Journal of Autoimmunity 34 (2010) J307–J313

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

The epidemiology of Graves' disease: Evidence of a genetic and an environmental contribution

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Keywords:
Familial risk
Sibling risk
Heritability
Major diseases
Disease genes
Genome scan

A B S T R A C T

Previous family and twin studies have indicated that Graves' disease has a heritable component. Family studies have also shown that some autoimmune disease cluster in families and genetic studies have been able to show shared susceptibility genes. In the present nation-wide study we describe familial risk for Graves' disease among parents and offspring, singleton siblings, twins and spouses with regard to age of onset, gender and number and type of affected family members. Additionally familial association of Graves' disease with any of 33 other autoimmune and related conditions was analyzed. The Swedish Multigeneration Register on 0–75-year-old subjects was linked to the Hospital Discharge Register from years 1987–2007. Standardized incidence ratios (SIRs) were calculated for individuals whose relatives were hospitalized for Graves' disease compared to those whose relatives were unaffected. The total number of hospitalized Graves' patients was 15,743. Offspring with an affected family member constituted 3.6% of all patients among offspring. The familial SIR was 5.04 for individuals whose sibling was affected but it increased to 310 when two or more siblings were affected; the SIR in twins was 16.45. Familial risks were higher for males than for females. The SIR was increased to 6.22 or 30.20 when parental age was limited to 50 or 20 years, respectively. Graves' disease associated with 19 other autoimmune and related conditions, including Addison's disease, type 1 diabetes mellitus, Hashimoto/hypothyroidism, pernicious anemia, polymyositis/dermatomyositis, myasthenia gravis, discoid lupus erythematosus and localized scleroderma. Remarkably, there was a high disease concordance of 2.75 between spouses. The clustering between spouses suggests environmental effects on Graves' disease which may contribute to the observed gender effects. The demonstrated high risks should be considered in clinical counseling and in prevention plans.

1. Introduction

Thyroid hormones stimulate the basal metabolic rate through regulation of carbohydrate and lipid metabolism. The thyroid gland synthesizes thyroid hormones in response to thyroid stimulating hormone (TSH or thyrotropin) which binds to its receptor TSHR on thyroid follicular cells. Thyroid hormones stimulate the basal metabolic rate through regulation of carbohydrate and lipid metabolism. Graves' disease is an autoimmune disorder in which antibodies towards TSHR cause a hyperfunction of the tissue [1]. Graves' disease is a common cause of hyperthyroidism or thyrotoxicosis with an annual incidence of 30/100,000 according to Swedish studies [2,3]. The prevalence of Graves disease is related to iodine intake, rather small changes of which may influence the prevalence [4]. Graves disease is more common in women than in men with a peak incidence at 30–60 years [2,3].

Graves' disease is thought to be caused by environmental triggers, such as psychosocial stress, smoking and immune modulators, in genetically susceptible individuals, as shown by a higher disease concordance in monozygotic than dizygotic twins [5–8]. The high risk in women at the reproductive age suggests some risk factors related to female sex hormone but no clear explanations have been found. Familial risks between siblings have been estimated to range from 5 to 12 but the studies are either old or small [5,9]. Graves' and Hashimoto's diseases are often associated with other autoimmune diseases such as systemic lupus erythematosus, Addison's disease and autoimmune polyendocrine syndrome [7,8,10,11]. Several disease susceptibility loci have been identified for Graves' disease,

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doi:10.1016/j.jaut.2009.11.019

including the HLA locus, CTLA-4, CD40, PTPN22, TSH and TSHR [7,8,12,13]. Some of these are shared with other autoimmune diseases.

The availability of a Multigeneration Register in Sweden provides a reliable access to families throughout the last century. This Register has been extensively used to study hospitalized diseases through linkage to the Hospital Discharge Register, including familial autoimmune diseases [14–19]. In the present article we study familial risks for Graves' disease among parents and offspring, singleton siblings, twins and spouses. Both concordant and discordant associations are studied with any of the other 33 autoimmune and related diseases. These 33 diseases were autoimmune, inflammatory and related conditions, selected because of etiological hypothesis or previous association studies. Because many autoimmune diseases show marked gender preferences in prevalence, sex-specific familial risks were also analyzed [20]. With a total patient population of 431,763, of whom 15,743 were diagnosed with Graves' disease, this is the largest family study published on these diseases; the associations of Graves' disease and many of the discordant diseases have never been reported before. The advantage of the present study is that all the results emanate from a single population of medically confirmed cases in a country of high medical standard and reasonably uniform diagnostics.

2. Methods

A thyroid research database was constructed by linking several national Swedish registers, based on the MigMed 2 datasets at Center for Primary Health Care Research, Malmö, Lund University. Statistics Sweden provided the Multigeneration Register where persons born in Sweden in 1932 and later (second generation) were linked to their parents (first generation), registered shortly after birth. Families could be defined by linking all the children to their parents. Sibships can only be defined for the second generation. Linkages were carried out to national census data, in order to obtain individual socioeconomic status. The final links were made by adding individual data from the Swedish Hospital Discharge Register that records data on all discharges after a minimal stay of one night with dates of hospitalization and diagnoses since the 1964 with a complete nation-wide coverage since 1986. A flowchart of the linkages has been published elsewhere [21]. All linkages were performed by the use of the individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each person in order to provide anonymity. The serial number was used to check that each individual was only entered once, for his or her first appearance with a defined diagnosis. Over 11.8 million individuals in 3.9 million families were included in this database; 8.9 million individuals belonged to the second generation which had reached age 75 years at the end of the follow-up, which spanned from 1987 to 2007 [22].

SIRs were calculated for concordant (same) or discordant (different) autoimmune disease, compared with men and women whose relatives were not affected by these conditions. Patients diagnosed with Graves' disease were retrieved from hospital discharges reported according to different versions of the International Classification of Diseases (ICD). Graves' disease was selected by code 242.0 'thyrotoxicosis with toxic diffuse goiter' in the 9th (1987–1996) and by code E05.0 'thyrotoxicosis with diffuse goiter' in the 10th (1997–2007) version. The individual variables controlled for in the analysis include gender (when not specifically analyzed), age at diagnosis (categorized in 5 year intervals), socioeconomic status (six groups: farmers, unskilled/skilled workers, white collar workers, professionals, self-employed and all others) and region (three groups: large cities, Stockholm, Gothenburg and Malmo, Southern Sweden and Northern Sweden), the latter allowing adjustment for regional differences in hospitalization. Person-years were calculated from start of follow-up on January 1, 1987 until hospitalization/diagnosis of disease, death, emigration, or closing date, December 31, 2007. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated for familial risks as the ratio of observed (O) to expected (E) number of cases. The expected number of cases was calculated for age, sex, period, region and socioeconomic status-specific standard incidence rates for those whose relatives were not hospitalized for Graves' disease or other defined autoimmune desease [23]. By this procedure all siblings in families of two or more affected sibling contribute cases and they are compared to single case families using the described person-year calculation. In rare families where more than two siblings were affected, each was counted as an individual patient. Separate familial risks were calculated for offspring whose parents were affected (sibling not affected), for siblings (parents not affected) and for offspring whose parents and at least another sibling were affected. Genetic modes of inheritance were search by using these three types of probands.

In the present results an estimate of the degree of environmental contribution to the familial risk is given by risks between spouses. Spouses were defined for the population older than 25

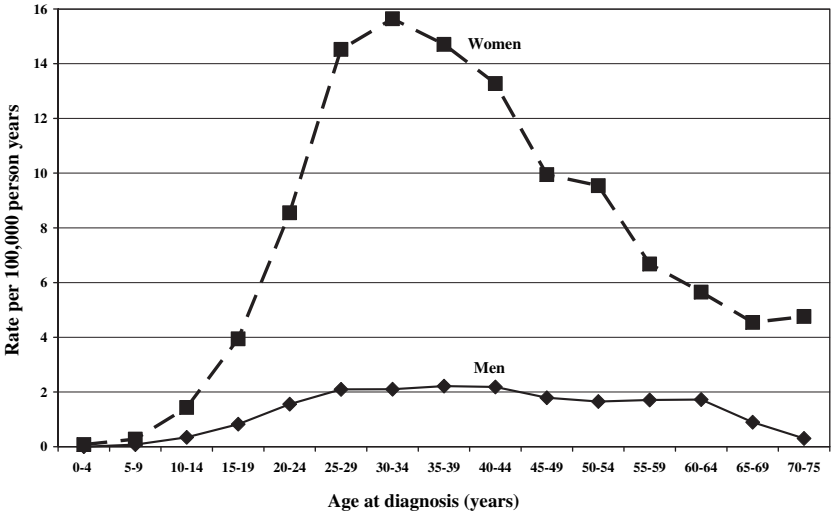

Fig. 1. Age-specific hospitalizations of Graves' disease in men and women.