

Familial Occurrence of Multiple Sclerosis with Thyroid Disease and Systemic Lupus Erythematosus

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Abstract

Multiple sclerosis (MS) has some features which suggest it is an autoimmune disease. Autoimmune diseases frequently occur in families, and patients and families often have more than one type of autoimmune disease. However, there are few reports of MS occurring in patients or families with other autoimmune conditions. It is difficult to make a separate diagnosis of MS in a patient who has a systemic autoimmune disease such as systemic lupus erythematosus (SLE) or Sjögren's syndrome, because these diseases can affect the nervous system directly. However, it is possible to make independent diagnoses of MS and an autoimmune disease confined to another single organ in the same patient, or diagnoses of MS and SLE (or other autoimmune diseases) in different family members. Here we describe clinically definite MS in 2 sisters, one of whom had Graves' disease, and the other of whom had a daughter with SLE and with a high titre of anti-thyroid antibodies. Other female family members over 4 generations had histories of thyroid disease, MS and Addison's disease. Available family members were HLA typed. The MS patients were positive for HLA DR2. All but one of the affected family members were related to the proband on the maternal side, and all of these affected females shared an HLA haplotype. However, this haplotype was also present in unaffected individuals. Thus HLA type alone cannot account for the familial occurrence of these disorders. We conclude that, in this family, MS, like autoimmune thyroid disease and SLE, may be an autoimmune disease developing in genetically predisposed individuals.

Keywords: multiple sclerosis; genetics; autoimmunity; thyroid disease; systemic lupus erythematosus

INTRODUCTION

Multiple sclerosis (MS) has features suggesting it is an autoimmune disease possibly triggered by environmental factors. It is probable that all autoimmune diseases result from a combination of environmental factors acting on patients with a genetic predisposition and that the relative contributions of environmental and genetic factors vary from patient to patient. Genetic susceptibility to autoimmune disease appears to be complex. HLA type plays a role, as different HLA types are present in increased frequency in different diseases (Jersild 1977; Reinertsen et al. 1978; Farid 1987). However, HLA associations do not fully explain the inheritance of autoimmune diseases in families, and it is postulated that other non-HLA autosomal dominant genes are associated with susceptibility to autoimmune disease (Lippman et al. 1982; Reveille et al. 1984) and that these interact with the HLA

genes (Farid 1987). An inherited tendency to develop autoimmune phenomena would account for the observations that certain families and individuals are susceptible to more than one autoimmune disease and that the same autoantibodies may be produced in patients with different types of autoimmune disease. Genetic factors are important in MS (Ebers et al. 1986; Hartung et al. 1988; Hauser et al. 1989) but there are few reports of MS occurring in patients or families with other autoimmune disorders. Indeed, it would be difficult to sustain a diagnosis of MS in an individual who has a systemic autoimmune disease, such as systemic lupus erythematosus (SLE), which may affect the nervous system directly. However, it is possible to make independent diagnoses of MS and an autoimmune disease confined to another single organ in the same patient, or diagnosis of MS and SLE (or other autoimmune diseases) in different family members. We report here the occurrence of clinically definite MS, autoimmune thyroid disease and SLE in close relatives, and suggest that, in this family, MS may be an autoimmune disease developing in subjects with a genetic predisposition to autoimmunity.

MATERIALS AND METHODS

The proband was seen at our hospital. When the family history was recorded, we obtained consent from all available family members to ascertain clinical details and HLA typing. HLA typing was performed by the Immunology Laboratory of Princess Alexandra Hospital, Brisbane, Australia.

RESULTS

Family history

The history of this family, which is of Northern European Caucasian origin, is illustrated in Fig. 1. Autoimmune conditions affected family members over 4 generations. There were 5 patients with hyperthyroidism, 3 with MS, 1 with SLE and 1 with Addison's disease. Another patient had sarcoidosis, which is a putative autoimmune disease. The histories of 3 key patients will be described in detail. In the other cases, the diagnosis of hyperthyroidism was made on the basis of treatment with antithyroid medication or surgery, and in the case of the deceased family members, the diagnosis of MS was obtained from a history from relatives of progressive neurological deterioration in middle life and a death certificate diagnosis of MS, and that of hyperthyroidism from the family history.

Case reports

Detailed clinical histories of the proband, her sister and daughter are given below.

Patient I (V-6), the proband, was a 39-year-old woman who presented with a history that 8 years previously, in 1980, she had noticed episodes of weakness of the left leg while mowing the lawn. In 1981 she noticed thinning of the left posterior thigh and buttock. In 1985 she began to experience episodes of left foot drop which came on after walking 100 m and disappeared after standing still. In the same year she noted weakness of the left arm, and had an episode of twitching of the left face and burning of the left cheek lasting for 10 days. Since then she had experienced episodes of formication of the left face. In 1987 she noted patchy loss of vision of the right eye, associated with pain in the eye aggravated by eye movement. This visual disturbance lasted for 3 months. When questioned about symptoms of connective tissue disease, she said that since 1982 she had experienced occasional episodes of a sensation of grittiness in the right eye and dryness of the mouth. She had the sensation of grittiness in the left eye for 2 weeks prior to her presentation in November 1987. On examination, in November 1987, the cranial nerves were normal. There was mild weakness of extension of the left elbow and left fingers. There was generalized mild atrophy of the muscles of

the left lower limb. Tone was increased in the left lower limb and there was mild weakness of dorsiflexion of the left hallux and left foot. The deep tendon reflexes were increased in the left upper and lower limbs and the

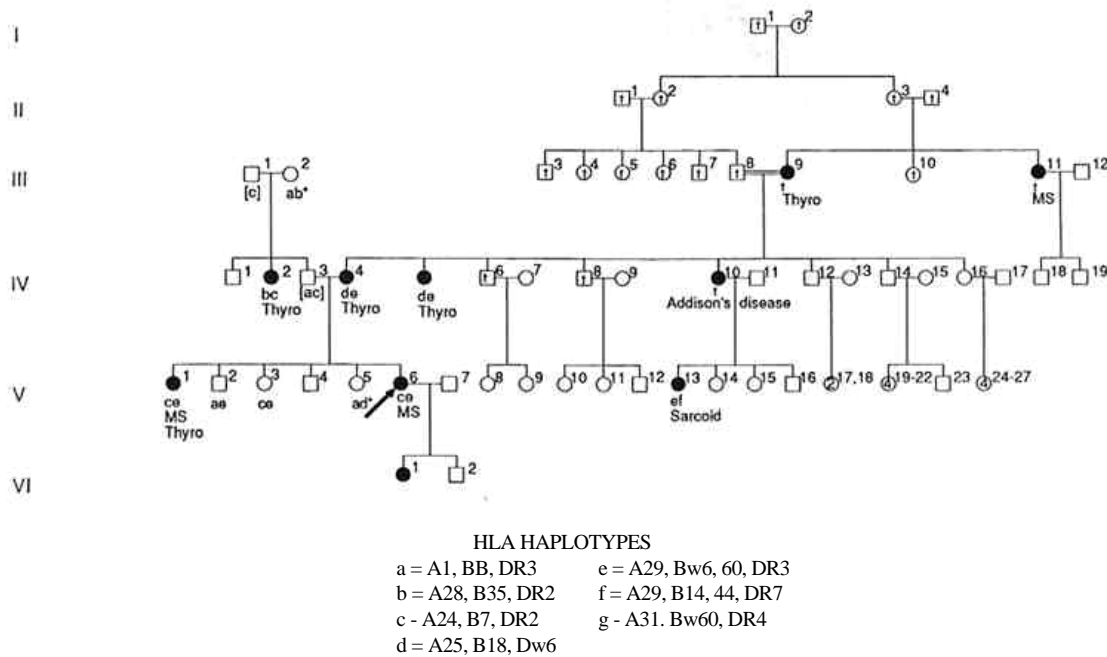


Fig. 1. Pedigree showing affected family members and HLA typing. Closed circles indicate family members with an autoimmune condition. MS = multiple sclerosis, thyro = hyperthyroidism except in the case of VI-1, who had positive anti-thyroid antibodies, SLE = systemic lupus erythematosus. [] HLA = typing was deduced from progeny. * = only HLA A and B typing was performed and HLA DR typing was deduced from pedigree information.

plantar responses were extensor. Sensory examination was normal and her gait was normal. A Schirmer's test performed at the time of symptoms of grittiness of the left eye was 3 mm after 5 min in the left eye (<5 mm is definitely abnormal) and was normal in the right eye. The Schirmer's test was normal in both eyes on two subsequent occasions. A biopsy of salivary glands from the lip was normal. The remainder of the physical examination was normal. An autoantibody screen was normal, and, in particular, antibodies to extractable nuclear antigens were not detected. The anti-cardiolipin antibody level was 2 units (normal <25). The serum C3 component of complement was 0.8 g/l (normal range (NR) 0.9-1.8 g/l). Serum C4 was normal. The ratios of C26/C22 and C24/C22 long chain fatty acids were normal. Cerebrospinal fluid (CSF) examination, including electrophoresis, was normal. Visual evoked response latencies were 100 msec and 119 msec with left and right eye stimulation respectively (NR 95-117 msec). A computerized tomographic (CT) brain scan was normal but a magnetic resonance imaging (MRI) scan (Fig. 2) showed multiple regions of increased signal intensity in the periventricular regions and deep cerebral white matter. A myelogram, performed at the onset of symptoms, was normal.

Patient 2 (V-1), the sister of the proband, first presented in 1976 at the age of 23 years with a history of ataxia for 6 months and diplopia on looking to the right for 4 weeks. In 1976, examination revealed a right sixth nerve palsy and left sided hyperreflexia. Optic fundi and visual acuity were normal. Investigations including a right carotid angiogram, autoantibody screen and EEG were normal. CSF examination revealed 1 leucocyte/ml, a protein concentration of 430 mg/l and IgG level of 80 mg/I (normal 10-50 mg/I). In 1976 the IgG/albumin ratio was 0.42 (normal <0.25). A serum electrophoretogram and gamma-globulin level were normal. Her sixth nerve palsy resolved after several weeks. In 1977 she had an episode of right optic neuritis. At this time she was noted to have bilateral extensor plantar responses and absent lower abdominal superficial reflexes. In 1983 after the birth of her second child she became aware of feeling tilted to the right and also noticed stiffness of the left leg, leading to a fall. These symptoms had persisted since then. Six months later she developed Graves' disease with symptoms of hyperthyroidism, which resolved after treatment with carbimazole. In 1987 the symptoms of hyperthyroidism reappeared and again responded to treatment. She had a third episode of hyperthyroidism in 1988 at which time she had a pulse rate of 100/min and a fine tremor of her outstretched hands. There was a small, soft goitre. Cranial nerve examination was normal. The upper limbs were normal. In the left lower limb there were increased tone, weakness, brisk reflexes and an extensor plantar response. In both lower limbs there was reduction in vibration and joint position sense.

The gait was ataxic, and Romberg's sign was positive. Serum electrolytes, urea, creatinine and liver function tests, hemoglobin, leucocyte count, platelet count and serum vitamin B₁₂ and folate levels were normal. An autoantibody screen including thyroid antibodies was negative. Serum thyroxine was 200 nmol/l (NR 64-160). TSH was <0.1 mU/l (NR 0.2-4.0). The ratios of C26/C22 and C24/C22 long chain fatty acids were normal. Visual evoked response latencies were 136 and 144 msec with left and right eye stimulation, respectively (NR 95-117 msec). A CT brain scan was normal, but the MRI scan showed multiple regions of increased signal intensity in the periventricular regions and deep cerebral white matter (Fig. 2).

Patient 3 (VI-1), the daughter of the proband, was 21 years old and had a history of SLE manifested by polyarthritis, Raynaud's phenomenon, butterfly rash, headaches associated with episodes of visual loss in the temporal field of the left eye, elevated antinuclear antibody titre (1:640), elevated antidouble-stranded-DNA antibodies (> 90), elevated antibodies to extractable nuclear antigens, elevated anticardiolipin antibodies (48 units; NR <20), elevated circulating immune complexes, low serum C3 and C4 components of complement and nephrotic syndrome with 4700 mg/day of proteinuria. She was euthyroid but the thyroid microsomal antibody titre was 1: 6400.

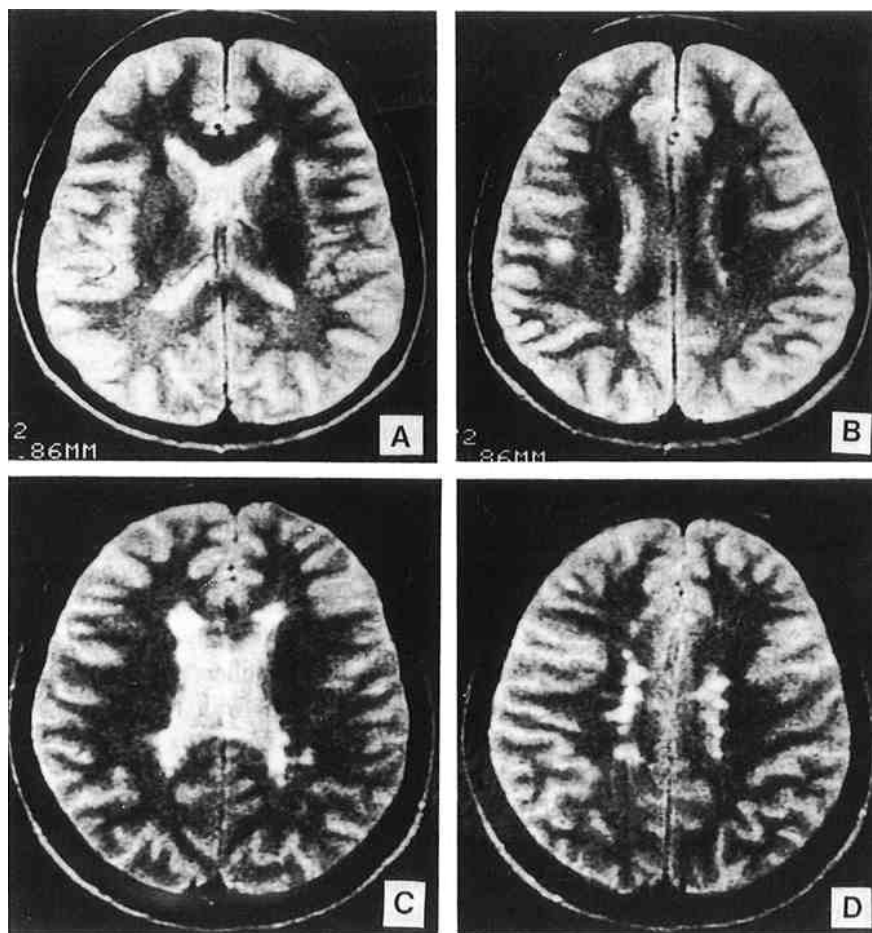


Fig. 2. T2 weighted MRI brain scans. (A, B) Scans from patient 1 showing areas of increased signal intensity in the periventricular regions and deep cerebral white matter. (C, D) Scans from patient 2 showing multiple regions of increased signal intensity in the periventricular regions and deep cerebral white matter.

HLA typing

The HLA types of all available family members are shown in Fig. 1. With the exception of Case III-2, who is related to the proband on the paternal side, all affected patients had the haplotype A29, BW6, 60, DR3. However, this haplotype was also detected in 2 unaffected siblings of the proband. The 2 sisters with MS, but none of the other affected

maternal relatives who were tested, were positive for HLA DR2. The HLA DR2 was inherited from the paternal side by the proband and her sister.

DISCUSSION

We have presented the histories of 2 sisters with clinically definite MS, one of whom had a history of Graves' disease which is an autoimmune thyroid disease (Farid 1987) and the other of whom had a daughter with SLE and with a high titre of anti-thyroid antibodies. The 2 patients with MS fulfilled the positive criteria of Poser et al. (1983) for clinically definite MS although, as with all cases diagnosed solely on clinical criteria, the underlying neuropathology is unknown. These patients were Caucasian, of Northern European origin, and lived in Queensland where the prevalence of MS is 18.3 per 100000 (Hammond et al. 1987). There are no local data on the prevalence of SLE but in standard textbooks the prevalence is 15-50 per 100000 (Hahn 1989). The prevalence of thyroid antibodies in a population in another state of Australia is 9.8% (Hawkins et al. 1980). In one MS case (patient 1) the occurrence of dry eyes and dry mouth raised the possibility that Sjögren's syndrome (SS) may have been present. However, a lip biopsy was normal and a Schirmer's test was abnormal on only 1 of 3 occasions, so that a diagnosis of SS was not confirmed. In the other MS case (patient 2) there was no evidence of a connective tissue disorder but the patient had hyperthyroidism. Although there are reports of reversible pyramidal signs developing in patients with hyperthyroidism (Mussio-Fournier et al. 1959) it seems unlikely that patient 2 developed spinal cord disease through a direct action of thyroid hormones, because the onset of neurological signs occurred when there was no evidence of thyroid disease. The patient with SLE met the criteria of the American Rheumatism Association for the diagnosis of SLE (Tan et al. 1982). In the extended family there was a history of other autoimmune diseases affecting female family members over 4 generations. There were patients with thyroid disease, another patient with MS, a patient with Addison's disease and one with sarcoidosis. Thus MS is occurring in a family with a predisposition to acknowledged autoimmune disease.

There have been occasional reports suggesting an association between MS and thyroid disease in the same patient. Thyroid antimicrosomal antibodies have been found in 13.5 % of sera from euthyroid MS patients compared with 4.5 % of controls (Kiesling and Pflughaupt 1980), and clinically evident autoimmune thyroid disease was detected in 1% of 326 MS patients (Baker et al. 1972). As mentioned above, there is difficulty in making a clinical diagnosis of MS and SLE or MS and SS in the same patient, because it has been suggested that SLE and primary SS can cause disorders mimicking MS (Fulford et al. 1972; Alexander et al. 1986; Pender and Chalk 1989). In the present family such difficulties did not arise because the disorders were present in different patients. Our patient with SLE had a mother and aunt with MS and relatives with thyroid disease. This is similar to the reports of SLE in one twin and MS in the other (Holmes et al. 1967), of MS and SLE in 2 generations of the same family (Sloan et al. 1987), of 2 kindreds with different members with SS, MS, thyroid disease and elevated antinuclear antibody titres (Reveille et al. 1984), and of a large kindred with different members with diabetes mellitus, thyroid disease, multiple sclerosis and other diseases (Jaworski et al. 1988).

Genetic factors are important in the development of MS, thyroid disease and SLE. These disorders may be familial and there is evidence that this is at least partly due to genetic as opposed to environmental factors (Ebers et al. 1986; Farid 1987; Arnett and Shulman 1976; Hartung et al. 1988). Furthermore, genetic factors are implicated in the

development of non-familial forms of these diseases because of findings of HLA associations. MS is associated with HLA DR2 (Jersild 1977). Hauser et al. (1989) suggested that the HLA DR2 association is stronger in non-familial MS than in familial MS although all of the patients with familial MS described by Hartung et al. (1988) were HLA DR2 positive. Graves' disease is associated with HLA DR3 (Farid 1987) and SLE with HLA DR2 and DR3 (Reinertsen et al. 1978). In the present family the presence of the HLA DR2 and DR3 antigens could be a factor predisposing to the development of the associated diseases. The proband and her sister with MS had identical HLA types and were both positive for HLA DR2 and DR3. The HLA DR2 marker was inherited from the paternal side. The two sisters with MS had the haplotype A29, BW6, 60, DR3 which was inherited from the maternal side and was present in all maternal relatives with autoimmune disease that were tested. However, 2 unaffected siblings of the proband also had the A29, BW6, 60, DR3 haplotype indicating that other factors may be involved in the development of autoimmune disease. It is clear that HLA DR inheritance does not fully explain the genetics of autoimmune diseases, as in the general population the presence of the HLA associated antigens is neither necessary nor sufficient for the development of autoimmune disease. Large studies of haplotype sharing in families with different autoimmune diseases, where the effects of HLA inheritance can be more fully examined, suggest that non-HLA genes are also involved in the inheritance of such diseases in families (Farid 1987; Lippman et al. 1982; Reveille et al. 1984; Sanders et al. 1985). In the present family the pattern of disease occurrence is consistent with autosomal dominant inheritance of predisposition to autoimmunity, although the diseases were only manifest in females and it seems possible that the presence of HLA DR2 had some additional role in influencing the type of disease which developed. One possible abnormality which could predispose to autoimmunity would be an inherited defect in immunoregulation. MS, thyroid disease and SLE have each been associated with non-specific disturbances in immunoregulation (Hafler et al. 1985 ; Davies and Platzer 1986; Morimoto et al. 1987). The non-specific nature of these defects would mean that various autoimmune conditions could develop and would imply that additional factors must determine which disease occurs in an individual. It can be argued that non-specific abnormalities of immune function could be secondary to the underlying disease, but, in SLE and Sjögren's syndrome, immune abnormalities have been found in unaffected family members (Miller and Schwartz 1979; Jabs et al. 1986), indicating that such defects may be inherited, could exist prior to the development of autoimmune disease, and could be primary rather than secondary changes.

In conclusion, we have reported the occurrence of MS in a family with acknowledged autoimmune diseases, namely autoimmune thyroid disease and SLE. This suggests that, at least in this family, MS may also be an autoimmune disease developing in subjects with a genetic predisposition to autoimmunity. It is of interest that the observation of an association of myasthenia gravis with other autoimmune conditions was one of the arguments used by Simpson to support the hypothesis that myasthenia gravis was of autoimmune etiology (Simpson 1960). However, the association of MS with acknowledged autoimmune diseases is infrequently observed. There are a small number of previous reports of an association between MS and thyroid disease, and of MS and SLE as reviewed above, but this is the first report of the occurrence of all 3 in such close relatives. An association between MS and inflammatory bowel disease in different family members and sometimes in the same individual has been reported by Sadovnick et al. (1989) who similarly suggested that there may be a general pre-disposition to autoimmunity in these families. The infrequency of association between MS and acknowledged autoimmune diseases may be because the autoimmune diseases are present in family members rather than in the patient with MS,

because the associated autoimmune disease is subclinical (for example, manifest only by elevated thyroid antimicrosomal antibodies as reported by Kiessling and Pflughaupt (1980)), because MS may be associated weakly with a variety of different autoimmune diseases rather than associated strongly with one particular disease, or because the other diseases do not occur simultaneously with MS (as with our Case 2). We suggest that the association between MS and acknowledged autoimmune diseases should be further defined and that advances in the understanding of autoimmune diseases could be profitably applied to the study of MS.

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