History of tonsillectomy is associated with glandular inflammation in Sjögren`s disease

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Key message: Past tonsillectomy may influence salivary gland inflammation and phenotype of Sjögren`s disease

Dear Editor,

Sjögren`s disease (SjD) is characterized by B cell hyperactivity and focal lymphocytic infiltration of salivary glands. The palatine tonsils are secondary lymphoid organs that are a first line of defense against pathogens, and a unique inductive site for B cell responses with selective homing to bronchial and nasal mucosae and lacrimal and salivary glands (1).

Tonsillectomy (TE) is a common surgical procedure that is often reported to have little effect on immune function (2) based on short-term studies. However, some studies have shown a

reduction in serum immunoglobulins over time, and a population-based study found TE to be associated with long-term risk of respiratory, infectious and allergic diseases (3).

Further, a recent Swedish population-based study found that TE was associated with increased risk of several autoimmune diseases, including SjD (4). Whether a history of TE is associated with the clinical and immunological phenotype of SjD has not been investigated to date.

New patients under investigation for SjD were recruited into the Optimising Assessment in Sjögren's Syndrome (OASIS) cohort established in Birmingham, UK in 2014 as previously described (5). Participants completed a questionnaire at enrolment that included history of TE and appendectomy (AE). This questionnaire was completed independently of, and subsequent to, clinical assessment. We included 183 participants recruited between 2014-2019 with a diagnosis of SjD (n=116) according to ACR/EULAR 2016 or non-SjD sicca syndrome (n=67). Sicca patients had objective and/or subjective dryness, did not meet ACR/EULAR classification criteria and were anti-Ro/SSA negative and had no physician diagnosis of SjD. One SjD patient who had TE around the time of symptom onset was excluded. All subjects provided written informed consent and the study was approved by the Wales Research Ethics Committee 7 (WREC 7) formerly Dyfed Powys REC; 13/WA/0392.

Age, sex and symptom duration did not differ between SjD and non-SjD sicca (Supplementary Table S1, available at *Rheumatology* online). Overall, 29% (53/183) had TE; 24.1% of SjD (28/116) and 37.3% of sicca patients (25/67) (p=0.043). The median age at TE was 8 (3-50) years and did not differ between SjD and sicca patients (p=0.629). SjD patients with TE showed a higher focus score on biopsy [median 2.1 (range 1.2-2.8) vs. 1.3 (0.0-4.3); p=0.049] and were more likely to have activity in the glandular (53.6 vs. 20.5%; p=0.001) and constitutional (39.3 vs. 14.9%, p=0.014) domains of the ESSDAI, but lower levels of serum IgG [12.2 (7.8-35.6) vs. 15.6 (5.7-56.4) g/l; p=0.012] and IgA [2.3 (0.9-6.6) vs. 2.9 (0.7-9.4) g/l; p=0.032] (Supplementary Table S2, available at *Rheumatology* online; Figure 1). VAS global health was significantly lower in SjD patients with TE (58 (10-78) vs. 70 (10-97); p=0.021). SjD patients with TE had a higher BMI (Supplementary Table S2). BMI might influence glandular swelling via immunometabolic effects or difficulties in clinical assessment. However, multivariable logistic regression analyses showed that TE was associated with glandular swelling and constitutional symptoms even when adjusted for BMI (OR: 3.88, 95%CI: 1.53-9.8; p=0.004 and OR: 4.31, 95%CI: 1.56-11.91; p=0.005, respectively; Supplementary Table S3, available at *Rheumatology* online). We observed no differences between sicca patients with and without TE (Supplementary Table S4, available at *Rheumatology* online).

For comparison we analysed AE. With the exception of lower salivary flow in SjD (0.09 (0.01-0.43) vs. 0.11 (0.0-1.3) ml/min; p=0.026), and higher age in sicca patients with AE (p=0.015) there were no differences (Supplementary Tables S5 and S6, available at *Rheumatology* online). We are unable to conclude if TE is a risk factor for the development of SjD or non-SjD sicca based on low numbers and the lack of an appropriate age-matched population-based control cohort with accurate TE data. Moreover, this study is limited by the number of histopathological samples in the TE group (n=9) versus the non-TE group (n=43).

In conclusion, TE was associated with lower IgG and IgA levels in SjD but not sicca implying a specific blunting of SjD associated systemic B cell hyperactivity. Moreover, history of TE in SjD was associated with higher focus scores and with glandular swelling and constitutional symptoms. One hypothesis to explain these findings is that a subtle immunodeficiency following TE was compensated by increased lymphoid tissue genesis in the glands. In fact, it has been established that mice deficient in mucosal secondary lymphoid organs develop more severe chemical-induced colitis characterised by high numbers of local tertiary lymphoid structures. This likely results from impairment of local regulatory immune responses and/or deficiency in anti-bacterial immunity (6) (7). Thus, the absence of normal tonsillar function may enhance a local mucosal inflammatory response within the salivary glands without impacting systemic responses.

As the number of lymphocytic foci are a key criterion in the histopathological assessment of SjD, TE status may be capable of influencing diagnosis and should be considered important information to record when patients first present. These findings also provide a strong rationale to expand this observation in other and larger cohorts as well as to determine mechanistic effects of TE on autoimmunity.

Conflict of Interest

FK is an employee of F. Hoffmann-La Roche, FB is an employee of Candel Therapeutics. All other authors declare no competing interests.

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publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Patient and Public Involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

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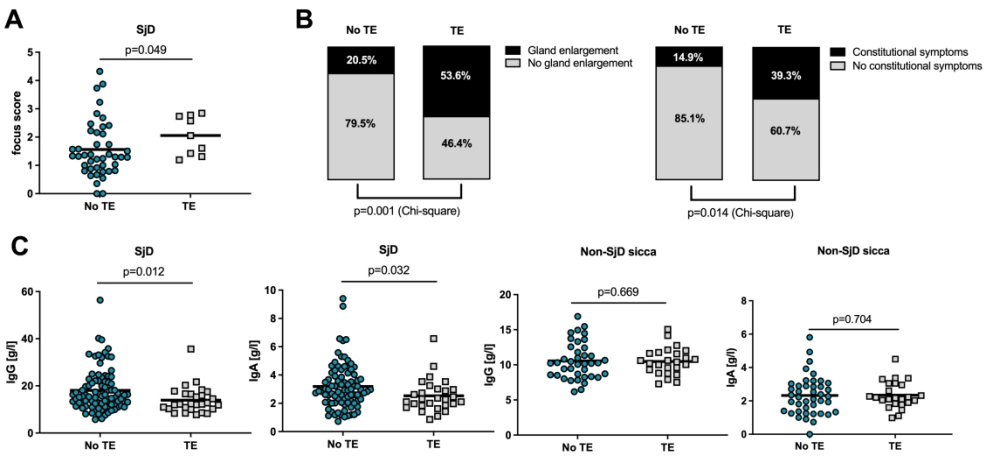
Figure 1: **Phenotype of patients with and without tonsillectomy**. A: histological focus score on minor salivary glands biopsy in SjD with/without TE (n=52); B: glandular enlargement (n=116) and constitutional symptoms (n=115) in SjD with/without TE; C: serum immunoglobulin G and A levels in SjD (n=116/n=115) and sicca (n=67/n=66) with/without TE. *Abbreviations: SjD: Sjögren`s disease; TE: tonsillectomy*



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