Down syndrome and coeliac disease: five new cases with a review of the literature

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Received: 9 March 1993 / Accepted: 4 June 1993

Abstract. We report five new patients with coeliac disease and Down syndrome and review the 11 cases previously reported in the literature. In 14 of these 16 patients diarrhoea was the presenting symptom and in 2 failure to thrive in combination with anaemia. The frequency of coeliac disease in children with Down syndrome was calculated as being 43 times greater than in children without Down syndrome. Delay between first symptoms and diagnosis in patients with combined coeliac disease and Down syndrome was 2.5 years, while in the other children with coeliac disease it was only 8 months. This distinctive difference could be caused by an underestimation of the seriousness of gastro-intestinal complaints in patients with Down syndrome. It is stressed that coeliac disease should be strongly considered in all children with Down syndrome and either persistent diarrhoea or failure to thrive.

Key words: Down syndrome – Coeliac disease

Introduction

The association of Down syndrome (DS) and coeliac disease (CD) has been previously described, 11 patients being reported so far in the literature [1, 3, 13, 14, 16–18]. The incidence of CD in patients with DS was estimated to be 0.8%–1.6% [1,18], 20 times greater than incidence of CD among other children [18].

Most cases of childhood CD are identified in the first 2 years of life [2]. However, CD was diagnosed before 2 years of age in only one patient with the association CD/DS [1, 3, 13, 14, 16–18]. We assume that CD as a cause of diarrhoea in children with DS is underestimated, resulting in a delay in diagnosing CD. We therefore wish to report five new cases with this association and to give a review of the literature.

Case reports

Case 1

Case 1, a boy with trisomy 21, presented at the age of 2 years with diarrhoea since 15 months. At presentation his height was 76 cm (P5, Down syndrome percentile chart [DSPC] [11]), while weight was 7500 g (P15, DSPC). On examination the abdomen was distended and hypertypanic. Laboratory investigations showed a haemoglobin of 6.2 mmol/l; anti-gliadin antibodies (AGA) were elevated: IgG-AGA: 439 arbitrary units (AU)/ml and IgA-AGA: 413 AU/ml (normal: IgG-AGA: < 80 AU/ml and IgA-AGA < 1 AU/ml) [21]. A proximal intestinal biopsy showed total villous atrophy. No Giardia lamblia were found. After initiating a gluten-free diet growth and mood improved greatly. Six months after the start of the diet his height was 83 cm (P40, DSPC) and weight 12.4 kg (P60, DSPC).

Case 2

Case 2 is a boy who was diagnosed as having DS at the age of 6 months, when developmental delay was noticed. At the age of 2 years he was seen because of diarrhoea since some months. Anaemia (haemoglobin 5.8 mmol/l) was present, for which iron was given. In addition loperamide was given. Despite medication diarrhoea and anaemia persisted. On examination at the age of 5 years

Abbreviations: AGA = anti-gliadin antibodies; AU = arbitrary units; CD = coeliac disease; DS = Down syndrome; DSPC = Down syndrome percentile chart
the abdomen was severely distended. Height was 94 cm (P35, DSPC) and weight 15 kg (P40, DSPC). Laboratory investigations showed a haemoglobin of 6.8 mmol/l; AGA were elevated (IgG-AGA: 4586 AU/ml and IgA-AGA: 20 AU/ml). A proximal intestinal biopsy showed a total villous atrophy and hyperplasia of the crypts. There were no Giardia lamblia present in the biopsy material. A gluten-free diet was started. After 3 months his height was 97.5 cm (P50, DSPC) and weight was 17.0 kg (P60, DSPC).

**Case 3**

Case 3 is a boy with trisomy 21, who presented at the age of 7 years with diarrhoea accompanied by loss of weight. Besides giardiasis, for which he was treated with metronidazole, no further diagnosis was made. Despite treatment of the giardiasis, the diarrhoea and loss of weight persisted as a result of which the child became dystrophic. Subsequently he was referred to the Wilhelmina Children’s Hospital. At that time the frequency of the watery diarrhoea was between 5 and 7 times a day; no blood or mucus was present in the stools. The abdomen was distended. Height was 115.5 cm (P75, DSPC) and weight 15.9 kg (P5, DSPC). Laboratory investigations showed a haemoglobin of 9.6 mmol/l. No Giardia lamblia was found in his stools. A proximal intestinal biopsy was compatible with the diagnosis of CD, so the patient was given a gluten-free diet. Within 6 months weight increased from P5 to P40 (DSPC). In September 1986 the child was admitted. On examination the abdomen was distended. Height was 115.5 cm (P75, DSPC) and weight 15.9 kg (P5, DSPC). Laboratory investigations showed a haemoglobin of 7.2 mmol/l, and elevated AGA (IgG-AGA: 6036 AU/ml and IgA-AGA > 700 AU/ml). A proximal intestinal biopsy showed total atrophy of the mucosal villi. The biopsy material revealed no presence of Giardia lamblia. A gluten-free diet was started and the child started growing again. One year after initiating the diet his height was 96 cm (P75, DSPC) and weight 17.8 kg (P60, DSPC).

**Case 4**

Case 4, a boy with trisomy 21, had diarrhoea since the age of 7 months. At 3.5 years of age he contracted pneumonia. During this illness his weight decreased from 11 to 9.1 kg, and the child was admitted. On examination the abdomen was distended. His stools were voluminous and frequent, but no blood or mucus were present. His height was 85.5 cm (P50, DSPC) and weight 9.1 kg (P5, DSPC). Laboratory investigations showed a haemoglobin of 7.2 mmol/l, and elevated AGA (IgG-AGA: 6036 AU/ml and IgA-AGA > 700 AU/ml). A proximal intestinal biopsy showed total atrophy of the mucosal villi. The biopsy material revealed no presence of Giardia lamblia. A gluten-free diet was started and the child started growing again. One year after initiating the diet his height was 96 cm (P75, DSPC) and weight 17.8 kg (P60, DSPC).

**Case 5**

Case 5, a boy with trisomy 21, had an AGA determination at the age of 6 years because he suffered from general malaise and failure to thrive. Abnormal values were obtained. At that time his weight was 9.2 kg, (below P5, DSPC) and his height 86 cm (far below P5, DSPC). His haemoglobin was 5.6 mmol/l. A proximal intestinal biopsy was done, which showed a total villous atrophy. A gluten-free diet was started and the child became more active and his mood improved. After 3 months a proximal intestinal biopsy was performed and an evident histological recovery could be seen. For several years the child continued to grow far below P5 (DSPC) for height as well as weight. Only recently, at the age of almost 12 years, height has shifted to the P15 (DSPC).

**Discussion**

Among 87 CD patients diagnosed in the period between 1983 and 1992 five had DS (5.7%). While the livebirth prevalence of DS in the Netherlands is 1.36 per 1000 [10], the expected frequency of DS among CD patients would be 1 : 735. However we encountered 1 : 17, which gives a relative risk of 43.

The relevant data of our cases and the 11 cases described in the literature are presented in Table 1. Diarrhoea was the presenting symptom in 14 of the 16 patients. In the other two patients the combination of severe failure to thrive and anaemia led to the diagnosis of CD. Anaemia was also present in almost 50% of the other patients and can be explained by the malabsorption due to the villous atrophy. One of our patients and one of those described by Amil Dias and Walker-Smith [1] had giardiasis, which was initially thought to be the cause of the persisting diarrhoea. The final diagnosis of CD was proven in our patient by a gluten challenge, and in the patient described by Amil Dias and Walker-Smith [1] by persisting villous atrophy after eradication of the parasite, in combination with a favourable response to a gluten-free diet.

The cause of the increased prevalence of CD in patients with DS remains obscure. However, it is known that patients with DS have defects in both the humoral and cellular immunity and are more prone to a variety of auto-immune disorders [7, 8]. Interestingly, in patients with DS the percentage of γδ T-cells in the circulation is greatly increased, especially the subset with the δTCS1 phenotype [4]. This subset seems to have a tissue tropism instead of remaining in the circulation [12]. It is indeed just this subset that can be observed in large numbers in between the enterocytes in patients with CD [20]. Although the exact role of the intra-epithelial lymphocytes in the pathogenesis of CD is not yet known, it is tempting to speculate that the abnormal numbers of γδ T-cells could be the link between these two disorders.

A possible way of determining whether CD is the origin of complaints as diarrhoea or failure to thrive in patients with DS, is the determination of IgG and IgG AGA [5, 6]. This was done in the present series in half of the patients (Table 1). The value of AGA screening in patients with DS has been studied by Storm [19] and Castro et al. [9]. In the first study, 6 out of 78 patients with DS had both an elevated IgG-AGA and IgA-AGA. Four of these patients were biopsied, and two had total villous atrophy. In the second study only the prevalence of elevated IgA-AGA levels in patients with DS was determined. In 40 out of 155 patients elevated levels were found. The 21 patients with gastro-intestinal complaints underwent a proximal intestinal biopsy and a total villous atrophy was found in...