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The co-occurrence of multiple sclerosis and type 1 diabetes: Shared aetiologic features and clinical implication for MS aetiology

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ABSTRACT

We reviewed the evidence for the co-occurrence of type 1 diabetes mellitus (T1D) and multiple sclerosis (MS), and assessed the clinical significance of this association and the shared aetiological features of the two diseases. T1D and MS contribute considerably to the burden of autoimmune diseases in young adults. The co-occurrence of MS and T1D has been reported by a number of studies, suggesting that the two conditions share one or more aetiological components. Both conditions have been associated with distinct human leukocyte antigen (HLA) haplotypes but share a number of similarities in clinical, epidemiological and immunological features, leading to suggestions of possible common mechanisms of development. While underlying genetic factors may be important for the co-occurrence of both conditions, some evidence suggests that environmental factors such as vitamin D deficiency may also modulate an individual's risk for the development of both conditions. Evidence on whether the co-occurrence of the two autoimmune conditions will affect the disease course and severity of MS is merely absent. Further studies need to be conducted to ascertain whether the neuropathology associated with T1D might influence the disease course and contribute to the severity of MS.

1. Introduction

Multiple sclerosis (MS) and type 1 diabetes mellitus (T1D) represent significant public health problems worldwide, because of their considerable contribution to medical and social management cost and eventual disability of affected individuals [1–3]. MS and T1D via diabetic neuropathy and accelerated cerebrovascular disease contribute substantially to the burden of neurologic disability [4,5] in young adults and significantly affect quality of life.

MS and T1D are considered to be organ-specific autoimmune disorders with an inflammatory component, but with marked differences in their pathogenesis and clinical manifestations [6]. While MS is predominantly associated with neurological and physical disabilities and loss of function resulting from inflammatory demyelination and neurodegeneration of the central nervous system (CNS) [7], the chronic hyperglycaemic condition characteristic of T1D results from the selective inflammatory autoimmune destruction of the pancreatic Islets of Langerhans responsible for insulin production [8]. Despite the organ specificity of these two disorders, a possible aetiologic and pathologic relationship between the two diseases has been suggested [9,10]. The framework behind the co-occurrence is unclear. While genetic predisposition appears to be involved in each of these autoimmune conditions, the low concordance among identical twins for MS and T1D and trends of increasing incidence for both diseases over time suggest that environmental factors are also important disease determinants in the occurrence of the two diseases [11].

In this review, we assessed the available data on the co-occurrence of MS and T1D, the clinical significance of T1D in patients with MS and the aetiologic similarities between these two autoimmune disorders. Understanding the similarities in aetiology and pathophysiology may help clarify causality and help in the management of both conditions.

2. Studies investigating the co-occurrence of MS and T1D

2.1. Incidence studies on the co-occurrence of MS and T1D

Table 1 summarises studies that have examined the risk of the co-occurrence of MS and T1D. A Danish population-based cohort study [9] assessed the risk of MS in individuals with T1D and the risk for T1D in first-degree relatives of MS patients. Data from the Danish Hospital Discharge Register, Danish MS Register and Danish Civil Registration System were used to identify patients with T1D (n = 6078), MS (n = 11,862) and first-degree relatives of MS patients (n = 14,771) respectively. Patients with T1D and first-degree relatives of MS patients were followed up for the occurrence of MS and T1D respectively. This work found that the expected incidence rate for MS in patients with T1D was more than three-fold higher than what was expected based on available incidence rate data in Denmark (relative risk (RR): 3.26, 95% CI: 1.80–5.88). The observed incidence rate for T1D was also higher in first-degree relatives of MS patients (RR: 1.44, 95% CI: 1.11–1.88).

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Table 1
Studies investigating the co-occurrence of MS and T1D.

Author	Study information	Outcome measure of interest	Main findings
Nielsen & colleagues [9]	Cohort study: 11,862 MS cases, 6078 T1D cases & 1st-degree relatives: 4771	1. RR of MS in T1D patients — Observed incidence rate for MS in patients with T1D compared to the expected incidence rate (based on available incidence rate data from Denmark) 2. RR of T1D in 1st degree relatives of MS patients — Observed incidence rate of T1D in 1st-degree relatives of MS patients MS compared to the expected incidence rate (based on available incidence rate data from Denmark)	1. RR for MS in T1D patients: 3.26 (95% CI: 1.80–5.88). 2. RR for T1D in 1st-degree relatives of MS patients: 1.63 (95% CI: 1.26–2.12).
Bechtold & colleagues [10]	Cohort study: 19 MS cases & 56,653 T1D cases	1. RR of MS in T1D patients — Observed prevalence rate for MS in a paediatric & adolescent T1D population compared to the expected prevalence rate (based on available prevalence data in Germany & Austria)	1. RR of MS: 3.35 (95% CI: 1.56–7.21) to 4.79 (2.01–11.39) for an observed prevalence of 7 to 10 patients per 100,000.
Marrosu & colleagues [12]	Cohort study: 1090 MS cases, 2180 parents & 3300 siblings	1. Prevalence of T1D in MS patients compared to healthy siblings of MS patients and the general population 2. Adjusted odds ratio for risk of T1D in people with MS & in their healthy siblings	1. Prevalence of T1D in MS patients (2.6%) was about 3-fold greater than that in healthy siblings of MS patients (1.0%) ($p = 0.001$) & 5-fold greater than that in the general population (0.4%) ($p < 0.001$). 2. MS patients with relatives with MS versus healthy siblings of MS patients without other relatives with the disease; OR: 6.03 (2.50–14.54). 3. Sibling with other relatives with MS versus sibling without other relatives with MS; OR: 3.41 (1.57–7.37).
Dorman & colleagues [14,90]	Case–control: 143 T1D female cases, 186 sisters & 160 controls	1. Prevalence of MS in women with T1D compared to the general population	1. 20-Fold increase in the prevalence of MS in T1D women (2%) compared with the female general population (~0.1% on average, $p = 0.003$ for difference). 2. 5-Fold increase in the prevalence of MS in non-diabetic sisters (0.5%) compared with the general population (non-significant).
Wertman & colleagues [15]	Cross-sectional: 334 MS cases & T1D in the general population in 1950	1. Prevalence of T1D in people with MS under the age of 30 years compared to that of the general population	1. PR of T1D: 94.53; $p < 0.001$.
Hussein & Reddy [16]	Cross-sectional: 1206 MS cases & T1D in the general population	1. Prevalence of T1D in people with MS compared to that of the general population	1. Prevalence of T1D: 0.92% (95% CI: 0.38–1.46); $p = 0.15$ for difference with general population. 2. 36% family history of diabetes among MS patients with T1D.

RR: relative risk; OR: odds ratio; PR: prevalence ratio; T1D: type 1 diabetes; MS: multiple sclerosis.

In summary, this study has demonstrated a higher risk of developing MS in people with T1D compared to the general population. Further to this, data on the risk of T1D in first-degree relatives of MS patients suggest an increased risk of T1D in people at higher risk of MS compared to the general population. Since there is only one study using incidence data, further studies are required to strengthen the evidence of this relationship.

2.2. Prevalence studies on the co-occurrence of MS and T1D

A number of epidemiological studies of MS and T1D co-occurrence have reported either similar or higher prevalence of T1D and MS compared to that in the general population or other comparison group. Table 1 summarises studies that have examined the prevalence of MS and T1D.

Bechtold and colleagues [10] investigated the co-occurrence of T1D and MS by estimating the relative risk for MS in a paediatric and adolescent diabetes population. Data on 56,653 patients with T1D in the Diabetes Patienten Verlaufsdokumentation (DPV) database were collected in 248 centres in Germany and Austria and published data on German and Mid-European MS prevalence were used for comparison. The relative risk for MS in the diabetes population was 3.35 (95% CI: 1.56 to 7.21) to 4.79 (95% CI: 2.01 to 11.39) based on the observed prevalence compared to the expected prevalence of 7 to 10 per 100,000 population.

Similarly, a Sardinian cohort study by Marrosu and colleagues [12] assessed the prevalence of T1D in 1090 individuals with MS and their parents ($n = 2180$) and siblings ($n = 3300$) to ascertain the risk of T1D in this cohort of MS patients. The population prevalence of T1D in the province of Oristano [13] was also used as a comparator. The prevalence of T1D in participants with MS was nearly three-fold greater than that of their healthy siblings (3.0 vs. 1.0%, $p = 0.001$) and five-times greater than that of the general population (3.0 vs. 0.5%); however, there was no difference in the T1D prevalence between MS cases and their parents (2.0 vs. 3.0%, $p = 0.23$). In multivariable analysis, the risk of T1D was six-fold higher in MS patients who had relatives with MS than in healthy siblings of MS patients without other relatives with MS (odds ratio (OR): 6.03, 95% CI: 2.50–14.54, $p > 0.001$). The presence of other relatives with MS also conferred a more than three-fold increased risk of T1D to healthy siblings of individuals with MS (OR: 3.41, 95% CI: 1.57–7.37, $p = 0.002$).

In the Familial Autoimmune and Diabetes Study by Dorman and colleagues [14], a significantly increased prevalence of MS in adults with T1D and their first-degree relatives was observed. Data on the clustering of autoimmune thyroid disease, rheumatoid arthritis and T1D were collected in a cohort of adult T1D subjects, as well as self-reported data on other autoimmune disorders. 94 non-diabetic control families were also recruited for comparison; however, no members of these families had any cases of MS. Compared with the average prevalence of MS in the female population of the USA (calculated by the authors as approximately 0.1%), the 2.0% prevalence of MS in this sample constituted a 20-fold increase in the prevalence of MS in women with T1D ($p = 0.003$). In parallel with this, the 0.5% prevalence of MS in the sisters of T1D women constituted a five-fold higher prevalence of MS compared with the