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

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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 SjS were recruited into the Optimising Assessment in Sjögren's Syndrome (OASIS) cohort established in Birmingham, UK in 2014 as previoulsy 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 (online supplementary table 1). 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 SjS 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] (Table 1 and 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. 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 5). We observed no differences between sicca patients with and without TE (supplementary table 2). 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 3 and 4). 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 histopatholgical 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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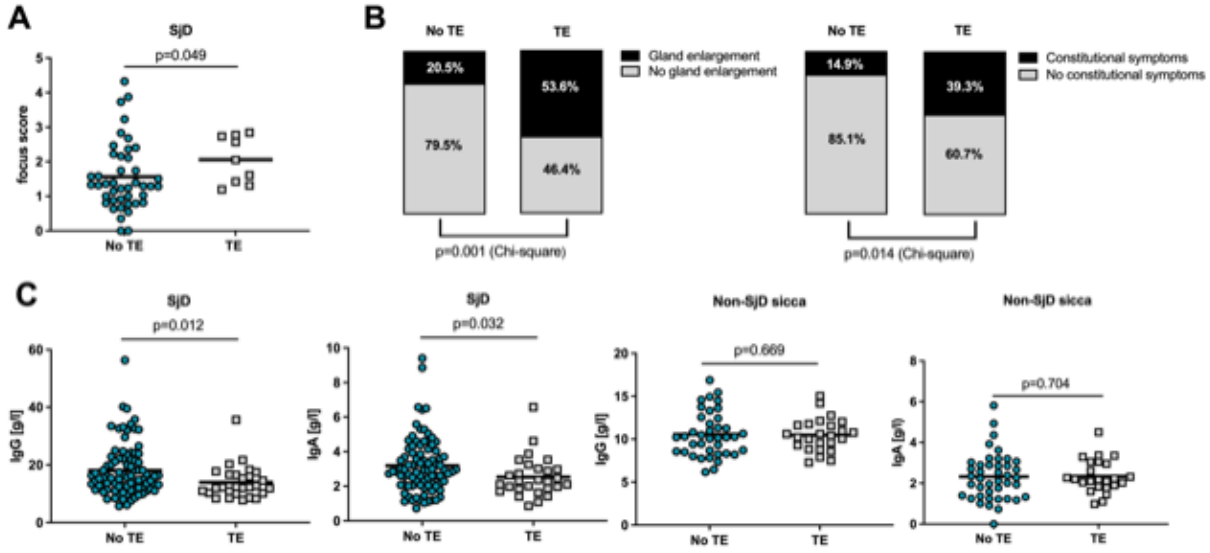
Figure 1: **Phenotype of patients with and without tonsillectomy**. A: histological focus score on minor salivary glands biopsy in SjD with/without TE (n=52); B: glandular enlargement (n=116) and constitutional symptoms (n=115) in SjD with/without TE; C: serum immunoglobulin G and A levels in SjD (n=116/n=115) and sicca (n=67/n=66) with/without TE. *Abbreviations: SjD: Sjögren`s disease; TE: tonsillectomy*


A
SjD
p=0.049
focus score
No TE
TE
B
No TE
TE
20.5%
79.5%
53.6%
46.4%
Gland enlargement
No gland enlargement
p=0.001 (Chi-square)
No TE
TE
14.9%
85.1%
39.3%
60.7%
Constitutional symptoms
No constitutional symptoms
p=0.014 (Chi-square)
C
SjD
p=0.012
IgG [g/l]
SjD
p=0.032
IgA [g/l]
Non-SjD sicca
p=0.669
IgG [g/l]
Non-SjD sicca
p=0.704
IgA [g/l]

Supplementary Information

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

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Supplementary Table 1. Patient`s characteristics Sjögren`s disease and Non-Sjögren`s Sicca

Variable	n	Sjögren`s disease (n=116)	n	Non-Sjögren`s sicca (n=67)	p-value (Mann-Whitney, Chi-square)
Age at inclusion [years]	116	55.7 (22.7-79.2)	67	59.6 (30.2-80.0)	0.175
Symptom duration [years]	109	5.7 (0.2-35.6)	60	5.5 (0.6-47.5)	0.979
Female % (n)	116	94.8 (110)	67	89.6 (60)	0.234
BMI [kg/m^2]	114	26.8 (18.1-46.8)	67	27.6 (15.7-49.3)	0.682
UWS [ml/min]	109	0.05 (0-0.67)	65	0.10 (0-1.3)	**<0.001**
Schirmer's test [mm/5min]	105	3 (0-40)	62	10 (0-40)	**<0.001**
Ro/SSA positivity % (n)	116	86.2 (100)	67	0 (0)	**<0.001**
La/SSB positivity % (n)	116	52.6 (61)	67	0 (0)	**<0.001**
Focus score	52	1.37 (0-4.32)	-	-	-
Focus ≥1	52	76.9 (40)	27	3.7 (1)	**<0.001**
IS treatment % (n)	114	33.3 (38)	67	11.9 (8)	**0.001**
Gland swelling % (n)	116	28.4 (33)	66	15.2 (10)	**0.030**
Lymphadenopathy % (n)	115	2.6 (3)	66	3.0 (2)	0.602
Constitutional symptoms % (n)	115	20.9 (24)	66	9.1 (6)	**0.030**
RF positivity	108	67.6 (73)	60	8.3 (5)	**<0.001**
IgG [g/l]	116	15 (5.7-56.4)	67	10.2 (6.2-16.9)	**<0.001**
IgA [g/l]	115	2.73 (0.72-9.4)	66	2.21 (0-5.81)	**0.002**
IgM [g/l]	115	1.12 (0.23-9.94)	66	1.04 (0-5.81)	0.103
C3 [g/l]	111	1.26 (0.79-2.05)	62	1.34 (0.78-2)	0.088
C4 [g/l]	112	0.22 (0.03-1.34)	63	0.26 (0.09-0.6)	**<0.001**
β2M [mg/l]	62	2.34 (1.27-4.69)	44	1.81 (1.24-3.08)	**<0.001**
FLCκ [mg/l]	94	24.9 (7-112)	60	13.2 (7-37)	**<0.001**
FLCλ [mg/l]	94	19.6 (1-117)	60	12.9 (7-40)	**<0.001**
ESSPRI	91	6 (0-10)	61	6.3 (1-10)	0.950
ESSDAI	116	3 (0-29)	65	0 (0-9)	**<0.001**
EQ5D	93	0.69 (-0.59-1)	63	0.69 (-0.17-1)	0.244
VAS global patient	63	65 (10-97)	48	65 (24-92)	0.870

Values are shown as median (range) or absolute numbers/percentages. Abbreviations: BMI: body mass index; UWS: unstimulated whole saliva flow; IS: immunosuppressive; RF: rheumatoid factor; β2M: β2-microglobulin; FLC: free light chains; ESSRPI: European League against Rheumatism Sjögren`s syndrome patient-reported index; ESSDAI: European League against Rheumatism Sjögren`s syndrome disease activity index; EQ5D: EURO-QOL 5-dimension; VAS: visual analogue scale.

Supplementary Table 2. Patient`s characteristics Sjögren`s disease with and without tonsillectomy

Variable	n	**Sjögren`s disease** Tonsillectomy	**Sjögren`s disease** No tonsillectomy	**p-value** (Mann-Whitney, Chi-square)
Age at inclusion [years]	108	56.4 (29.6-76.4)	54.8 (22.7-79.2)	0.122
Symptom duration [years]	109	2.6 (0.4-26.1)	6.1 (0.2-35.6)	0.623
Female % (n)	116	92.9 (26/2)	95.5 (84/4)	0.630
BMI [kg/m^2]	114	29.3 (18.2-49.8)	26.4 (19.1-44.8)	**0.019**
UWS [ml/min]	109	0.04 (0.0-0.29)	0.05 (0.00-0.67)	0.740
Schirmer's test [mm/5min]	105	2 (0-23)	3 (0-40)	0.515
Ro/SSA positivity % (n)	116	78.6 (22/6)	88.6 (78/10)	0.211
La/SSB positivity % (n)	116	42.9 (12/16)	55.7 (49/39)	0.280
Focus score	52	2.1 (1.2-2.8)	1.3 (0.0-4.3)	**0.049**
Focus ≥1	52	100 (9/0)	72.1 (31/12)	0.097
IS treatment (y/n) % (n)	114	28.6 (8/20)	34.9 (30/56)	0.647
Gland swelling % (n)	116	53.6 (15/28)	20.5 (18/70)	**0.001**
Lymphadenopathy % (n)	115	7.1 (2/26)	1.1 (1/86)	0.146
Constitutional symptoms % (n)	115	39.3 (11/17)	14.9 (13/74)	**0.014**
RF positivity	108	63 (17/10)	69.1 (56/25)	0.636
IgG [g/l]	116	12.2 (7.8-35.6)	15.6 (5.7-56.4)	**0.012**
IgA [g/l]	115	2.3 (0.9-6.6)	2.9 (0.7-9.4)	**0.032**
IgM [g/l]	115	1.0 (0.3-2.9)	1.2 (0.2-9.9)	0.187
C3 [g/l]	111	1.2 (0.8-1.8)	1.3 (0.8-2.1)	0.770
C4 [g/l]	112	0.2 (0.03-0.93)	0.2 (0.03-1.3)	0.962
β2M [mg/l]	62	2.39 (1.31-3.52)	2.31 (1.27-4.69)	0.717
FLCκ [mg/l]	94	22.6 (8-79)	25.9 (7.0-112.0)	0.065
FLCλ [mg/l]	94	18.5 (1-117)	19.8 (8-58)	0.554
ESSPRI	91	6.0 (2.7-10)	6.3 (0-10)	0.996
ESSDAI	116	5 (0-22)	3 (0-29)	0.274
EQ5D	93	0.69 (0.03-1.0)	0.69 (-0.59-1.0)	0.718
VAS global patient	63	58 (10-79)	70 (10-97)	**0.021**

Values are shown as median (range) or absolute numbers/percentages. Abbreviations: BMI: body mass index; UWS: unstimulated whole saliva flow; IS: immunosuppressive; RF: rheumatoid factor; β2M: β2-microglobulin; FLC: free light chains; ESSRPI: European League against Rheumatism Sjögren`s syndrome patient-reported index; ESSDAI: European League against Rheumatism Sjögren`s syndrome disease activity index; EQ5D: EURO-QOL 5-dimension; VAS: visual analogue scale.

Supplementary Table 3. Patient`s characteristics non-Sjögren`s sicca with and without tonsillectomy

Variable	n	**Non-Sjögren`s sicca** Tonsillectomy	**Non-Sjögren`s sicca** No tonsillectomy	**p-value** (Mann-Whitney, Chi-square)
Age at inclusion [years]	67	63.3 (36.0-80.0)	57.7 (30.2-76.5)	0.091
Symptoms duration [years]	60	5.3 (0.6-26)	5.5 (0.6-47.5)	0.873
Female % (n)	67	84 (21)	92.9 (39)	0.411
BMI [kg/m^2]	66	28 (18.9-48.3)	27.5 (15.7-43.9)	0.890
UWS [ml/min]		0.06 (0-0.85)	0.11 (0-1.3)	0.434
Schirmer's test [mm/5min]	62	7 (0-40)	10 (0-40)	0.154
Ro/SSA positivity % (n)	67	0 (0)	0 (0)	-
La/SSB positivity % (n)	67	0 (0)	0 (0)	-
Focus ≥1 % (n)	27	7.7 (1)	0 (0)	0.481
Gland swelling % (n)	66	16 (4)	14.6 (6)	1.000
Lymphadenopathy % (n)	66	4 (1)	2.4 (1)	1.000
Constitutional symptoms % (n)	66	8 (2)	9.8 (4)	1.000
RF positivity	60	9.1 (2)	7.9 (3)	1.000
IgG [g/l]	67	10.4 (7.3-15)	10.2 (6.2-16.9)	0.669
IgA [g/l]	66	2.2 (1-4.5)	2.3 (0-5.8)	0.704
IgM [g/l]	66	0.9 (0.3-2.9)	1.1 (0.3-2.7)	0.182
C3 [g/l]	62	1.3 (0.1-0.6)	1.4 (0.8-1.9)	0.410
C4 [g/l]	63	0.3 (0.1-0.6)	0.3 (0.1-0.5)	0.858
β2M [mg/l]	44	1.9 (1.2-2.4)	1.8 (1.3-3.1)	0.087
FLCκ [mg/l]	60	14.6 (9-37)	13.1 (7-23)	0.284
FLCλ [mg/l]	60	13.1 (8-40)	12.8 (7-23)	0.826
ESSPRI	61	6.2 (2.7-8.7)	6.7 (1-9)	0.702
ESSDAI	65	0 (0-9)	0 (0-8)	0.623
EQ5D	63	0.57 (-0.02-1)	0.69 (-0.17-1)	0.144
VAS global patient	48	60 (30-85)	70 (24-92)	0.583

Values are shown as median (range) or absolute numbers/percentages. Abbreviations: BMI: body mass index; UWS: unstimulated whole saliva flow; IS: immunosuppressive; RF: rheumatoid factor; β2M: β2-microglobulin; FLC: free light chains; ESSRPI: European League against Rheumatism Sjögren`s syndrome patient-reported index; ESSDAI: European League against Rheumatism Sjögren`s syndrome disease activity index; EQ5D: EURO-QOL 5-dimension; VAS: visual analogue scale.

Supplementary Table 4. Patient`s characteristics Sjögren`s disease with and without appendectomy

Variable	n	**Sjögren`s disease** Appendectomy (n=12)	**Sjögren`s disease** No Appendectomy (n=102)	**p-value** (Mann-Whitney, Chi-square)
Age at inclusion [years]	114	56.5 (41.7-78.7)	55.2 (22.7-79.2)	0.319
Symptoms duration [years]	107	6.8 (1.0-35.6)	5.6 (0.2-34.4)	0.574
Female % (n)	114	91.7 (11)	95.1 (97)	0.495
BMI [kg/m^2]	112	26.1 (20.6-31.2)	26.9 (18.2-46.8)	0.572
UWS [ml/min]	109	0.086 (0.01-0.43)	0.11 (0.0-1.3)	**0.026**
Schirmer's test [mm/5min]	104	3 (0-16)	3 (0-40)	0.802
Ro/SSA positivity % (n)	114	75 (9)	87.3 (89)	0.371
La/SSB positivity % (n)	114	66.7 (8)	50 (51)	0.365
Focus score	51	1.3 (1.0-2.2)	1.4 (0.0-4.3)	0.679
Focus ≥1	51	100 (6)	73.3 (33)	0.315
IS treatment (y/n) % (n)	112	16.7 (2)	36.0 (36)	0.217
Gland swelling % (n)	114	16.7 (2)	29.4(30)	0.505
Lymphadenopathy % (n)	113	0 (0)	3.0 (3)	1.000
Constitutional symptoms % (n)	113	33.3 (4)	19.8 (20)	0.278
RF positivity	107	72.7 (8)	66.7 (64)	0.487
IgG [g/l]	114	12.7 (8.4-21.7)	15.1 (5.7-56.4)	0.234
IgA [g/l]	113	2.6 (1.1-4.9)	2.8 (0.7-9.4)	0.918
IgM [g/l]	113	1.5 (0.7-4.9)	1.0 (0.23-9.9)	0.081
C3 [g/l]	109	1.22 (0.96-1.65)	1.26 (0.79-2.05)	0.578
C4 [g/l]	110	0.22 (0.09-0.93)	0.2 (0.03-1.34)	0.598
β2M [mg/l]	61	2.16 (1.31-4.63)	2.34 (1.27-4.25)	0.379
FLCκ [mg/l]	92	18.3 (8-44)	24.8 (7-112)	0.186
FLCλ [mg/l]	92	17 (7-32)	19.6 (1-117)	0.512
ESSPRI	89	6.2 (3-8.7)	6 (0-10)	0.740
ESSDAI	91	2.5 (0-17)	3 (0-29)	0.654
EQ5D	91	0.69 (0.06-1)	0.69 (-0.59-1)	0.864
VAS global patient	62	70 (50-90)	65 (10-97)	0.303

Values are shown as median (range) or absolute numbers/percentages. Abbreviations: BMI: body mass index; UWS: unstimulated whole saliva flow; IS: immunosuppressive; RF: rheumatoid factor; β2M: β2-microglobulin; FLC: free light chains; ESSRPI: European League against Rheumatism Sjögren`s syndrome patient-reported index; ESSDAI: European League against Rheumatism Sjögren`s syndrome disease activity index; EQ5D: EURO-QOL 5-dimension; VAS: visual analogue scale.

Supplementary Table 5. Patient`s characteristics non-Sjögren`s sicca with and without appendectomy

Variable	**n**	**Non-Sjögren`s sicca** Appendectomy	**Non-Sjögren`s sicca** No appendectomy	**p-value** (Mann-Whitney, Chi-square)
Age at inclusion [years]	67	64.7 (56.5-80.0)	59.0 (30.2-75.3)	**0.015**
Symptoms duration [years]	60	5.5 (2-47.5)	5.5 (0.5-20)	0.992
Female % (n)	67	90.9 (10)	89.3 (50)	1.000
BMI [kg/m^2]	66	26.9 (15.7-32.5)	28 (18.4-49.3)	0.394
UWS [ml/min]		0.09 (0.01-0.43)	0.11 (0-1.3)	0.820
Schirmer's test [mm/5min]	62	6.3 (0-40)	9.8 (0-40)	0.916
Ro/SSA positivity % (n)	67	0 (0)	0 (0)	-
La/SSB positivity % (n)		0 (0)	0 (0)	-
Focus ≥1 % (n)	27	0 (0)	4.5 (1)	1.000
Gland swelling % (n)	66	18.2 (2)	14.5 (8)	0.668
Lymphadenopathy % (n)	66	0 (0)	3.6 (2)	1.000
Constitutional symptoms % (n)	66	9.1 (1)	9.1 (5)	1.000
RF positivity	60	0 (0)	5 (9.8)	1.000
IgG [g/l]	67	10 (7.3-12.6)	10.3 (6.2-16.9)	0.402
IgA [g/l]	66	2.6 (0.7-5.8)	2.2 (0-4.9)	0.221
IgM [g/l]	66	1 (0.3-2.2)	1 (0.3-2.9)	0.491
C3 [g/l]	62	1.3 (1-1.8)	1.4 (0.8-2)	0.983
C4 [g/l]	63	0.3 (0.2-0.4)	0.3 (0.1-0.6)	0.694
β2M [mg/l]	44	1.8 (1.2-3.1)	1.8 (1.3-3.1)	0.875
FLCκ [mg/l]	60	16 (11-21)	13.1 (7-37)	0.184
FLCλ [mg/l]	60	12.3 (8-20)	13.5 (7-40)	0.428
ESSPRI	63	7.3 (2.7-10)	6.3 (1-9)	0.328
ESSDAI	65	0 (0-9)	0 (0-8)	0.784
EQ5D	63	0.52 (0.06-1)	0.69 (-0.17-1)	0.670
VAS global patient	48	80 (30-91)	65 (24-92)	0.398

Values are shown as median (range) or absolute numbers/percentages. Abbreviations: BMI: body mass index; UWS: unstimulated whole saliva flow; IS: immunosuppressive; RF: rheumatoid factor; β2M: β2-microglobulin; FLC: free light chains; ESSRPI: European League against Rheumatism Sjögren`s syndrome patient-reported index; ESSDAI: European League against Rheumatism Sjögren`s syndrome disease activity index; EQ5D: EURO-QOL 5-dimension; VAS: visual analogue scale.

Supplementary Table 6. Multivariable logistic regression analysis for glandular swelling and constitutional symptoms

Variable	Odds ratio	95%CI	p-value
Glandular swelling:			
BMI [kg/m2]	1.05	0.97-1.14	0.255
Tonsillectomy	3.88	1.53-9.83	**0.004**
Constitutional symptoms:			
BMI [kg/m2]	0.97	0.88-1.06	0.512
Tonsillectomy	4.31	1.56-11.91	**0.005**

Abbreviations: BMI: body mass index; CI: confidence interval.