

## AUTOIMMUNITY

# Autoimmunity puzzle in Down syndrome

Corin Badiu<sup>1,2</sup>, Simona Verzea<sup>2</sup>, Maria Picu<sup>2</sup>, Cornelia Pencea<sup>3,4</sup>

One of the most common genetic abnormalities, Down syndrome is associated with intellectual disabilities as well as increased incidence of autoimmune diseases. Endocrine disorders, such as diabetes and thyroid dysfunction are amongst the most common. We describe the case of a 27 year old woman diagnosed with diabetes at the age of 9, who had associated crises of loss of consciousness from the age of 23 and developed primary autoimmune hypothyroidism from the age of 25 years with chronic pericardial effusion. Neurological examination considered the diagnosis of absence crises; therefore she started taking Carbamazepine 400 mg daily since the age of 23. At admission, the patient was obese (BMI =32 kg/m<sup>2</sup>), with neck localised acanthosis nigricans. The clinical examination revealed signs of hypothyroidism without goitre. Diagnosis was confirmed by TSH = 350 mU/L, anti TPOAb = 329.9 U/ml as well as pericardial effusion on echocardiography. She started thyroxine replacement therapy, while being on basal/bolus insulin regimen (short and intermediate acting insulin). Full control of diabetes was not achieved until she also received metformin and basal insulin analog. TSH level reached normal values of 2.4 mU/L only after a LT<sub>4</sub> substitution dose of 150 µg daily. Evolution of thyroid status and diabetes under progressive thyroxine substitutive treatment is discussed. Compliance to diet, diabetes and myxoedema treatment is severely influenced by her intellectual disabilities. Screening for thyroid status and autoimmunity in order to detect subclinical hypothyroidism, should be performed in patients with Down syndrome.

(1) "C. Davila" University of Medicine and Pharmacy, Department of Endocrinology, Bucharest, Romania

(2) "C.I Parhon" National Institute of Endocrinology, Bucharest, Romania

(3) "N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Disorders

(4) "C. Davila" University of Medicine and Pharmacy, Department of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

**Correspondence to** Corin BADIU MD, PhD, Associate Professor in Endocrinology, Institute of Endocrinology, "C. Davila" University of Medicine and Pharmacy Bd. Aviatorilor 34-36, 011863 Bucharest, Romania • Tel: +40 722524002 • Fax: +4021 3198718 • email:badicrin@yahoo.co.uk

doi:10.3104/case-studies.2138

© 2009 The Authors. Journal Compilation © 2010 Down Syndrome Education International.

Down syndrome is the most common identified cause of intellectual disabilities, with an average prevalence of 1 per 1000 registered births. Down syndrome is associated with increased incidence of treatable disorders which, if undiagnosed, impose an additional but preventable burden of secondary disability<sup>[1]</sup>.

It is well known that patients with Down syndrome have an increased prevalence of autoimmune disorders affecting both endocrine and non-endocrine organs (Addison's disease, allergic dermatitis, coeliac disease, diabetes mellitus, hypo- and hyperthyroidism, autoimmune haemolytic anaemia, dermatomyositis, multiple sclerosis, pernicious anaemia, polyarteritis nodosa, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and systemic lupus erythematosus)<sup>[2]</sup>. The most common autoimmune disease in Down syndrome is related to the thyroid gland. Thyroid autoantibodies are found in 13-34% of patients with Down syndrome<sup>[3]</sup>. Both hypo- and hyperthyroidism have been reported and overt hypothyroidism was related with thyroid autoimmunity<sup>[3,4]</sup>. The reported prevalence of

hypothyroidism in adults with Down syndrome has varied between 3% and 54%<sup>[3,5]</sup>. Recently, larger studies showed that the frequency of thyroid dysfunction in patients with Down syndrome rises with age, particularly after the age of 40<sup>[3,6]</sup>. Hypothyroidism can be subclinical, particularly challenging to detect in patients with intellectual disabilities and language impairments. Symptoms of hypothyroidism overlap with features of Down syndrome, including impaired intellectual development in young children, decreased linear growth, dry skin, dentition abnormalities, and decreased physical activity<sup>[7]</sup>. Pericardial effusion may be the first sign of hypothyroidism, since a delayed diagnosis is likely, and usually, will completely resolve after thyroxine therapy, without pericardiocentesis. Any patient with Down syndrome who presents with dyspnoea and cardiomegaly should be suspected of having pericardial effusion due to hypothyroidism and echocardiography should be performed<sup>[4]</sup>. There is also evidence that the prevalence of diabetes mellitus is four<sup>[8]</sup> to eight times<sup>[9]</sup> higher in people with Down syndrome than in the general

population. Both type 1 and type 2 diabetes have been reported, but type 1 is more frequent<sup>[10]</sup>. The average age at onset of type 1 diabetes in trisomy 21 individuals is also lower than in the background population, according to some studies<sup>[8,10]</sup>. As the symptoms of diabetes in patients with Down syndrome may be more difficult to detect and there is an increased risk of complications such as hyperosmolar coma, special attention has to be taken to symptoms as polydipsia and polyuria<sup>[9]</sup>.

## Case report

A 27 year old woman with Down syndrome was admitted to the Thyroid Related Disorders Department of “C. I. Parhon” National Institute of Endocrinology for reevaluation. The investigation and therapy protocol were explained in detail to the patient and her mother and they agreed to fulfil its requirements. The institutional ethics committee agreed the study design.

The patient was born to a healthy, unrelated 28-year-old mother and her husband, both with no relevant medical history, at term, after a normal pregnancy and full-term normal vaginal delivery. Her weight at birth was 4000g and she had no congenital heart disease. Her previous medical history included: bilateral congenital cataract, congenital hip dysplasia, insulin dependent diabetes mellitus diagnosed at the age of 9, crises of loss of consciousness with retrograde amnesia from the age of 23 and autoimmune hypothyroidism (serum TSH = 350 mU/L, anti TPO Ab = 329.9 U/ml) from the age of 25 years with chronic pericardial effusion, in remission since her last presentation. She was genetically confirmed as trisomy 21 by chromosomal banding technique. The patient was treated with L-thyroxin 125 µg daily, Carbamazepine 400 mg daily and rapid insulin 46 UI/day (four injections).

On physical examination she had a typical Down syndrome appearance: slanted palpebral fissures, hypotelorism, epicanthic folds (FIGURE

1a); her blood pressure was 100/65 mm Hg, heart rate 86 beats/minute, BMI=32 kg/m<sup>2</sup>, height = 146 cm. She was afebrile and pale, but acanthosis nigricans was localised on her neck (FIGURE 1b). On auscultation, she had no pericardial rub and no rales on chest examination; there were no peripheral oedemas or other signs of heart failure.

Routine laboratory findings were: normal haemogram excepting low leukocytes (3100/mm<sup>3</sup>), normal liver and renal parameters, elevated serum glucose level (221.7 mg/dl) and slightly decreased calcium level (8.13 mg/dl) suggesting the possibility of autoimmune hypoparathyroidism, in addition to insulin dependent diabetes mellitus and autoimmune hypothyroidism. For this reason, PTH and 25 OH vitamin D levels were tested, suggesting secondary hyperparathyroidism due to vitamin D deficiency: elevated serum PTH level (84 pg/ml) and decreased 25 OH vitamin D level (8.68 ng/ml).

Thyroid function tests revealed low normal free T4 level (0.8 ng/dl), slightly elevated TSH (6.7 mUI/L) showing subclinical hypothyroidism; thyroid autoantibodies were not determined again. Also, HbA1c level was high (10.3%), showing lack of control of diabetes mellitus.

The ECG showed normal sinus rhythm, low T waves voltage in all leads and right bundle branch block. Transthoracic echocardiography revealed normal sized and normokinetic right and left ventricles, without atrial or ventricular septal defect or other heart abnormality, and pericardial effusion measuring 9mm on the posterior wall of left ventricle. In this setting, we increased the L-thyroxin dose to 150 µg/day and Insulin doses to 54 UI/day, continued Carbamazepine 400 mg/day and started Calcium and vitamin D therapy.

Four months later, the patient was euthyroid under LT<sub>4</sub> 150 µg/day (TSH=2.4 uUI/ml), serum calcium level increased in the normal range (8.79 mg/dl) and pericardial effusion was in remission since her last presentation (2-3 mm on the

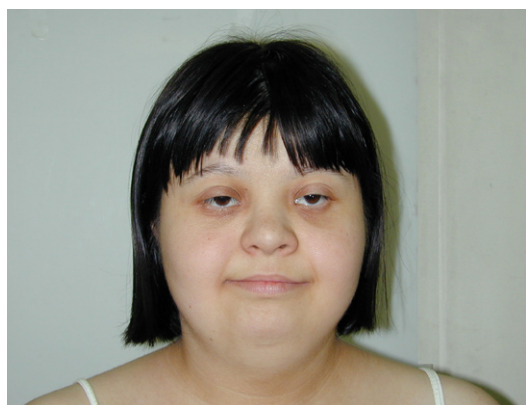


Figure 1|a Physical appearance of the patient; b Acanthosis nigricans localised on the patient's neck

posterior wall of left ventricle). HbA1c level was still high (9.3%), showing however an improved control of diabetes. Regular insulin doses were increased, and a basal insulin analog in the evening was used. Taking into account that this patient probably had a degree of insulin resistance (obesity, *achantosis nigricans*), biguanide therapy was considered. Metformin dose was gradually titrated to 850 mg twice daily. A good glycaemic control, without gastrointestinal side effects was achieved.

## Discussion

It is well-known that patients with Down syndrome are predisposed to autoimmune disorders like insulin dependent diabetes mellitus, autoimmune thyroid disorders, alopecia, vitiligo, hypoparathyroidism and coeliac disease<sup>[11]</sup>.

We report a case of a 27 year old woman with Down syndrome and autoimmune polyglandular syndrome type II (type 1 diabetes mellitus and autoimmune hypothyroidism). The most common autoimmune condition in patients with Down syndrome is thyroid disease<sup>[11]</sup>. There seems to be no statistical correlation between the coexistence of cardiovascular or gastrointestinal disease in patients with Down syndrome and thyroid abnormalities<sup>[12]</sup>. However, some studies have shown that coeliac disease may predispose patients to other autoimmune disorders and long-term exposure to gluten may increase the patients' susceptibility to type 1 diabetes mellitus and autoimmune thyroiditis<sup>[11]</sup>.

Human leukocyte antigen typing might be of value for predicting increased susceptibility to autoimmune conditions in Down syndrome. Some specific genes have been linked to different autoimmune diseases, for instance the HLA haplotype DRB1\*0301-DQA1\*0501-DQB1\*0201 (DR3-DQ2) is a major susceptibility haplotype for both type 1 diabetes and thyroid disease<sup>[10]</sup>. An excess of this haplotype in Down syndrome could potentially contribute to increased risk of autoimmunity in trisomic patients. However, it seems that patients with Down syndrome with type 1 diabetes are less likely to carry the highest risk genotype DR4-DQ8/DR3-DQ2 than patients with type 1 diabetes from the general population, but more likely to carry low risk genotypes<sup>[10]</sup>. So, susceptibility to type 1 diabetes mellitus in Down syndrome is only partially HLA mediated and other factors are likely to be involved. Some recent reports based on the linkage results on chromosome 21 identified an area of interest on this chromosome (21q21.11-q22.3) that may increase the penetrance of type 1 diabetes in Down's syndrome<sup>[13,14]</sup>. Also, a possible relationship between Down syndrome and some mitochondrial muta-

tions were suggested: mitochondrial DNA 3357 (G-A) mutation was demonstrated in a woman with Down syndrome complicated with type 1 diabetes and chronic thyroiditis<sup>[11]</sup>. However, apart from the karyotype, we were unable to do further genotyping in our case.

Diabetes has a higher prevalence in Down syndrome than in the general population. It can appear as an autoimmune disorder (type 1 diabetes mellitus) or as a disorder in which the insulin resistance is the predominant physiopathological factor (type 2 diabetes mellitus). Our case was initially registered as type 1 diabetes, due to age of onset (9 years) and clinical features. However, the actual doses of insulin, increased from 46 to 54 UI/day with difficulties in achieving good glycaemic control as well as associated obesity and *achantosis nigricans* show a degree of insulin resistance. This further can modify the therapeutic attitude, in addition to nutrition changes and diet<sup>[15]</sup>.

Down syndrome can be associated with thyroid autoimmune disease, more often hypothyroidism than hyperthyroidism. The natural history of thyroid function in Down syndrome over 10 years shows a slow increase of thyroid dysfunction, with an average prevalence in one third of the patients. This has an impact of thyroid evaluation, recommended at several years interval. Subclinical hypothyroidism might become overt hypothyroidism, as in our case, or be just transient<sup>[16]</sup>.

A particularity of this case was the fact that, after the crisis of loss of consciousness, the patient was chronically treated with Carbamazepine 400 mg/day. Although it is well tolerated, this drug is related to various adverse effects involving several organs and endocrine and metabolic functions. In particular, relevant effects on thyroid function have been described<sup>[17]</sup>.

Carbamazepine typically decreases thyroid hormone concentrations, especially T4 levels – both total and free T4. This effect has been explained by interference with thyroid hormone competitive binding to thyroxine-binding globulin and by activation of liver microsomal enzymes and increasing the peripheral metabolism of thyroid hormones. In patients with no thyroid disorder, Carbamazepine causes hormonal changes with no clinical relevance because there is a compensatory reaction in order to keep them euthyroid. In patients supplemented with thyroxine for hypothyroidism, this compensation may be ineffective and Carbamazepine may precipitate more severe symptoms and may increase the demand for thyroid hormones<sup>[18]</sup>. This could explain the increasing requirement for thyroxine replacement in our case.

In conclusion, Down syndrome is associated with a predisposition to develop autoimmune disorders which include diabetes and thyroid dysfunctions. Screening for thyroid autoimmunity i.e. ATPO and TSH, in order to detect sub-

clinical hypothyroidism, should be performed annually, especially when other autoimmune disorders, like diabetes mellitus, are associated. Other conditions and related treatment might also impair the thyroid function.

- Henderson A, Lynch SA, Wilkinson S, Hunter M. Adults with Down's syndrome: the prevalence of complications and health care in the community. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners*. 2007; 57(534):50-55.
- Goldacre MJ, Wotton CJ, Seagroatt V, Yeates D. Cancers and immune related diseases associated with Down's syndrome: a record linkage study. *Archives of Disease in Childhood*. 2004;89(11):1014-1017.
- Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Anneren G. Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. *Archives of Disease in Childhood*. 1998;79(3):242-245.
- Dinleyici EC, Ucar B, Kilic Z, Dogruel N, Yazar C. Pericardial effusion due to hypothyroidism in Down syndrome: report of four cases. *Neuro Endocrinology letters*. 2007;28(2):141-144.
- Chen MH, Chen SJ, Su LY, Yang W. Thyroid dysfunction in patients with Down syndrome. *Acta Paediatrica Taiwanica*. 2007;48(4):191-195.
- Gibson PA, Newton RW, Selby K, Price DA, Leyland K, Addison GM. Longitudinal study of thyroid function in Down's syndrome in the first two decades. *Archives of Disease in Childhood*. 2005;90(6):574-578.
- Carroll KN, Arbogast PG, Dudley JA, Cooper WO. Increase in incidence of medically treated thyroid disease in children with Down Syndrome after rerelease of American Academy of Pediatrics Health Supervision guidelines. *Pediatrics*. 2008;122(2):e493-e498.
- Bergholdt R, Eising S, Nerup J, Pociot F. Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: A nationwide population-based study. *Diabetologia*. 2006;49(6):1179-1182.
- Van Goor JC, Massa GG, Hirasings R. Increased incidence and prevalence of diabetes mellitus in Down's syndrome. *Archives of Disease in Childhood*. 1997;77(2):186.
- Gillespie KM, Dix RJ, Williams AJ, Newton R, Robinson ZF, Bingley PJ, Gale EAM, Shield JPH. Islet autoimmunity in children with Down's syndrome. *Diabetes*. 2006; 55(11):3185-3188.
- Kinik ST, Ozcay F, Varan B. Type I diabetes mellitus, Hashimoto's thyroiditis and celiac disease in an adolescent with Down syndrome. *Pediatrics International*. 2006;48(4):433-435.
- Unachak K, Tanpaiboon P, Pongprot Y, Sittivangkul R, Silvilairat S, Dejkhamron P, Sudasna J. Thyroid functions in children with Down's syndrome. *Journal of the Medical Association of Thailand*. 2008;91(1):56-61.
- Concannon P, Onengut-Gumuscu S, Todd JA, Smyth DJ, Pociot F, Bergholdt R, Akolkar B, Erlich HA, Hilner JE, Julier C, Morahan G, Nerup J, Nierras CR, Chen WM, Rich SS. A human type 1 diabetes susceptibility locus maps to chromosome 21q22.3. *Diabetes*. 2008; 57(10):2858-2861.
- Bergholdt R, Nerup J, Pociot F. Fine mapping of a region on chromosome 21q21.11-q22.3 showing linkage to type 1 diabetes. *Journal of Medical Genetics*. 2005; 42(1):17-25.
- Fonseca CT, Amaral DM, Ribeiro MG, Beserra IC, Guimaraes MM. Insulin resistance in adolescents with Down syndrome: a cross-sectional study. *BMC Endocrine Disorders*. 2005;5:6.
- Prasher V, Gomez G. Natural history of thyroid function in adults with Down syndrome – 10-year follow-up study. *Journal of Intellectual Disability Research*. 2007;51(Pt 4):312-317.
- Verrotti A, Scardapane A, Manco R, Chiarelli F. Antiepileptic drugs and thyroid function. *Journal of Pediatric Endocrinology and Metabolism*. 2008;21(5):401-408.
- Simko J, Horacek J. Carbamazepine and risk of hypothyroidism: a prospective study. *Acta Neurologica Scandinavica*. 2007;116(5):317-321.

Received: 11 July 2009; Revised version accepted: 5 November 2009; Published online: February 2010

## Specialist Editor's note-

The natural history of thyroid function is known to be different in people with Down syndrome, although we do not have a clear understanding of many of the details, such as the factors that may define individual risk of thyroid dysfunction, or help to guide diagnosis and treatment. The consequences for the individual regarding other related conditions or risks are also not settled. This paper is a well thought review built around a patient who presents with a version of the story that aids discussion of several relevant topics in long term management, particularly the related autoimmune implications, as well as potential for drug interactions and other issues.

Papers like this one help to update our current medical understanding and to guide clinical decisions for individuals, while building consensus towards broad standards of clinical care. However, we need to review many more cases of individual variety, to fully understand the clinical implications that will determine appropri-

ate standards of care. There are many medical professionals around the world with particular interest in Down syndrome; many of us are connected through "Down Syndrome Medical Interest Groups" (DSMIG), with national and international versions (DSMIG-US, and DSMIG-UK, with a fragile new international version - iDSMIG). We are moving closer to development of collaborative networks of medical Down syndrome clinics that can share data about patients like the case in this paper. The power of pooled numbers in our combined experience would speed our ability to optimise medical management for our individual patients.

We encourage clinicians to consider submission of case reports such as this article, to provide clinical reality to some of the medical topics that persistently recur in people with Down syndrome. Discussion of unique cases often helps to remind us of similarities as well as individual differences, and can put faces on the questions while we look for answers.