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Characteristics of patients with subacute thyroiditis

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ABSTRACT

INTRODUCTION. The diagnosis and management of subacute thyroiditis (SAT) may be challenging, and more evidence on patient and disease characteristics is warranted.

METHODS. This was a retrospective cohort study of all patients in the North Denmark Region with a SAT diagnosis in the Danish National Patient Registry, 2016-2018. The medical records and biochemical results prior to the diagnosis and during a two-year follow-up period were reviewed.

RESULTS. A total of 71 patients with a SAT diagnosis were identified, and the diagnosis was verified in 44 (62.0%) cases with an incidence rate of 2.4/100,000/year. Patients with verified SAT were predominantly females (72.7%) with a median age of 50.7 years. Biochemical results showed thyrotoxicosis at the initial examination in 69.8% and elevated C-reactive protein in 86.5% of patients. Longitudinal biochemical assessment showed a biphasic response (median thyroid-stimulating hormone, initially: 0.02 mIU/l, at three months: 4.7 mIU/l and 2.4 mIU/l after two years). Treatment with non-steroidal anti-inflammatory drugs, beta-blockers and/or prednisolone was initiated in 23 of the 38 patients (60.5%) evaluated, and ten of 33 patients (30.3%) with follow-up data received thyroid hormone replacement therapy.

CONCLUSION. In the North Denmark Region, a hospital diagnosis of SAT was verified in less than two thirds of cases. Further large studies are warranted to extend the findings concerning the treatment and outcome of SAT.

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Subacute thyroiditis (SAT), also referred to as de Quervain's thyroiditis, giant cell thyroiditis or granulomatous thyroiditis, is a subtype of thyroiditis that may pose a challenge regarding diagnosis, treatment and follow-up [1, 2]. Inflammation of the thyroid gland is a key pathophysiological finding in SAT and has been linked to viral infections. SAT is often characterised by a biphasic response in thyroid function with an initial thyrotoxic phase, a subsequent hypothyroid phase and restoration to euthyroidism [2]. Furthermore, the absence of thyroid peroxidase antibodies is a hallmark of SAT [2]. However, these thyroidal characteristics in combination with low radioiodine uptake on thyroid scintigraphy are also often seen in painless thyroiditis. Thus, the main characteristic used to differentiate SAT from painless thyroiditis is patient-reported pain of the thyroid gland [3, 4]. Furthermore, biochemical inflammation markers may be considered, and elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) may favour a diagnosis of SAT [3, 4]. Still, uncertainties prevail

regarding the diagnosis and management of SAT [5]. More evidence to substantiate the characteristics of this disorder is important to improve clinical care, provide valid measures of disease incidence and ensure proper identification of cases in scientific outcome studies.

This study aimed to evaluate all SAT cases diagnosed in hospitals in a Danish region during a three-year period to provide figures on the validity of the diagnosis, the incidence of the disorder and patient characteristics concerning diagnosis, treatment and follow-up.

METHODS

This was a retrospective cohort study of all patients diagnosed with SAT in a hospital in the Northern Denmark Region during a three-year period (from 1 January 2016 to 31 December 2018). All hospital visits are registered in the Danish National Patient Registry (DNPR) and coded according to the tenth edition of the International Classification of Diseases (ICD-10) [6]. We identified all patients in the North Denmark Region with a primary or secondary diagnosis of SAT (ICD-10: E06.1) during a hospital in- or outpatient visit. The study was registered according to the General Data Protection Regulation in the North Denmark Region (2021-077).

For patients identified with a diagnosis of SAT, the medical records were reviewed prior to the first hospital diagnosis and during the two-year follow-up. A small number of patients (n = 3) moved in or out of the North Denmark Region during the study period, which restricted the period of assessment in these patients. The information available in the medical records was collected from visits at the Endocrine Department following referral for specialist treatment and not from visits in general practice. From the medical records, symptoms, clinical findings, thyroid imaging and medications were retrieved along with biochemical results requested during the endocrine visit and any prior or subsequent visit in general practice.

A group of experts (specialists in endocrinology and clinical biochemistry) agreed on whether a diagnosis of SAT could be verified according to clinical guidelines [3, 4]. Thus, the diagnosis was retrospectively evaluated, and painful and/or tender thyroid gland was a main diagnostic criterion in combination with one or more of the following: biphasic response in thyroid function, elevated inflammatory markers, low radioiodine uptake on thyroid scintigraphy and diffusely hypoechogenic/low flow on ultrasound.

A group of patients (n = 17) was diagnosed with SAT as part of an ongoing monitoring programme entitled the Danish Investigation on Iodine Intake and Thyroid Diseases (DanThyr) [7]. DanThyr included a register of new biochemical cases of hyper- and hypothyroidism. Upon laboratory identification, the requesting physician was contacted and the patient was invited to participate in the study [8]. Among these cases, the verification of SAT relied on the review of project data rather than the hospital medical record.

Data were collected and managed using Research Electronic Data Capture (REDCap) hosted at Aalborg University Hospital [9, 10]. The positive predictive value (PPV) of a SAT diagnosis in the DNPR was calculated as the number of verified cases among all cases identified. The SAT incidence rate was calculated as the average number of verified cases per year divided by the total number of individuals in the North Denmark Region as of 1 July 2017 and adjusted according to the age distribution of the Danish population.

Analyses were performed using Stata 17.0 (StataCorp, College Station, Texas, USA).

Trial registration: not relevant.

RESULTS

A total of 71 patients were registered with a diagnosis of SAT, and 44 had a verified diagnosis corresponding to a PPV of 62.0% and an age-adjusted incidence rate of 2.4/100,000/year. In 27 cases (38.0%), the diagnosis could not be verified. The most common diagnosis among non-verified cases was painless thyroiditis (n = 10) followed by other types of thyroid disease (drug-induced or acute infectious thyroiditis (n = 5), Graves' disease, toxic multinodular goitre or toxic adenoma (n = 5), autoimmune hypothyroidism (n = 3) and non-thyroidal or unclassified disease (n = 4)). Among patients with verified SAT, the median age at initial symptoms was 50.7 years (range: 28.0-71.6 years) and most patients were women (72.1%). Verified cases were mainly registered as a primary diagnosis (72.1%), and 51.1% had their first endocrine visit within 30 days of initial contact in general practice (range: 1-267 days).

Pain was a dominant patient-reported symptom (**Table 1**) in accordance with the applied diagnostic criteria. Thus, 43 of 44 verified cases reported pain from the thyroid gland, the throat, the jaw, the ear and/or painful swallowing. In the case of no patient-reported pain, all additional findings were compatible with a SAT diagnosis. At the clinical examination, an enlarged and/or tender thyroid gland was found in 61.1% of the cases. Thyroid imaging was performed in around 75% of patients and characteristic findings on scintigraphy and ultrasound were seen in 70% of the examined patients (Table 1). Notably, characteristic findings were seen in 90.9% of patients when scintigraphy was performed within 30 days of symptoms and in only 27.3% when performed more than 30 days after initial symptoms (p = 0.001). A similar but non-significant trend was seen for thyroid ultrasound (82.4% versus 60.0%, p = 0.2). Considering the initial biochemical findings, 70% of the patients had thyrotoxicosis and nearly 90% had elevated CRP (Table 1), whereas less than three patients had a measurement of ESR. Evaluation of the longitudinal development in thyroid function tests and CRP (**Table 2**) revealed a biphasic response with initial thyrotoxicosis followed by a hypothyroid phase after three months and normalisation of thyroid function from six months and beyond. CRP normalised during follow-up (Table 2); and after one month, CRP was persistently elevated in four of the 12 patients (33%) with initial elevation.

TABLE 1 Clinical characteristics of the 44 patients with a verified diagnosis of subacute thyroiditis at the initial examination.

	N[a]	n[b] (n/N, %)
Symptoms		
Pain from the area of the thyroid gland/ throat pain	44	42 (95.5)
Hyperthyroid symptoms	44	26 (59.1)
Fatigue	44	17 (38.6)
Fever	44	14 (31.8)
Painful swallowing	44	12 (27.3)
Jaw pain	44	7 (15.9)
Pain from the ears	44	6 (13.6)
Myalgia	44	6 (13.6)
Anorexia	44	4 (9.1)
Upper chest pain	44	< 3
Clinical examination		
No clinical findings	36	14 (38.9)
Enlarged and tender thyroid gland by palpation	36	10 (27.8)
Enlarged thyroid gland	36	7 (19.4)
Tender thyroid gland by palpation	36	5 (13.9)
Imaging studies		
Thyroid scintigraphy:	43	33 (76.7)
Low radioiodine uptake	33	23 (69.7)
Ultrasound examination:	43	32 (74.4)
Diffusely hypoechogenic and/or low flow	32	23 (71.9)
Biochemical findings		
Thyrotoxicosis[c]	43	30 (69.8)
Thyroid autoantibody positive[d, e]	29	< 3
Elevated CRP[f]	37	32 (86.5)

CRP = C-reactive protein; T3 = triiodothyronine; T4 = thyroxine; Tg-Ab = thyroglobulin antibodies; TPO-Ab = thyroid peroxidase antibodies; TRAb = TSH-receptor antibodies; TSH = thyroid-stimulating hormone.
a) Individuals with available information.
b) Individuals with the specific characteristic.
c) Defined as: TSH < 0.3 mIU/l and total T3 > 2.5 nmol/l and/or total T4 > 140 nmol/l and/or free T4 > 18.8 pmol/l.
d) Defined as: TRAb ≥ 1.0 IU/l and/or TPO-Ab ≥ 60 kU/l and/or Tg-Ab ≥ 60 kU/l.
e) Biochemical methods used: TRAb (DYNOtest TRAK human, Brahms Diagnostica), TPO-Ab and Tg-Ab (Kryptor Compact, Thermo Fisher Diagnostics).
f) Defined as: CRP ≥ 8 mg/l.

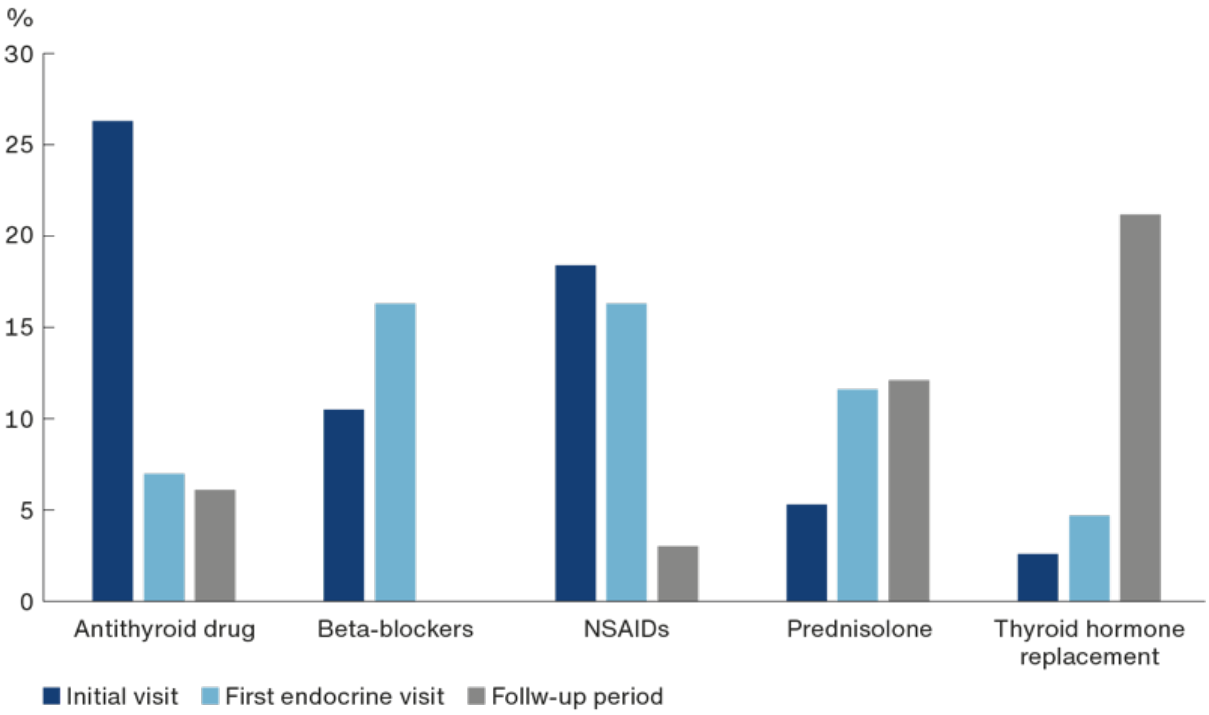
TABLE 2 Biochemical findings among the 44 verified cases of subacute thyroiditis at the initial examination and at different time points during follow-up. Patients who received treatment with levothyroxine at a certain time point of biochemical assessment were not included.

		Initial		1 month		3 months		6 months		2 years	
		n	median (IQR)	n	median (IQR)						
TSH, mIU/l[a]	0.3-4.5	43	0.02 (0.005-0.1)	35	0.05 (0.01-1.3)	32	4.7 (2.3-8.1)	25	2.5 (2.0-3.6)	16	2.4 (1.4-3.9)
Total T3, nmol/l[a]	1.1-2.5	37	2.6 (2.2-3.6)	35	1.5 (1.1-2.0)	32	1.7 (1.4-1.8)	22	1.6 (1.4-1.7)	9	1.5 (1.5-2.1)
Total T4, nmol/l[a]	60-140	33	178 (134-206)	33	99 (59-132)	31	80 (68-91)	23	85 (76-98)	11	99 (77-109)
CRP, mg/l[a]	< 8.0	37	38 (23-61)	13	4.5 (1.6-14)	4	1.3 (0.7-4.8)	4	0.8 (0.4-4.2)	4	1.7 (0.5-3.6)

CRP = C-reactive protein; IQR = interquartile range; ref. = reference interval; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.
a) Biochemical methods used: TSH (Cobas, Roche Diagnostics or Dimension Vista, Siemens Healthineers), total T3 and total T4 (Cobas, Roche Diagnostics or Centaur XPT, Siemens Healthineers), and CRP (Cobas, Roche Diagnostics or Dimension Vista, Siemens Healthineers).

Different types of medical treatment were initiated among patients at different time points (**Figure 1**). Antithyroid drugs are not recommended for treatment of SAT but were prescribed in some patients and mainly at the initial visit in general practice. Complete follow-up regarding treatment was available for 33 patients, and ten (30.3%) received thyroid hormone replacement, mainly prescribed by endocrine specialists (Figure 1) and initiated within six months of initial symptoms. In this group, median age was 52.5 years, 90% had elevated CRP, 70% had thyrotoxicosis and 80% were females. The treatment was either discontinued during follow-up (n = 3) or continued beyond the follow-up period (n = 5), whereas details on the course of treatment were missing in the remaining cases.

FIGURE 1 Frequency of therapies used at different time points among the 44 patients with subacute thyroiditis. Treatment was assessed at the initial visit, at the first endocrine visit and during a two-year follow-up period. Missing values not included: initial visit (n = 6), first endocrine visit (n < 3), follow-up period (n = 11).



NSAIDs = non-steroidal anti-inflammatory drugs.

A total of 23 of 38 patients (60.5%) received one or more of the recommended SAT treatments (non-steroidal anti-inflammatory drugs (NSAIDs), prednisolone and/or beta-blockers) (**Table 3**). These patients were more often women, of lower age, reported more hyperthyroid symptoms and more often had a tender thyroid gland. A subgroup of 11 patients (28.9%) received treatment with prednisolone and these patients were overall comparable to patients not receiving such treatment, although their thyroid gland was more often enlarged (70.0%) and tender (80.0%).

TABLE 3 Characteristics of the 38 patients with subacute thyroiditis and available treatment data. Results are stratified into patients who received medical treatment recommended for the disorder (non-steroidal anti-inflammatory drugs, beta-blockers and/or prednisolone) (group 1) or no such treatment (group 2).

	n (%)	median (IQR)	n (%)	median (IQR)	p value[a]
Patients	23		15		
Female sex	20 (87.0)		8 (53.3)		0.03
Symptoms					
Hyperthyroid symptoms	18 (78.3)		7 (46.7)		0.05
Clinical examination[b]					
Enlarged thyroid gland	11 (52.4)		5 (38.5)		0.4
Tender thyroid gland	13 (61.9)		< 3		0.003
Imaging studies[b]					
Thyroid scintigraphy:	14 (60.9)		14 (93.3)		
Low radioiodine uptake[c]	13 (92.9)		8 (57.1)		0.08
Ultrasound examination:	17 (73.9)		10 (66.7)		
Diffusely hypoechogenic and/or low flow[c]	12 (70.6)		7 (70.0)		1.0
Biochemical findings[b]					
Thyrotoxicosis[d]	13 (56.5)		13 (86.7)		0.08
Elevated CRP[e]	20 (90.9)		10 (83.3)		0.6
Patient age, yrs		49.5 (36.8-53.0)		55.5 (45.5-66.7)	0.03
TSH, mIU/l		0.03 (0.005-0.1)		0.02 (0.005-0.1)	0.6
Total T3, nmol/l[b]		2.4 (2.2-3.8)		2.6 (2.5-3.2)	0.8
Total T4, nmol/l[b]		167 (127-224)		157 (144-204)	0.8
CRP, mg/l[b]		42 (23-63)		34 (24-61)	0.8

CRP = C-reactive protein; IQR = interquartile range; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.
a) Mann-Whitney U-test, χ^2 test, or Fisher's exact test.
b) Missing values not included.
c) % corresponds to the % among those with thyroid scintigraphy or ultrasound examination.
d) Defined as: TSH < 0.3 mIU/l and total T3 > 2.5 nmol/l and/or total T4 > 140 nmol/l and/or free T4 > 18.8 pmol/l.
e) Defined as: CRP ≥ 8 mg/l.

DISCUSSION

In a Danish regional investigation, retrospective evaluation of all consecutive patients managed in hospital during a three-year period verified a SAT diagnosis in 62% of cases. Patient and disease characteristics confirmed that the disease is predominant in middle-aged patients and characterised by a female predominance. Furthermore, our results substantiated the biphasic biochemical thyroid response. They also indicated that CRP is elevated in a substantial number of cases and that scintigraphy performed more than 30 days after symptom debut is of limited value. Figures on treatment showed that two in every three patients received treatment recommended for SAT (NSAIDs, prednisolone and/or beta-blockers), and one in every three patients initiated thyroid hormone replacement therapy, which was continued beyond two years of follow-up in half of the cases, suggesting an outcome of permanent hypothyroidism in 10-15%.

SAT may be difficult to differentiate from other subtypes of thyroiditis and other types of thyroid disease at the initial examination, but correct diagnosis is important to ensure proper treatment and patient information regarding disease aetiology, course and prognosis [3, 4]. Observational studies constitute the main source of evidence; moreover, to provide valid information on disease outcomes, a high validity of the exposure is also of considerable importance. In general, the validity of a diagnosis in the DNPR varies with reported PPVs in the range from less than 15% to 100% [11]. A previous study validated the diagnosis of hyper- and hypothyroidism in the DNPR and reported that the review of medical records revealed misclassification in less than 2% of the cases [12]. This suggests a higher validity of the subgroups of hyper- and hypothyroidism than for the specific diagnosis of SAT. We found that the diagnosis of SAT was verified in 62% of patients, which is in line with a study from China [13]. Here, the authors found a PPV of 58% among 309 patients suspected of having SAT and referred for in-hospital thyroid imaging.

Among verified SAT cases from 2016-2018, we found an incidence rate of 2.4/100,000/year, which was age-adjusted to the Danish population. Another Danish study previously found an age-adjusted incidence rate of 2.0/100,000/year in 1997-2000 [8]. Although the studies were conducted at a 20-year interval, the observed incidence rates are similar. The previous study was part of the DanThyr monitoring programme of iodine fortification in Denmark [7]. Mandatory iodine fortification was initiated in Denmark in July 2000. Thus, the previous Danish study within DanThyr reports from the time prior to iodine fortification when mild to moderate iodine deficiency was seen [8]. DanThyr monitored all new cases of thyroid dysfunction from laboratory results, including cases managed in general practice alone. The patients were invited for in-hospital verification of the diagnosis. Thus, this procedure may have captured more SAT cases, e.g., mild cases that would otherwise have been followed in general practice alone [8]. The DanThyr monitoring was still ongoing during the present study, and seven cases were identified via DanThyr. These study similarities may explain the quite similar incidence rates observed in our and the previous Danish study. Fatourechi et al. reported an incidence rate of 3.6/100,000/year in the 1990s in the United States; slightly higher than the Danish figures, but with a similar methodology [14].

Our findings regarding patient and disease characteristics and treatment are overall comparable with previous reports [13-17]. However, numbers were small in our stratified treatment groups, which limited further investigation. An important clinical aspect regarding SAT patients is thyroid hormone replacement therapy and the outcome of permanent hypothyroidism. Our evaluation of this outcome was challenged by the retrospective design of our study and the lack of information regarding patient follow-up in general practice. It is a characteristic of SAT that thyroid function often recovers, and an attempt should be made to withdraw thyroid hormone replacement therapy to avoid unnecessary lifelong treatment [3, 4]. Our results suggest that such treatment withdrawal was not attempted in all patients, which is an important focus of future investigations. Regarding inflammatory markers, previous studies mainly assessed ESR. However, this parameter could not be

evaluated in our study since very few measurements were available. This may be explained by the fact that ESR performed in general practice is not registered in the laboratory system. Other reports have indicated that ESR is superior to CRP [13, 16], but also that high levels of CRP may be a predictor of hypothyroidism during SAT [18]. More studies on CRP and other potential biomarkers in diagnosing and monitoring SAT patients are warranted to extend these findings.

This was a retrospective cohort study, and the consecutive inclusion used reduces the risk of selection bias. However, the conditioning on hospital diagnosis may have introduced a risk of referral bias [19]. Since symptoms of thyroid disease may be sparse or unspecific [20], it likely differs whether and when patients seek medical care, which may have challenged the assessment at different time points. Our study population was identified from the DNPR. Thereby, we were able to provide figures on PPV. However, our study was not designed to evaluate the completeness of a SAT diagnosis in the register or to provide figures on the negative predictive value. A detailed review of all information gathered in the medical record was prepared retrospectively for each case with no contact with the patient or the responsible physician. However, we consider potential information bias non-differential in relation to the diagnosis of SAT.

CONCLUSION

This study provided figures on the validity, incidence and characteristics of SAT. The findings inform clinical practice and future scientific work. Further studies are warranted to extend the findings made, including studies exploring subtypes of thyroiditis and other thyroid disorders for comparison of patient and disease characteristics.

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