Discussion

Mosaicism involving more than two cell lines in Down syndrome patients has been described. However, the reports of mosaicism involving two different Robertsonian translocations are very few. In 1965, Zellweger and Abbo\(^8\) reported a case where mosaicism was observed in a girl with Down syndrome. She had four different cell lines, balanced and unbalanced translocations involving D;D and D;G lines, as well as a normal cell line. However, pictures were not available and banding techniques were not in use at that time. Chromosomal mosaicism was observed in other members of the family also. They attributed this familial mosaicism to an autosomal dominant gene. Another case of Down syndrome with two different Robertsonian translocations (15;21 and 21;21) was reported by Atkins and Bartsocas in 1974.\(^1\) In this case and the case of Zellweger and Abbo the patients appeared to have a Down phenotype.

In the present case, approximately 50% of the patient’s blood cells were trisomic for chromosome 21 and 50% were normal (table). This could explain why he did not present with typical Down syndrome features. This again shows that, in a mosaic, when a percentage of a particular cell line is less than 1 or 2%, it may go unnoticed in a routine count of 30 cells.

In our case, we could not determine whether q21q21 was an isochromosome or a translocation. The formation of an isochromosome in one cell line and chromosomal breakage leading to q13;q21 translocation in another cell line of a normal zygote could be one of the explanations of this mosaicism. Another possibility is that the zygote started out as normal 46,XY, non-disjunction at the second mitotic division resulted in a 46/47 mosaicism (non-disjunction at the first mitotic division would result in a regular trisomy), or the zygote started out as trisomic for a chromosome 21. Anaphase lagging of a chromosome 21 at one of the first mitotic divisions can also result in a 46/47 mosaic. Since there was no 47 cell line, chromosomal breakage might have occurred immediately in a cell with 47 chromosomes giving rise to a 21;21 translocation. Since there was no 47 cell line, chromosomal breakage might have occurred immediately in a cell with 47 chromosomes giving rise to a 21;21 translocation.

Considering that the normal cell line represents only 1% in the distribution of three cell lines, this chromosomal breakage might have occurred in the early cleavage division. We were unable to carry out blood group studies for chimaerism.

References


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Autoimmune chronic active hepatitis in Down’s syndrome

SUMMARY Hashimoto’s thyroiditis, autoimmune adrenalitis, pernicious anaemia, and diabetes mellitus are all recognised associations with Down’s syndrome. In addition chronic active hepatitis (CAH) resulting from chronic hepatitis B antigenaemia is known to occur in these patients, but an association of autoimmune CAH and Down’s syndrome has not previously been described. We report a case in which Down’s syndrome was associated with autoimmune CAH, Hashimoto’s thyroiditis, and alopecia areata.

Case report

A 29-year-old man with Down’s syndrome was referred in May 1980 with a 9-month history of increasing lethargy and dyspnoea, dryness of the
skin, and cold sensitivity. There was no family history of thyroid or other autoimmune disease. He had not received any regular medication nor had he previously been admitted to hospital. Examination revealed overt hypothyroidism but no goitre. Patchy alopecia typical of alopecia areata was noted. He was clinically anaemic. His liver and spleen were palpable but there was no ascites, jaundice, or other stigmata of chronic liver disease.

His haemoglobin was 7-8 g/dl, mean cell volume 111 μm, and erythrocyte sedimentation rate 140 mm/h. Platelet, reticulocyte, and white cell counts were normal. Coomb’s test was negative. Serum iron, vitamin B₁₂, and folate were normal. Blood urea and electrolytes were normal, serum albumin was 30 g/l, and total protein 102 g/l. Protein electrophoresis showed a polyclonal increase in globulin. Immunoelectrophoresis showed IgG 71 g/l (9.5 to 16.5), IgM 1.2 g/l (0.65 to 2.0), and IgA 0.3 g/l (0.9 to 4.5). Serum bilirubin was 24 mmol/l (<17), AST was 63 U/l (<20), and alkaline phosphatase (solely of liver origin) was 532 IU/l (28 to 93). Serum HbsAg, HbcAg, and HbCAB were negative. Serum thyroid microsomes and cytoplasmic antibodies were strongly positive, as was antinuclear antibody. Smooth muscle antibodies were negative. DNA binding activity was >140 U/l (<20). Serum thyroxine was 13 mmol/l (60 to 140) and thyroid stimulating hormone was 78 mU/l (<7). Serum complement showed low CH50 and C4 suggesting activation of the classical pathway. IgG and IgA containing immune complexes were detected in the circulation. The human leucocyte antigen (HLA) type was A1, A3, B8, Bw41.

Chromosome analysis confirmed trisomy 21. A liver scan showed patchy hepatic uptake of colloid and splenomegaly. A liver biopsy showed the features of CAH progressing to cirrhosis. A barium swallow demonstrated oesophageal varices.

His clinical state was improved by thyroxine therapy although he later developed ascites for which spironolactone was prescribed. In September 1980, 4 months after presentation, he had a major gastrointestinal haemorrhage and his varices were injected endoscopically. He died one month later following a further gastrointestinal haemorrhage.

Necropsy showed that death was the result of massive gastrointestinal haemorrhage from ulcerated oesophageal varices. Ascites, bilateral hydrothorax, and a moderate pericardial effusion were noted. The liver was small (1010 g), with a finely nodular capsular surface. On section the organ was fibrous with a thickened capsule. The portal vein was occluded by recent thrombus. There was moderate splenomegaly (420 g). The thyroid gland was small (8·3 g) and fibrous.

Microscopical examination of the liver showed cirrhosis, less advanced in the left lobe, arising on the basis of chronic active hepatitis (figure). The thyroid gland showed diffuse fibrosis in which only minimal amounts of parenchyma remained, showing plasma cell and lymphocytic infiltration, Hürthle cell change, and 'squamous metaplasia'. The appearances were those of end stage thyroiditis consistent with an autoimmune origin. There was no evidence of adrenalinitis.

Discussion

Although immune disturbance is common in Down's syndrome, the mechanism of its production is uncertain and is probably multifactorial, being further complicated in those who possess the allele HLA-B8. In this case immune disturbance was particularly severe and was manifest by Hashimoto's thyroiditis, alopecia areata, antinuclear antibodies in high titre, increased DNA binding activity, circulating immune complexes, complement activation, and, it appears, chronic active hepatitis. We suggest that CAH be added to the list of autoimmune conditions seen in association with Down's syndrome.

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An adult female with spondyloepiphyseal dysplasia tarda

SUMMARY We report a sporadic adult female with a distinctive variety of spondyloepiphyseal dysplasia tarda characterised by universal platyspondyly, short metacarpals, short metatarsals, genu valgum, mild thoracic kyphoscoliosis, and severe generalised epiphyseal distortion with premature osteoarthrosis.

Spondyloepiphyseal dysplasia tarda (SEDT) is characterised by primary and usually progressive involvement of the spine and epiphyses with onset in later childhood.\(^1\) Most commonly SEDT is inherited as an X linked recessive trait but genetic heterogeneity appears probable.\(^1,2\) We report a sporadic female with SEDT who provides further evidence for heterogeneity in this condition.

Case report

The proband was born in 1934. She was the fifth child of non-consanguineous parents and no other family members are similarly affected. Her father was 39 years old and her mother 32 years old at the time of her birth. She was normal at birth but stopped growing at about 14 years of age. In 1960, aged 26 years, she underwent left total hip replacement because of severe osteoarthrosis. This relieved her symptoms, but two years later the prosthesis became infected and a left pseudarthrosis was created. She was then asymptomatic until 39 years of age when she developed pain in the region of her right hip, and in 1974 required right total hip replacement. The excised femoral head showed severe anatomical distortion in addition to secondary osteoarthrosis (fig 1). Since 1980 she has had symptoms from osteoarthrosis of the left shoulder and in 1981 she underwent cholecystectomy for gallstones. Her periods started at the age of 16 years and have been regular. She has never been pregnant. Despite her disabilities she has been a full-time sewing machinist since 1954.

Examination at 47 years of age revealed a height of 127 cm, upper segment 62 cm, lower segment 65 cm, arm span 141 cm, and weight 50 kg (fig 2).

FIG 1 Severe osteoarthrosis of the right hip at 39 years of age. Pseudarthrosis of left hip.

FIG 2 Patient aged 47 years beside a nurse, height 170 cm.

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