

FULL-LENGTH RESEARCH PAPER

Associations between Klinefelter's syndrome and autoimmune diseases: English national record linkage studies

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Abstract

There are reports suggesting that people with Klinefelter's syndrome (KS) may be at increased risk of some autoimmune diseases, but the evidence is not substantial. We wanted to add to the evidence by systematically assessing the risk of autoimmune diseases in a national cohort of people with KS. We selected records of all people with KS in a record-linked dataset of all hospital day cases and inpatient admissions in England, 1999–2011; and we followed them up by electronic record linkage to identify the occurrence of autoimmune diseases. We compared their occurrence in the KS cohort with a control cohort, studied in the same way, and expressed the results as rate ratios (RR). Of 30 autoimmune diseases studied in people with KS, there were significantly increased risks of seven—Addison's disease (RR 11.7, 95% confidence interval 2.4–34.4), diabetes mellitus type 1 (6.1, 4.4–8.3), multiple sclerosis (4.3, 1.2–11.0), acquired hypothyroidism (2.7, 1.8–4.0), rheumatoid arthritis (3.3, 2.0–5.2), Sjogren's syndrome (19.3, 4.0–57.0) and systemic lupus erythematosus (18.1, 2.2–65.6). We concluded that people with KS have increased risk of some autoimmune diseases, particularly those that are female-predominant. The increased risk of autoimmune diseases associated with the XXY karyotype may hold clues to the pathogenesis of some aspects of autoimmunity.

Keywords

Autoimmune diseases, chromosomal disorder, Klinefelter's syndrome, record linkage, X chromosome

History

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Introduction

Autoimmune diseases affect about 5 in 100 people and tend to be more common in women than men [1], although the sex ratio varies according to the specific disease. The mechanisms behind the gender difference in autoimmune diseases are unclear. They could include effects determined by genes located on the sex chromosomes, effects mediated through sex hormones, acquired characteristics that are more common in women than men or a combination of these [2–5]. A number of genes that regulate the function of the immune system are located on the X chromosome [4,6,7]. It is therefore possible that the X chromosome might be responsible for some of the observed differences between women (chromosomes XX) and men (XY) in risks of autoimmune diseases. It is also possible that disorders affecting the X chromosome might alter the risk of autoimmune diseases. We have recently reported an elevated risk of several such diseases in people with Turner syndrome (which is typically XO or monosomy X) [8]. Here, we report on a study that aimed to determine the risk of autoimmune diseases associated with Klinefelter's syndrome

(KS) which is a chromosomal disorder, affecting males, in which the subject has an extra X chromosome (i.e. XXY).

The birth prevalence of KS is about 150 per 100 000 males [9,10]. Although most of the genes located on the extra X chromosome undergo inactivation, some do not, and this results in the development of the specific clinical features of KS which include hypogonadism, infertility and other symptoms. It is possible that the genes on the additional X chromosome which have escaped inactivation in men with KS might increase their risk of some autoimmune diseases. There are case reports suggesting that some autoimmune diseases may be more common in people with KS than in others [11], but evidence is sparse.

We hypothesised that men with KS might have an increased risk of autoimmune diseases, particularly those with female-predominance. To test this, we analysed a dataset of routine statistical extracts from hospital medical records to assess the risk, systematically, of a wide range of autoimmune diseases in a cohort comprising all people admitted to hospital with KS in England from 1999 to 2011.

Methods

Dataset

We used a national linked dataset of Hospital Episode Statistics (HES) and mortality data to identify records of people with KS. HES is an administrative dataset extracted

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from hospital discharge records (similar to hospital discharge statistical systems in many other developed countries). It includes records of all hospital discharges, including day cases (people admitted to hospital who do not stay overnight), from all National Health Service (NHS) hospitals in England. A team at the Oxford University Unit of Health-Care Epidemiology (UHCE), in which the authors work, have built a multi-purpose all-England linked dataset of HES from 1999 to 2011. The dataset contains successive episodes of hospital care for each person, linked together, and the HES records are also linked to death registration records. The HES data were supplied to the UHCE by the Health and Social Care Information Centre. The mortality data were supplied by the Office for National Statistics. The data items used for record linkage, which were supplied to the UHCE in encrypted form, were the NHS number (unique for each individual) and the person's date of birth, sex and postcode.

Selection of records

We constructed a cohort of all people with a HES record with the code for KS (Q 98 in the 10th revision of the International Classification of Diseases), with date of entry to the cohort defined as the date of the first recorded day case or inpatient admission with KS. This cohort was compared with a male-only cohort of people with a wide range of other, mainly minor, medical and surgical conditions (see footnote, Table 1), indexed for cohort entry by date of first record of a control condition. The KS and control cohorts were

Table 1. Risk of autoimmune diseases in patients with Klinefelter's syndrome: number of observed cases of each condition in the KS cohort, and the standardised risk ratios^a comparing the KS cohort with the control cohort^b, with 95% confidence intervals.

Autoimmune conditions	No. of observed cases	RR ^b (95%CI)
Addison's disease	3	11.7 (2.4–34.4)
Diabetes mellitus type 1	41	6.1 (4.4–8.3)
Multiple sclerosis	4	4.3 (1.2–11.0)
Autoimmune hypothyroidism	25	2.7 (1.8–4.0)
Psoriasis	4	1.1 (0.3–2.7)
Rheumatoid arthritis	18	3.3 (2.0–5.2)
Sjogren's syndrome	3	19.3 (4.0–57.0)
Systemic lupus erythematosus	2	18.1 (2.2–65.6)
Ulcerative colitis	5	1.1 (0.3–2.4)
Coeliac disease	4	3.0 (0.8–7.8)

^aStandardised for age group (in 5 year intervals), calendar year of admission (in single years), Government Office region of residence, and quintile of the Index of Multiple Deprivation.

^bConditions used in control cohort, with Office of Population, Censuses and Surveys (OPCS) code edition 4 for operations and ICD10 code for diagnosis: appendectomy (OPCS4 H01–H03), adenoidectomy (E20), dilation and curettage (Q10–Q11), hip replacement (W37–W39), knee replacement (W40–W42), squint (ICD10 H49–H51), cataract (H25), otitis (H60–H67), sebaceous cyst (L72.1), upper respiratory tract infections (J00–J06), varicose veins (I83), haemorrhoids (I84), deflected septum, nasal polyp (J33 + J34.2), impacted tooth and other disorders of teeth (K00–K03), hernia (K40), head injury (S06), ingrowing nail, toenail and other diseases of nail (L60), contraceptive management (Z30), internal derangement of knee (M23), bunion (727.1), dislocations, sprains and strains (S03, S13, S23, S33, S43, S53, S63, S73, S83 and S93), selected limb fractures (S42, S52, S62, S82 and S92), superficial injury and contusion (S00, S10, S20, S30, S40, S50, S60, S70, S80 and S90).

followed-up by record linkage to identify subsequent admissions for the autoimmune diseases. We analysed the same list of 29 autoimmune conditions that are included in our recent paper on Turner syndrome and autoimmune diseases [8]. We added one more condition, mixed connective tissue disease (MCTD), since we became aware of a case report suggesting its increased risk in men with KS [11].

Statistical methods

Analysis of each of the 30 autoimmune diseases was treated as a separate cohort study. Accordingly, the finding for each individual autoimmune disease is independent of the findings for others. We describe the method using KS and systemic lupus erythematosus (SLE) as the example (KS and each of the other autoimmune diseases were analysed in the same way). Analysis was based on person-days at risk, with censoring in each cohort at first record of the autoimmune disease, death or end of the data collection (31 December 2011). To calculate the rate ratio, first, we combined the KS cohort and control cohort to create a standard population. We divided the standard population into strata by age group (in 5 years), calendar year of first recorded admission for KS or control cohort condition, geographical region (9 Government Office regions of residence) and socio-economic status (quintile of the Index of Multiple Deprivation, a standard measure used in England). We calculated stratum-specific rates of SLE in the standard population; and applied these rates to the number of people in each equivalent stratum in, first, the KS cohort and, second, the control cohort. This gave the 'expected' numbers of cases of SLE in each stratum in each cohort. We then summed the stratum-specific expected numbers in each cohort to give the all-strata total expected number in the KS cohort and in the control cohort. We compared the expected number with the observed number in each cohort. The rate ratio for SLE, comparing the KS and control cohort, was calculated using the formula $(O^{KS}/E^{KS})/(O^{control}/E^{control})$, where the O's and E's are the observed and expected numbers of people hospitalised with SLE in, respectively, the KS and the control cohort. The analysis included patients with KS and SLE (and the other autoimmune diseases) recorded in any diagnostic position. The methods, including study design, description of the control cohort, and the calculation of the RRs and confidence intervals, with continuity corrections for small numbers, are described in greater detail elsewhere [12].

Results

There were 2208 men with a hospital record of KS and almost 5 million men in the control cohort. Table 1 shows the results of associations where there were three or more men with the autoimmune disease in the KS cohort or fewer men and a statistically significant finding. Of the 30 autoimmune diseases studied, there were elevated risks for 7 of them: Addison's disease, diabetes mellitus type 1, multiple sclerosis, acquired hypothyroidism, rheumatoid arthritis, Sjogren's syndrome and SLE (Table 1). There were three or more observed cases, but no significant elevation of risk, for coeliac disease, ulcerative colitis and psoriasis. There were fewer than three observed cases, and no statistically significant findings,

for ankylosing spondylitis (1 case), alopecia areata (no cases), autoimmune haemolytic anaemia (1), chronic active hepatitis (0), Crohn's disease (1), dermatomyositis (0), Goodpasture's syndrome (0), Hashimoto thyroiditis (0), idiopathic thrombocytopenic purpura (2), myasthenia gravis (0), pemphigus and pemphigoid (0), pernicious anaemia (1), polyarthritis nodosa (0), primary biliary cirrhosis (0), scleroderma (1), thyrotoxicosis (2), Dupuytren contracture (0), vitiligo (0), halo nevus (0) and mixed connective tissue disease (0).

Discussion

Main findings and comparisons with other studies

We found a significantly increased risk of seven autoimmune conditions. Consistent with our findings, there are published reports of an increased risk associated with KS for four of these seven, namely, for diabetes mellitus, rheumatoid arthritis, Sjogren's syndrome and SLE [13–18]. This adds face validity to our study. We are the first to report, as far as we are aware, on an increased risk associated with Addison's disease, acquired hypothyroidism and multiple sclerosis.

We found a high risk of SLE in patients with KS, as have others [16–18]. People with KS have been reported to have an increased risk of abnormal glucose metabolism [13,18]. We reported on a six-fold elevation of risk of diabetes associated with KS. These findings are consistent with an elevated risk of diabetes mellitus type 1 among men with KS in a Danish study [13]; and with a study of mortality in people with KS in England which reported a standardised mortality ratio for diabetes of 5.8 (3.4–9.3) [19]. A high risk of hypothyroidism among KS patients was suggested in the Danish study [13], but this did not reach statistical significance. However, the number of cases in the Danish study was small: it had 6 cases, compared with the 25 in our study, and our finding of elevated risk of hypothyroidism was significant. Furthermore, laboratory studies have shown high levels of autoantibodies to the thyroid gland among people with KS [20]. This suggests that our finding of increased risk of autoimmune hypothyroidism has some established pathophysiological basis. A review paper suggested elevated risks of rheumatoid arthritis and Sjogren's syndrome, consistent with our findings, and of psoriasis and MCTD which we did not find [14]. Clinical remission of Sjogren's syndrome and SLE in patients with KS after a course of testosterone therapy has been reported [21].

The diseases with increased risk are mainly female-predominant autoimmune conditions [3,4], including multiple sclerosis, acquired hypothyroidism, rheumatoid arthritis, Sjogren's syndrome and SLE. We did not find evidence of increases in risk of autoimmune diseases that predominantly occur in men, such as ankylosing spondylitis and Goodpasture's syndrome. Given that men with KS have an extra X chromosome, these findings are important in the context of recent evidence that abnormalities of the X chromosome might have a pathogenetic role in autoimmunity [6,7].

We have reported an elevated risk of some autoimmune diseases associated with Turner syndrome which is another disorder of the X chromosome [8]. Although KS and Turner syndrome result from different types of chromosomal

abnormalities – one develops as a result of an additional X-chromosome, while the other is an X monosomy – both have been reported to be associated with an increased risk of some autoimmune disorders [5]. Autoantibodies are more frequently detected in patients with Turner syndrome than in the general population [22–25]. Our findings add to the growing evidence in support of an important role of the X chromosome in autoimmunity.

Strengths and limitations

Strengths of the study include the fact that it is a national study covering a population of about 55 million. We were able to study a wide range of autoimmune diseases in the same population using the same methods and the same large dataset of routine medical statistics. Nonetheless, an unavoidable limitation is that KS and many of the autoimmune diseases are uncommon, and observed numbers of cases for many combinations were small (see “Results” section). Other weaknesses are that we lack data on potential confounders and information on the type of X chromosome defects.

We made multiple comparisons and therefore need to consider the play of chance even with significant findings. We studied 30 autoimmune diseases. The threshold for statistical significance of estimated RR was $p \geq 0.05$. Although this level of significance is widely accepted, in statistical terms $p \geq 0.05$ means that 1 in 20 observations might occur by chance alone. Thus, in this study one might expect significant associations with one or two autoimmune diseases out of 30 by chance. We found statistically significant increased rates for seven, even though, for many diseases, statistical power was low. It is possible that our study lacked statistical power to detect any real increase in risk in some of the conditions that did not show significant findings.

The fact that the study only includes hospitalised patients is a limitation. The results represent what was found in a very large, linked, routinely collected administrative dataset. The use of big datasets of routinely collected electronic clinical data can be an efficient way of studying the co-existence of rare diseases. However, our findings and their interpretation should be regarded as suggestive rather than definitive. Further work is needed, in different study designs, to confirm or refute the findings. Alternative epidemiological study designs – such as case-control studies, e.g. interviewing patients with KS and controls about the co-existence of immune-mediated diseases, or prospective cohort studies to identify risk of autoimmune diseases – would be very substantial undertakings. Further research should look at KS and individual autoimmune diseases in greater depth aiming to understand mechanisms behind any association.

Conclusions

We conclude that, in our study, men with KS had an increased risk of some autoimmune diseases. If confirmed, doctors caring for patients with KS should be aware of the increased risk of autoimmune conditions in them. It may also be important for clinicians to check for chromosomal abnormalities in men who present with female-predominant autoimmune conditions.

Declaration of interest

Authors have no conflict of interest to declare.

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