Diabetologia (2009) 52:371–372
DOI 10.1007/s00125-008-1213-7

LETTER

Congenital rubella, diabetes and HLA

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Received: 18 September 2008 / Accepted: 14 October 2008 / Published online: 20 November 2008

Keywords Congenital rubella · HLA · Type 1 diabetes · Virus

Abbreviation
CRS Congenital rubella syndrome

To the Editor: In a recent Editorial, Edwin Gale reviewed the congenital rubella syndrome (CRS) and the postulated role of viruses in type 1 diabetes, pulling together most of the literature that links congenital rubella and diabetes [1]. He concluded that the case appears sound for type 2 diabetes, but is at most only suggestive for type 1 diabetes. However, he did not reveal the whole story, in particular, the evidence for HLA associations with diabetes in CRS.

Gale quotes Menser et al. [2] on the incidence of diabetes following CRS, but fails to mention that these investigators also reported that the HLA A1-B8 haplotype was present in 44% (eight out of 18) of their CRS participants with diabetes. HLA A1-B8 was first documented as being increased in frequency in insulin-dependent diabetes just 2 months earlier in the same journal in 1974 [3]. In the CRS participants, this haplotype was present in 75% (three out of four) who were insulin-dependent, with ages at onset of 1.5, 12, 12 and 24 years, and in 36% (five out of 14) who were on oral agents or diet alone, with ages of onset of 28–34 years. The frequency of HLA A1-B8 in the background white population is 10%. Gale states that these studies were carried out 'by authors with no special interest in diabetes', but in fact co-author J.A. Burgess was, and still is, a diabetologist.

HLA A1-B8 (-DR3-DQ2) is the classic autoimmune haplotype—associated not only with susceptibility to type 1 diabetes in the non-CRS population but also with other autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus, chronic active hepatitis and coeliac disease—and has been associated with the epidemiology of rubella [4, 5]. The CRS–diabetes–HLA association was confirmed in the New York cohort of 274 patients [6]. In this case, Gale acknowledges the high rate of insulin-requiring diabetes following the rubella epidemic of 1964–1966 in New York, but judges that 'given the interest of the investigators, the sample may have included a disproportionate number of children with diabetes', and, 'ascertainment bias may have contributed to this very high rate, which is otherwise unexplained'. In the context of a critical evaluation of the literature, these statements appear distinctly subjective. The New York data strengthened the association of CRS with type 1 diabetes, because not only was the frequency of HLA DR3 higher in the CRS patients, but also the frequency of HLA DR2, known to be protective against type 1 diabetes in non-CRS populations [7], was decreased.

Further evidence for an autoimmune mechanism in CRS-associated diabetes comes from other studies not included in the review. These demonstrated that T cell clones from both CRS and non-CRS type 1 diabetic individuals, raised in response to epitopes in the islet autoantigen glutamic acid decarboxylase, reacted to peptides from rubella virus [8]. There are several cogent reasons why CRS could have set the stage for type 2 diabetes. Babies with CRS were 'small for dates' and had a reduced beta cell mass, and may

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have had persisting rubella virus infection with reduced postnatal beta cell proliferation. Catch-up growth, resulting in a large child, or puberty with increasing body size and insulin resistance leading to a demand for insulin that exceeds supply, may then lead to type 2 diabetes. Moreover, insulin resistance is now a recognised risk factor for type 1 diabetes [9]. Therefore, in the presence of HLA susceptibility genes for type 1 diabetes, the mechanisms leading to type 2 diabetes after CRS could also promote development of type 1 diabetes. In our view, the evidence, although incomplete, indicates that CRS was associated with diabetes across the spectrum of clinical stereotypes.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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