



Type 1 diabetes and other autoimmune disorders in Down's syndrome

Summary of a presentation by Dr Julian Shield
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Autoimmunity is very prevalent in people with Down's syndrome, but it is a much under-researched area. Type 1 diabetes is one of the manifestations of autoimmune dysregulation which is over represented. Other disorders which occur in excess are listed in Panel 1.

Panel 1: Autoimmune manifestations in Down's syndrome

- Type 1 diabetes
- Thyroid disease
- Vitiligo
- Alopecia areata
- Chronic active hepatitis
- Coeliac disease

In the general population, approximately 2 out of 1000 (0.2%) children will develop type 1 diabetes in childhood. It is generally acknowledged that for people with Down's syndrome, there is around a 10 times increased prevalence. Estimates vary and range from 0.33 to 10.6%.

Not only is the prevalence of type 1 diabetes increased in those with Down's syndrome, but the condition also develops at a younger age. In the general population very few children develop type 1 diabetes (IDDM) under one year of age. By contrast, in a recent study of 59 children with Down's syndrome and IDDM, 22% developed type 1 diabetes before two

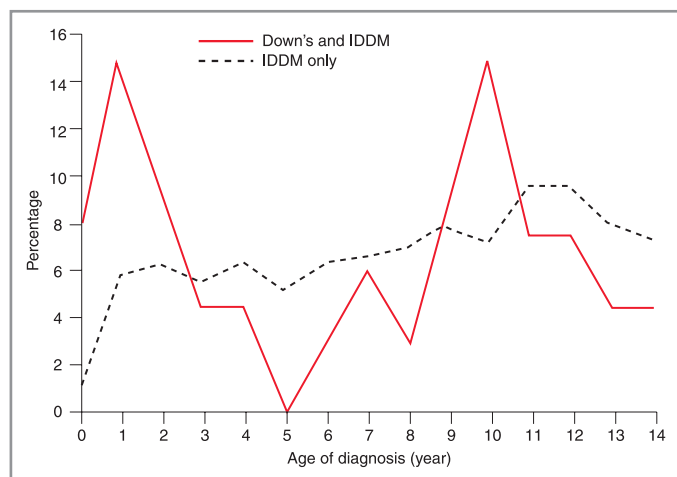


Figure 1: Variations in age of diagnosis of type 1 diabetes in children, illustrating the earlier onset in children with Down's syndrome (Arch Dis Child 1999;81:147-50, with permission from the BMJ Publishing Group).

years ($p > 0.0001$) and 15% before one year of age (Figure 1, Shield et al, 1999). This is in line with clinical experience and reports from other studies.

Clinical presentation in those with Down's syndrome is no different than in the general population other than it may be more acute and is often at a younger age. This is important as this young age group can be very difficult to treat. Younger children can have very arbitrary eating and feeding patterns. Doctors like to give insulin at certain times and may find it difficult to adapt schedules to a young child's variable eating habits.

Putative reasons for earlier onset of type 1 diabetes

- *There may be a more aggressive autoimmune condition.* When considering the range of autoimmune conditions which occur, sometimes concurrently, in people with Down's syndrome, it is possible to argue that around one-third may have a very aggressive autoimmune phenotype. In the general population, whether diabetes develops at 2 or 15 years of age, auto-antibodies will have been present from an early age, possibly from birth. If the autoimmune process is not very aggressive there will only be a gradual reduction of islet cell mass so the condition may not present clinically until around age 15 years. If however, as may be the case in Down's syndrome, there is a particularly aggressive autoimmune phenotype, islet cells will be destroyed more rapidly and the condition will present earlier.
- *The islet cell population may be more prone to cell-mediated destruction.* It is possible that in children with Down's syndrome, the islet cells are weaker and more liable to be destroyed, or they may be reduced in number and therefore any culling of islet cells by autoimmune destruction will result in an earlier manifestation.

Other autoimmune disorders

Thyroid disease

Thyroid disease is commonly screened for in people with Down's syndrome. As with type 1 diabetes, the condition is more prevalent and age at onset is earlier than in the general population. Approximately 30% of those with Down's syndrome will develop thyroid disorder, most commonly hypothyroidism, before age 25 years. Autoimmunity often underlies the



problem and about 40% of children with Down's syndrome have thyroid antibodies before age 20, thus more manifest surrogate markers of autoimmunity than have overt disease. This appears to be a recurrent theme in Down's syndrome.

Coeliac disease

The prevalence of coeliac disease in Down's syndrome is also much higher than in the general population and is particularly prevalent, though often sub-clinical, among those with diabetes. When treated with a gluten-free diet many of these children suddenly feel a lot better, and the risk of small bowel lymphoma later in life is reduced. Strong consideration should therefore be given to routine coeliac screening for those with Down's syndrome who have diabetes.

Why is autoimmune disease more prevalent among people with Down's syndrome?

There is abundant evidence of immune dysregulation in people with Down's syndrome which may make this group more predisposed to autoimmune disease. Known factors suggesting immune dysregulation in Down's syndrome include:

- Abnormal thymus development /morphology
- Altered lymphocyte sub-populations in peripheral blood and thymus with evidence of 'T' cell activation and premature ageing effects
- Increased susceptibility to infections
- Increased risk of malignancy.

How is the genetic susceptibility to autoimmune disease conferred?

There are two ways in which genetic susceptibility to autoimmune disease is conferred in Down's syndrome:

- The HLA alleles which confer genetic susceptibility to autoimmunity may be more prevalent in the Down's syndrome population.
- The three copies of chromosome 21 may cause disordered function of some genes which may be responsible for autoimmunity in general.

HLA genotypes

The prevalence of different HLA types in children with Down's syndrome was investigated in a pilot study. The HLA region which controls the immune system is found on chromosome 6. Those in the general population who develop diabetes are usually DR3/4 (one DR3 and one DR4 from their parents). The study showed that only about 30% of children with Down's syndrome and diabetes possess DR3/4 in contrast to a general population figure between 60 and 70%. This suggests that there is a different genetic factor in people with Down's syndrome that predicts whether or not they are going to develop diabetes. An interesting finding was an excess of DR4 in the children with Down's syndrome who did not have diabetes. If this is confirmed in a larger study it could be related not only to diabetes, but also to the higher prevalence of thyroid and coeliac disease.

Gene dose effects

There are several mechanisms by which the presence of an extra chromosome 21 could influence autoimmunity. One of these is the possibility of disomic homozygosity. If two identical chromosomes are inherited from the parent of origin of the trisomy this may increase the propensity to develop cer-

tain conditions. This possibility was investigated by looking at the AIRE gene on chromosome 21 which causes autoimmune polyglandular syndrome type 1 – a condition which shares many features with Down's syndrome. However no increase in disomic homozygosity was found.

Another cause could be overexpression of one of the genes on chromosome 21 – if there are three identical genes they may all be active and therefore strongly expressed. This is true of superoxide dismutase (SOD) which exhibits 150% normal activity in people with Down's syndrome as all three copies of the regulatory gene are active. If there is an autoimmune gene which is over expressed in this way in people with Down's syndrome, this may increase their likelihood of developing diabetes or other autoimmune conditions.

Potential autoimmune genes on chromosome 21

Chromosome 21 has between 500 and 800 genes. Possibly less than 20 are responsible for the major phenotypic features of the syndrome. These lie in a critical region on the distal segment of the long arm (22.3q). However, the genes for other frequently associated conditions are located outside this critical region which may explain the phenotypic variation among those with the syndrome. Panel 2 lists genes which map to chromosome 21 but outside the critical region whose overexpression may cause autoimmune disorder.

Panel 2: Potential autoimmune genes

AIRE – causes autoimmune polyglandular syndrome type 1.

Amyloid precursor protein (APP) – overexpression may lead to tissue destruction, increased tissue inflammation and organ damage.

Superoxide dismutase (SOD) – increased SOD activity in Down's syndrome, saturation of the system by excessive amounts of hydrogen peroxide causes hydroxyl ions to be formed (Fenton's reaction), resulting in organ damage.

Ligand of ICOS (LICOS) – overexpression leads to increased lymphocyte damage and cytokine production, thereby increasing the severity of organ damage.

Summary

- Autoimmunity is very prevalent in people with Down's syndrome. However, this is a much under researched area.
- Type 1 diabetes, thyroid disease and coeliac disease are just some of the autoimmune conditions which are over represented in those with Down's syndrome.
- Genetic susceptibility to autoimmune disease in Down's syndrome may be conferred by the prevalence of certain HLA types and/or gene dose effects relating to the extra copy of chromosome 21.

Further reading

Anwar AJ, et al. *Diabetic Medicine* 1998;15:160–3.

Book L, et al. *Am J Med Genet* 2001;98:70–744.

Ivarsson S A, et al. *Acta Paediatr* 1997;86:1065–1067.

Shield JP, et al. *Arch Dis Child* 1999;81:147–50.

A complete transcript of this presentation, together with references, is available at www.dsmig.org.uk.