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Prognosis of Good syndrome: mortality and morbidity of thymoma associated immunodeficiency in perspective

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ABSTRACT

Good syndrome (GS) or thymoma-associated immunodeficiency, is a rare condition that has only been studied in retrospective case series. General consensus was that GS has a worse prognosis than other humoral immunodeficiencies. In this study, physicians of GS patients completed two questionnaires with a two year interval with data on 47 patients, 499 patient years in total. Results on epidemiology, disease characteristics, and outcome are presented. Mean age at diagnosis was 60 years and median follow-up from onset of symptoms was 9 years. There was a high frequency of respiratory tract infections due to encapsulated bacteria. Median survival was 14 years. Survival was reduced compared to age-matched population controls (5-year survival: 82% versus 95%, p = 0.008). In this cohort survival was not associated with gender (HR 0.9, 95% CI 0.3–3.0), autoimmune diseases (HR 2.9, 95% CI 0.8–10.1) or immunosuppressive use (HR 0.3, 95% CI: 0.1–1.2).

1. Introduction

In 1954 Robert Good described three patients with thymoma and hypogammaglobulinemia [1]. Today, the condition is designated as Good syndrome (GS) [1]. It is typically an adult-onset immunodeficiency rendering patients susceptible to bacterial, viral, fungal and opportunistic infections. Immunological features of GS include hypogammaglobulinemia, a reduction in peripheral B-cells, CD4+ lymphopenia and reversal of CD4/CD8 ratio. In one series comprising 18 thymoma patients, whose immunophenotype was assessed, 12 patients were found to have immunological abnormalities such as B-cell and T-cell lymphopenia, whereas hypogammaglobulinemia was found in only 4 patients [2]. So far, GS has only been studied retrospectively in case reports and small retrospective case series. Therefore, the course of disease is not well understood. Reviews suggest that GS has a worse prognosis than other immunodeficiencies [3] with a mortality of 44.5% [4] to 57% [5], although follow-up time is unclear. In the present study, performed in 2012 and 2014, we collected new data, to assess the course and prognosis of GS by means of a prospective cohort study.

2. Methods

2.1. Subjects

Due to lack of diagnostic criteria and differing definitions in the literature, the following inclusion criteria were employed: 'Classical Good syndrome': patients with a combination of a thymoma and hypogammaglobulinemia. 'Probable Good syndrome': patients who either have thymoma or thymic carcinoma and any unclassified immunodeficiency, but do not meet the criteria for classical Good syndrome. Patient data were collected in two ways. A PubMed search was

Abbreviations: BAFF-R, B-cell activating factor receptor; CMV, Cytomegalovirus; CVID, common variable immunodeficiency; ESID, European Society for Immunodefiencies; GS, Good syndrome; G-CSF, Granulocyt e-Colony Stimulating Factor; TACI, Transmembrane activator and CAML interactor.

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conducted applying the terms 'thymoma' and 'immunodeficiency'. Articles dating back to 1984 written in English, German and French were assessed for suitability. This yielded 53 articles describing 67 patients. All 53 corresponding authors were sent an anonymised questionnaire regarding their patients, and were also asked to include any other patients that they had under their care. In addition, the European Society for Immunodeficiencies (ESID) facilitated us to contact all 13 centers that had registered patients with GS in the ESID online database. We asked them to complete the same anonymised questionnaire for the 54 patients that were registered. The questionnaires were sent out in 2012 (n = 53 + 13). In 2014 we sent a second questionnaire to the authors (n = 12) and centers (n = 5) that responded to the first questionnaire and reported data of non-deceased patients.

This study did not fall under the Medical Research Involving Human Subjects Act (WMO) because it concerned anonymised data from patient records, and therefore did not need to undergo a medical ethical review.

Table 1
Country of origin.

Country	Total number of included GS patients
Europe	
United Kingdom	13
Spain	7
Czech Republic	5
The Netherlands	4
Finland	4
France	1
Germany	1
Poland	1
Asia	
Japan	7
China	3
USA	1

2.2. Instruments

In the first questionnaire, data was collected on age, gender, age at diagnosis characteristics of the thymoma associated infections and autoimmune disease alongside immunological parameters, therapy and course of the disease so far. Two years later, a follow-up questionnaire, focusing on the course of the disease since the first questionnaire, was compiled consisting of questions about thymoma recurrence, hospital admissions, infections and the development of malignancy.

2.3. Statistical analysis

Statistics were performed using Graphpad Prism v5.03. A p-value of <0.05 was considered statistically significant. Descriptive statistics were generated (mean, standard deviation, median and range) where applicable and the frequency distribution was calculated for categorical data. The Wilcoxon signed rank test was used to calculate differences when medians were provided, whereas categorical data was analysed with the Fisher's exact test. Correlation was assessed using Spearman's rank correlation coefficient and survival analysis was performed with the Kaplan Meier analysis. Probabilities of survival after diagnosis of GS were compared to the expected survival of the general population of similar mean age, based on the European life tables from 2005 [6]. Differences in survival were assessed with the Log-Rank test. A multivariate Cox regression analysis was performed, using the fixed covariates gender, immunosuppressives use (including periodically used steroids) and presence of autoimmune diseases at any time during the course of the disease. The hazard ratios (HR) and the 95% confidence intervals were calculated.

3. Results

The 2012 questionnaire was completed and returned by 12 authors (response rate 23%) and 5 centers (38%) and comprised 18 and 29 (total 47) patients respectively. Patients originated from different countries as is shown in Table 1. Of these 47 patients, 35 were alive and 12 were deceased. The 2014 questionnaire was returned by 7 authors (response rate 58%) and 5 centers (100%) and comprised follow-up data of 27 patients, 23 of them were still alive and 4 had succumbed in the last 2 years. See Fig. 1.

3.1. Baseline characteristics

Median age at diagnosis was 58 years (range 38 to 85 years) with the exclusion of one paediatric case (detailed below). No significant difference was found between men and women in terms of age at diagnosis. There were 23 men and 24 women at baseline; in the second questionnaire, men represented 44% (of 27 patients). The median age at diagnosis of the thymoma was 58 years (range 30–80 years) and the median age relating to the start of infections was 57 years (range 31–82). In 5 patients (11%) the thymoma was the first sign of GS, in 20 patients (42%) the symptoms started almost simultaneously (within a year) and infections preceded the diagnosis of the thymoma in 19 patients (40%). The mean delay in diagnosis was 3.1 years (range 0 to 17 years), with a median of 1 year. There was no correlation between the first sign (thymoma or infections) and the duration of delay. We had a total follow-up of 498.8 patient years, with a median of 9 years per patient (range 0.25–27 years), from onset of symptoms to the final data collected.

The paediatric case involved an eleven-year-old patient with a thymoma and hypogammaglobulinemia. Infections started at 6 years of age. This patient is of unusually young age for GS and does meet the classic criteria for this condition. Only one paediatric case of GS has been described in the literature [7].

3.2. Thymoma

Thymoma was an incidental finding on a CT or X-ray in 41% of patients; in 59% (of 44 patients) symptoms prompted diagnostic investigations (CT-scan or X-ray). These symptoms included: chronic or persistent cough (n = 10), shortness of breath (n = 3), weight loss (n = 3), respiratory tract infections (n = 7), and other symptoms such as superior vena cava obstruction (n = 1) or sternal pain (n = 1). In three cases an associated autoimmune syndrome or paraneoplastic syndrome was the reason for the diagnostic workup for thymoma. The most commonly found type according to the WHO system of thymoma was A (37.8%), other types such as B (all subtypes), AB and C were found in 24.3%, 35.1%, and 2.7% of patients respectively, from a total of 37 patients.

3.3. Immunodeficiency and infections

All patients presented with marked hypogammaglobulinemia (Table 2), often accompanied by decreased or absent numbers of circulating B-cells. Only two patients (of 38 patients) presented with a B-cell count of more than 200×10^6/l. Reduced numbers of CD4+ T-cells were reported in 62% of patients, usually mild, while 20% had a frank CD4+ T-cell lymphopenia.

Only one patient with classical GS had not experienced infections at the time of the first questionnaire (5 years of follow-up). Thirty-five patients (74%) had at least one lower respiratory tract infection, which was the most frequently reported infection followed by upper respiratory tract infections (n = 25). Seventeen patients had gastrointestinal tract infections (36%), 10 patients had infections of skin and soft tissue (21%), 7 patients had urinary tract infections (15%), 5 systemic infections (11%) and 15 (32%) had other infections which consisted mostly