

# Incidence of De Quervain's Thyroiditis in an Area With High Prevalence of Sars-Cov-2 Infection

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## Research Article

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# Abstract

**Purpose:** To evaluate the possible association between Covid-19 infection and subacute thyroiditis.

**Patients and Methods:** We reviewed the medical and imaging records of patients referred to our outpatient setting dedicated to “thyroid emergency” (“bollini verdi”) from April 2020 to October 2020 of our Department. This out-patient clinic is devoted to patients who required an evaluation for severe hypothyroidism, thyrotoxicosis and neck discomfort or pain. All patients with a newly diagnosed subacute thyroiditis were selected. A retrospective collection of the data of all patients receiving a diagnosis of subacute thyroiditis was performed taking into account the same period of time (April-October) starting from 2016.

**Results:** During the COVID-19 outbreak in our Region, (April 2020 to October 2020), 396 patients attended the out-patient emergency clinic. Among them, 10 (2.7%) patients received a diagnosis of subacute thyroiditis. In a single patient, a 44 yr old man, Covid-19 pulmonary infection had been diagnosed seven weeks before the diagnosis of subacute thyroiditis. All of the remaining patients were and still are Covid-19 free as confirmed by phone interview. The percentage of patients who received diagnosis of subacute thyroiditis in the same period starting from 2016 was superimposable (2.9%, 2.9%, 2.6% and 3.0% in 2016, 2017, 2018 and 2019, respectively).

**Conclusions:** Our data do not demonstrate an increase of the incidence of subacute thyroiditis in Brescia areas, a region with the highest prevalence of COVID-19 in Italy during the period of the pandemic outbreak.

**Trial registration:** no. 4631

## Introduction:

Covid-19 infection drastically developed in Italy, among the European Countries, in February 2020. Northern of Italy, and in particular Bergamo and Brescia areas, showed the highest number of patients affected by Covid-19, with a dramatically increase of death related to the infections between February and April 2020 [1].

Subacute thyroiditis (SAT) or de Quervain's thyroiditis has been described for the first time in 1904 and it is characterized by neck pain or discomfort, general symptoms, and thyroid dysfunction [2]. SAT is often caused by a viral infection or a postviral inflammatory process mainly of the upper respiratory tract [3]. Many patients have in fact a history of an upper respiratory infection prior to the onset of thyroiditis, mainly two to eight weeks beforehand. Thyrotoxicosis represents the typical presentation followed by euthyroidism, transient hypothyroidism, and ultimately restoration of normal thyroid function. The diagnosis of subacute thyroiditis is largely based upon clinical symptoms, but laboratory findings [i.e high erythrocyte sedimentation rate (ESR) and/or C-reactive protein level (CRP)], and/or a low radioiodine

uptake during the thyrotoxic phase or typical ultrasound features are helpful in confirming the diagnosis [4].

Recently, several reports describe patients affected by Covid-19 infection who developed subacute thyroiditis suggesting thyroid tissue as possible target of the virus.

The aim of the present study was to further evaluate the possible association between Covid-19 infection and subacute thyroiditis.

## **Subjects And Methods:**

We reviewed the medical and imaging records of patients referred to our outpatient setting dedicated to “thyroid emergency” (“bollini verdi”) from April 2020 to October 2020 of our Department. This out-patient clinic is devoted to patients who required an evaluation for severe hypothyroidism, thyrotoxicosis and neck pain or discomfort. All patients with a newly diagnosed subacute thyroiditis were selected. The diagnosis was mainly clinical and supported by elevation of CRP and/or EAS levels, thyrotoxicosis and at least one instrumental imagine between both low radioiodine uptake at scintiscan or typical ultrasound features [4].

Serum concentrations of TSH (normal range  $0.4 \pm 4.5$  mIU/L, analytical sensitivity 0.004 mIU/L) and fT4 (normal range 8.0–19.0 pg/mL, analytical sensitivity 1 pg/mL) were measured using a fully automated Architect i2000 analyzer (Abbott Diagnostics, Abbott Park, IL, USA) using chemiluminescent magnetic immunoassays. For WBC count, specimens were collected in peripheral blood sampling microtainer tube containing K<sub>2</sub>EDTA and analyzed using an automated blood analyzer (Coulter LH 750) within 4 h from collection. To determine hsCRP plasma levels, blood was collected in lithium-heparin tube and concentrations were measured using an immunoassay technique (Siemens Healthcare Diagnostics, Den Hague, the Netherlands) with a lower detection limit of 0.2 mg/L. The instruments were calibrated against appropriate proprietary reference standard material and verified by using the registered quality controls.

The scintigraphy (technetium-99m pertechnetate) was performed using a gamma camera fitted with a low-energy high-resolution collimator. Multiple views were acquired including anterior, lateral and oblique views.

Ultrasounds were performed by a skilled sonographer with more ten years of experience, in blind respect to both TSH values and scinigraphy results and skilled to SAT diagnosis (4); an AplioTM500 (Toshiba Medical Systems Corp, Otawara, Japan) ultrasonographic scanner was used, fitted with a 10–14-MHz linear transducer for morphological study.

All patients provided written informed consent for the storage and use of their data. The study was approved by the Local Ethical Committee (no. 4631).

## **Statistical analysis:**

All data were collected in an electronic case report database. Comparisons between groups and difference between proportions were calculated using  $\chi^2$  for categorical variables and ANOVA test for quantitative variables, as appropriate. Two-tailed  $p < 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS 20.0 software (SPSS, Inc., Evanston, IL, USA).

## Results:

During the Covid-19 outbreak in our Region, (April 2020 to October 2020), 396 patients attended the "bollini verdi" outpatient emergency clinic. Among them, 10 (2.5%) patients received a diagnosis of SAT. Nine patients showed neck pain and one arthralgia and tremor spreading to the extremities.

In a single patients, a 44 yr old man, Covid-19 pulmonary infection had been diagnosed seven weeks before the diagnosis of SAT; he did not require hospitalized, and he treated by azithromycin, chloroquine, corticosteroids and low molecular weight heparin by subcutaneous injection at home. All of the remaining patients were and still are Covid-19 free as confirmed by phone interview.

All the patients were submitted to thyroid ultrasound that was suggestive of SAT. Three subjects had previously performed technetium-99m pertechnetate scintigraphy that showed absence or very low radioiodine uptake.

The retrospective collection of the data of all patients receiving a diagnosis of SAT was performed taking into account the same period of time (April-October) starting from 2016.

The clinical characteristics of all patients are shown in Table 1.

Of note, the number of patients, receiving a diagnosis of SAT appeared superimposable over the last 5 years. Furthermore, similar gender and age characterized patients developing SAT in the years before Sars-CoV-2 pandemic and in 2020. Similarly pre-pandemy and during-pandemy SAT did not differ in terms of WBC, EAS and CRP levels were observed, as well as for thyroid hormonal profile.

## Discussion:

The results of the present study show a similar incidence of subacute thyroiditis over the last 5-years. In particular, throughout the 7-month period concomitant to the outbreak of Covid-19 infection, no enrichment in the diagnosis of SAT was registered. This observation appears strengthened by the fact that the present study was carried out in the Brescia areas, the region with the highest prevalence of Sars-CoV-2 infection in Italy [1]. It should be noted that, a previous diagnosis of Covid-19 was detected in one patient out of 10 developing SAT from April 2020 to October 2020.

De Quervain's thyroiditis shows a typical seasonal variation in its incidence with a higher prevalence in spring and summer [5]. Thus, the present study was specifically designed to take into account the number of SAT diagnosis rendered in the April-October period of different years.

According to the Rochester Epidemiology Project, SAT is estimated to display an incidence of 12.1 cases per 100,000/year, 5 times higher in women than in men [6], and it is presumed to be caused by a viral infection or a postviral inflammatory process possibly associated to entero, coxsackie or adenovirus [3, 7].

It is interesting noting, that these data are very closed to what observed in the Brescia areas through the last years. Indeed, on a population of about 200.000 inhabitants we should have 24 cases/years. Thus, the effective number of cases observed in seven months this year as well as in the previous ones are indeed those expected in Brescia areas yearly.

Brancatella and colleagues recently described the first case of SAT in a patient affected by SARS-CoV-2 [8]; the Authors alerted “clinicians to additional and unreported clinical manifestations associated with Covid-19” on the basis of a chronological association between Covid and SAT disease observed in that patient. Since then, several other case reports were published [9-16].

The pathophysiology of the association between SAT with Covid-19 infection is reported to be similar to the association with other viral conditions targeting the thyroid of genetically susceptible individuals. Muller et al. suggested that this could be due to the presence of the angiotensin-converting enzyme 2 (ACE2) receptors which are more prevalent in thyroid than lung cells [17]. ACE2 receptors are present in different tissue such as myocardium, gastrointestinal mucosa and respiratory tract [18, 19], all tissue shown to harbour Covid-19 virus [20, 21]. More recently, Rotondi et al, demonstrated that the mRNA encoding for the ACE2 receptor is expressed in thyroid follicular cells in human thyroid surgical specimens and in primary cultures of thyroid cells, making them a potential target for Sars-Cov-2 [22]. Taken together the above evidences, the hypothesis that Sars-Cov-2 could be responsible for subacute thyroiditis appears plausible. However, if Covid-19 would represent a major clinical condition for subsequent SAT development, due for example to a specific tropism of this virus for the thyroid, one would expect an increase of SAT incidence during the Covid-19 outbreak. At difference with this statement, we did not observe any increase in the incidence of SAT during the 7-month period of 2020 as compared to similar periods over the last years. Furthermore, no differences in the male/female ratio nor in the clinical phenotype at presentation were observed in patients developing SAT in “the Sars-Cov-2 year”.

Another and likely more intriguing aspect could be due to the possibility that Covid-19 patients have assumed corticosteroids masking a contemporary subacute thyroiditis. Unfortunately, we have no possibility to demonstrate or rebut this possibility. In addition, it could be theoretically possible that few patients with SAT were cured by their family physician and did not attend the endocrine out-patient clinic. However, the above possibility should be considered of negligible relevance in view of the fact that from April 2020, an endocrinological remote consultation for patients and physicians was established and active and no query or cases of SAT were received. Thus, although potential limitations might be present, the here reported results appear reliable.

In conclusion, the possibility that Covid-19 could be responsible for the development of subacute thyroiditis, although theoretically possible and documented by several case reports, appears not to be a frequent event. The here reported data do not demonstrate an increase of the incidence of SAT in Brescia areas, a region with the highest prevalence of Covid-19 in Italy during the period of the pandemy outbreak.

## **Declarations:**

### **Funding:**

This study received no financial support.

### **Conflicts of interest/Competing interests (include appropriate disclosures):**

The authors declare that they have no conflicts of interest.

### **Availability of data and material (data transparency):**

The data supporting the findings of this study are available from the corresponding author, upon request.

### **Ethics approval:**

The study was approved by the Local Ethical Committee (no. 4631).

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## Table:

**Table 1.** Clinical and biochemical characteristics of all patients enrolled in the study.

From April 2020 to October of each years						
	2016	2017	2018	2019	2020	p value
Gender (f/m)	6/3	8/3	6/4	9/3	7/3	.954
Age (yrs)	41.6 (3.2)	42.1 (2.6)	41.9 (3.6)	42.2 (3.6)	41.9 (3.1)	.993
WBC	13 (1.4)	12.6 (1.2)	13.1 (1.5)	12.4 (1.2)	12.8 (1.3)	.757
CRP (mg/L)	26.2 (5.5)	26.9 (7.4)	33.9 (5.6)	29.4 (5.1)	27.2 (6.6)	.254
ESR (mm/h)	58.3 (8.7)	58.2 (8.4)	55.4 (7.1)	56.9 (8.9)	55.5 (8.5)	.884
TSH (mIU/L)	0.08 (0.02)	0.03 (0.03)	0.06 (0.11)	0.06 (0.04)	0.05 (0.04)	.745
fT4 (pg/mL)	21.3 (1.6)	21.5 (1.7)	22.1 (1.0)	22.2 (1.2)	21.1 (1.5)	.309