in a certain pattern if endomysial antibody is present.

- Tissue transglutaminase

This is a relatively new test which some laboratories, including our laboratory at Kings Mill, have moved to as it's an ELISA test and they can do it themselves which means they don't incur the costs associated with sending it away. I'm almost certain the tissue transglutaminase test will replace the EMA in the next few years because it does seem to be almost as good, although there's not a lot of reference data to share or veracity(?) studies yet. There's a human tissue transglutaminase test as well. *(Note to Dr Charlton – tape is unclear here, is there anything you would like to add?)*

There is a study from Italy looking at screening for coeliac disease in DS.<sup>6</sup> They, as I mentioned, have a higher incidence and in the children under age 14 years we find that quite a significant number, 3 of 60 (5%) were EMA antibody positive and over age 14, 4 of 52 (8%). (*Note to Dr Charlton – the figures from the slide are inconsistent please could you confirm the preceding sentence is correct.*) Of the seven, four had biopsy-confirmed coeliac disease and three had declined a biopsy because they had no symptoms. Interestingly, through studying other cases they concluded that it was the patients who had presented with chronic diarrhoea who had actually had a biopsy. Looking at the literature they had then recognised that all the patients that seemed to be asymptomatic did in fact have some symptoms even if just a mild anaemia. So I feel that this is part of the information needed for making a judgement.

Endoscopically the normal upper GI intestine has a sort of velvety appearance due to the villi and with a high enough resolution you can actually see the villi roughness. In coeliac disease the surface is featureless and gives a more shiny impression. If we look at the biopsies of normal patients (Figure 4a) there's a very large villous height-to-crypt depth and a normal number of intraepithelial lymphocytes (they look like little black dots and you can count them to give a score). Figure 4b is a very gross case of total villous atrophy with a completely flat surface, very fine crypts and a very heavy infiltrate so it looks reddish blue. Comparing a) and b), b) has very few cells and you can see that it's dense with inflammatory cells.

My view of screening is that doing coeliac screening on every child with Down's syndrome is a bulldozing mechanistic approach which leads to overinvestigation, so I feel that routine testing is not indicated. We should assess all children at review for diarrhoea, chronic anaemia and failure to thrive and, if indicated, test for coeliac serology. If they're positive for EMA or gliadin antibody, or have a low IgA they need a biopsy on a gluten diet to confirm the diagnosis.

**Audience:** I'm a paediatric nurse. We're getting a higher incidence of CD and have diagnosed as late as 14 years. What is the age at which it is most likely to occur?

If you imagine a graph – you're getting a peak incidence around 8 years old and then a drop off at around 10 and a bump in early adulthood, so there's presentation all the way through adolescence.

**Audience:** Do you think that's also true for Down's syndrome? For instance the incidence of hypothyroidism goes up exponentially.

I don't know with Down's syndrome. I think certainly it seems the view that your risk is lifelong, but it may be different because we are talking about this definite propensity for an autoimmune disease process. There is a feeling that there is some chromosomal/genetic link.

#### *Autoimmune hepatitis*

The other autoimmune disorder to consider is hepatitis. This may present with jaundice, but the key thing with jaundice is hypothyroidism, then we have gall stones although, as I said earlier, there's not much literature on them actually causing problems. Autoimmune hepatitis may present with general malaise and aches and some children may have other symptoms such as problems with their joints. We looked after a patient for many years with autoimmune hepatitis. She was from the Asian community and did remarkably well with very low-dose treatment of steroids that kept things under control. We only did the one biopsy because we didn't really want to subject her to a lot of investigations and unfortunately she did have more generalised autoimmune problems and died quite recently. She had incredible support from her parents and we and they miss her very much. She presented with an arthropathy and although her liver enzymes weren't very elevated, she had quite an active hepatitis. After the diagnosis it was awful for the family as the father had died not long before of hepatitis C infection. That is a very complex case and it isn't in the literature and I would not want to dwell on it too much.

## Conclusion

So we've classified the GI disorders of increased frequency:

- Structural/embryological – atresias and Hirschprung disease
- Motility – constipation, things like gastro-oesophageal reflux and feeding problems
- Autoimmune conditions - coeliac disease and AI hepatitis.

We've discussed common presentations, diagnoses and management and I've looked at screening for coeliac disease in children with Down's syndrome and I've rejected that.

## References

1. Quinn FM, Surana R, Puri P. The influence of trisomy 21 on outcome in children with Hirschprung disease. *J Ped Surg* 1994;**6**:781–3.
2. Heaton (Bristol stool scale chart)
3. *Childhood Soiling*
4. *Drugs and Therapeutics Bulletin* (leaflet)
5. Miller et al. (decreasing roughage in diarrhoea)
6. (Coeliac disease – Italian study)

Table 1: The Bristol stool form scale

	<b>Description</b>	<b>Action</b>
<b>Type 1</b>	Separate, hard lumps. Like nuts (hard to pass)	Maintain iso-osmotic laxative dose
<b>Type 2</b>	Sausage-shaped, bit lumpy	Maintain iso-osmotic laxative dose
<b>Type 3</b>	Like a sausage but with cracks on the surface	Normal
<b>Type 4</b>	Like a sausage or snake, smooth and soft	Normal
<b>Type 5</b>	Soft blobs with clear-cut edges (passed easily)	Decrease iso-osmotic laxative dose
<b>Type 6</b>	Fluffy pieces with ragged edges, a mushy stool	Decrease iso-osmotic laxative dose
<b>Type 7</b>	Watery, no solid pieces, entirely liquid	Decrease iso-osmotic laxative dose

Figure 1: Barium enema showing the constricted rectum (R) and dilated sigmoid colon (S).

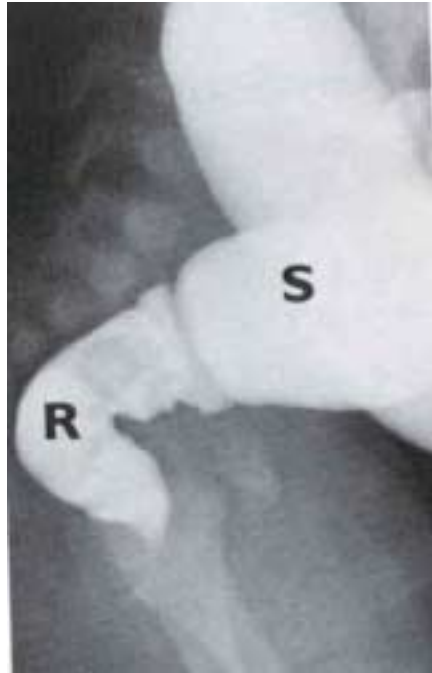


Figure 2: Bristol stool form scale chart

*The Bristol stool form scale*

Type 1		Separate hard lumps, like nuts (hard to pass)	Minimize Medical dose
Type 2		Sausage-shaped but lumpy	Minimize Medical dose
Type 3		Like a sausage but with cracks on its surface	✓
Type 4		Like a sausage or snake, smooth and soft	✓
Type 5		Soft blobs with clear-cut edges (passed easily)	Decrease Medical dose
Type 6		Fluffy pieces with ragged edges, a mushy stool	Decrease Medical dose
Type 7		Watery, no solid pieces ENTIRELY LIQUID	Decrease Medical dose

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Figure 3: Information leaflets for parents

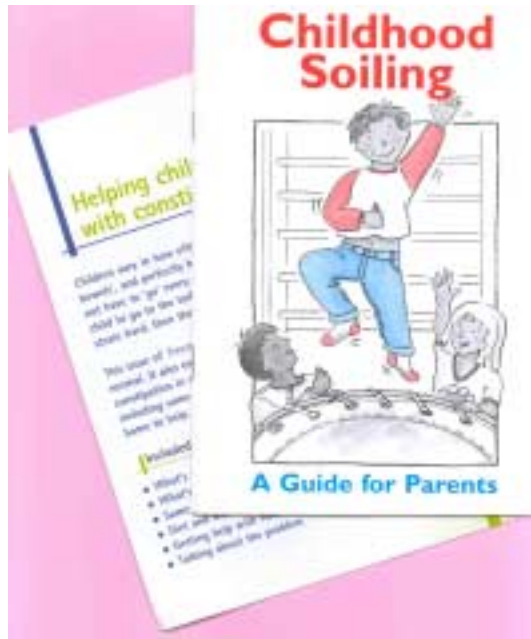


Figure 4: Biopsies of a) healthy patient and b) with coeliac disease.

a)



b)

