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# Thyroid Involvement In Behçet's Disease

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## Abstract

Thyroid disorders are among the most common endocrine diseases with a global prevalence estimated at 10%. Autoimmunity plays a crucial role in the majority of cases of thyroid dysfunctions. Frequent association of these thyropathies with other systemic and/or organ-specific dysimmune pathologies, including systemic antibodies-associated vasculitis is reported. However, thyroid disorders remain exceptional and unusual during other systemic vasculitis especially those of medium and large vessels and only sporadic observations are reported.

As a result, the exact significance of thyroid involvement during systemic vasculitis is not well known: fortuitous association? Specific endocrine involvement of the angiitis? Or two conditions of the same predisposing profile?

Behçet's disease (BD) is a systemic vasculitis of vessels of all types and all sizes, particularly common in young subjects, and with an important clinical polymorphism. Thyroid involvement is rarely studied in this disease.

The aim of this paper is to review thyroid dysfunctions during BD and their possible pathogenic mechanisms.

**Keywords:** Behçet's disease; Vasculitis; Thyroid disorders; Thyroid gland; Hypothyroidism; Autoimmunity;

## Abbreviations

**TSH:** thyroid stimulating hormone,

**TT4:** total thyroxine, T3: triiodothyronine,

**fT4:** free thyroxine,

**anti-Tg:** anti-thyroglobulinantibodies,

**anti-TPO:** anti-thyroid peroxidaseantibodies.

## Introduction

Thyroid disorders are among the most common endocrine diseases and are often primary due to damage of the thyroid gland itself [1-5]. Their global prevalence is estimated at 10% and are by far dominated by subclinical or asymptomatic forms (hypo- or hyper-thyroidism); overt or symptomatic forms are much rarer [6].

Autoimmunity plays a crucial role in the majority of cases of thyroid dysfunction (Hashimoto's thyroiditis, Graves' disease, postpartum lymphocytic thyroiditis, Riedel's fibrous thyroiditis, DeQuervain'ssubacute thyroiditis) [7]. Frequent association of these thyropathies with other systemic and/or organ-specific dysimmune pathologies [7,8], including systemic antibodies-mediatedvasculitis such as granulomatosis with polyangiitis(GPA), eosinophilicgranulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA) [9-12], cryoglobulinemia [13,14], and vasculitis of connective tissue diseases [7,8,12]. The common dysimmunesignature is at the base of the pathogenesis of the two affections.

In addition to these "dysimmune/autoimmune" angiitis, endocrine and especially thyroid disorders remain exceptional during systemic vasculitis [15]. They are mostly reported in association with angiitis of small size vessels suggesting a direct attack of the glandular parenchyma by the inflammatory vasculitic process [16]. Thyroid involvement during other systemic primary vasculitis (vasculitis of medium and large size vessels) is unusual [17] and only sporadic observations are reported [18-24].

As a result, the exact significance of thyroid dysfunctions during systemic vasculitis is not well known: fortuitous association?Specific endocrine involvement of vasculitis?Or two specific conditions of the same predisposing profile?[15].

Behçet's disease (BD) is a systemic vasculitis of vessels of all types (arteries, veins, and capillaries) and all size (small, medium, and large) particularly common in young subjects [25]. Its typical clinical presentation is that of recurrent oral and genital aphthousulcers and anterior uveitis with hypopyon[26]. The systemic manifestations of this vasculitis are very polymorphous, often severe and potentially fatal, affecting the heart and vessels (angio-Behçet), the nervous system (neuro-Behçet), the digestive tract (entero-Behçet), the eyes (oculo-Behçet), kidneys, lungs, joints, etc. .. [27-32].

In view of the important clinical polymorphism, its diagnosis is often based on diagnostic criteria, the most used of which are those of the International Study Group for Behçet's Disease (International Study Group for Bethet's Disease (ISGBD)) of 1999 [33] (table 1). New international criteria for the diagnosis of BD were established in 2006, revised in 2010 and recently in 2013.

The final criteria were published in 2014 "The International Criteria for Behcet's Disease (ICBD)" (table 2) [34], and characterized by a sensitivity of 93.9% and a specificity of 92.1%; far better than the long-standing 1990 ISGBD criteria where the sensitivity is only 81.2% and the specificity is 95.9%.

The aim of this paper is to review thyroid dysfunctions during BDand their possible pathogenic mechanisms.

**Table1**: Diagnostic criteria of Behcet's disease according to the ISGBD 1990 [33].

| Criterion | Description |
|---|---|
| Major criterion | recurrent oral aphthousulcers observed by a doctor or patient with at least three episodes during the last 12 months |
| Minor criteria | |
| Recurrent genital ulcer | Aphthous ulceration or scarring observed by a physician or reported reliably by patient |
| Skin lesions | Erythemanodosum-like lesions, pseudofolliculitis, papulopustular lesions, or acneiform nodules. |
| Eye involvement | Anterior or posterior uveitis or retinitis/retinal vasculitis documented by an ophthalmologist |
| Positive pathergy test | Performed with oblique insertion of a ≤21-gauge needle under sterile conditions and interpreted by a physician at 24-48 hours |

Diagnosis= major criterion + at least two minor criteria.
**ISGBD**: the International Study Group for Behcet's Disease.

**Table 2**: The International Criteria for Behcet's Disease (ICBD 2014) [34].

| Signs/symptoms | Points |
|---|---|
| Oral aphthosis | 2 |
| Genital aphthous ulcer | 2 |
| Ocular injuries | 2 |
| Cutaneous lesions | 1 |
| Central nervous system involvement | 1 |
| Vascular manifestations | 1 |
| Positive pathergy test | 1 |

Diagnosis = if total score of four points or more.

## a. Endocrine involvement during BD

Endocrine involvement in BD is rare and little known, and the review of the world's literature finds only a few cases of pituitary gland, pituitary stalk, adrenalgland, ovarian, testicles involvement, and a clear resistance to insulin [35-43].

The exact mechanism of these attacks remains unclear. Associated autoimmune disease seems more plausible than direct attacks (via the underlying systemic vasculitis that characterizes BD) despite the hyper-vascularization of almost all endocrine glands [36].

Pituitary involvement (partial or total: panhypopituitarism) is most frequent during BD by specific inflammatory vascular mechanism (hypothalamic-pituitary leukocytoclasticvasculitis) because the pituitary gland is the best vascularized organ of the human body [ 41] and some of these endocrinopathies, particularly prolactin, growth hormone (GH), and dihydroepiandrosterone sulfate (DHEAS) disturbances appear to be correlated with Behcet'sdisease activity [40].

## b.Thyroid gland involvement during BD

Affections of the thyroid gland during BD are the least known and the least reported. The first study to have systematically screened for thyroid function in BD was that ofMuderrisoglu H et al, conducted in 1988, testing the baseline fT4, T3, and TSH in 13 patients with BD would not have shown any abnormality [42].

Then, Aksu K et al, in 1999 in a small sample of Turkish patients with BD, concluded that baseline thyroid tests (T3, fT4, and TSH) were within the normal range of the general population [20] .

Larger scale, comparative, and dynamic studies of thyroid function and thyrotropic axis during BD followed one another:

- The study by Cebeci F et al, comparing 124 Turkish patients with BD to a sex- and age-matched healthy population sample, did not show significant differences in the frequency of autoimmune thyroiditis, positivity of anti-thyroid antibodies : anti-Tg and/ or anti-TPO antibodies, frequency of hypothyroidism, frequency of uncomplicated hypothyroidism, frequency of autoimmune hyperthyroidism, and the mean value of TSH between the two groups. In contrast, the mean value of fT4 was significantly lower during BD compared to the general population: 1.11 ± 0.19 ng/dl versus 1.21 ± 0.19 ng/dl, p = 0.000 [ 21].

- The clinical-biological and radiological study of Ersoy R et al, comparing 50 subjects with BD to a matched sample of healthy controls found no significant difference between the two groups in the mean values of TSH, T3 and fT4, the prevalence of antithyroid antibodiespositivity, thyroid morphological abnormalities (goiter, nodule, atrophy, etc..) and the thyroid volume appreciated by imaging [44].

- The analysis of baseline thyroid tests by Akdeniz S et al in 30 patients with BD showed no significant difference compared to a group of healthy controls matched for age and sex for thyroid hormones and their free fractions including T3, TT4, fT3 and fT4. In contrast, TSH was significantly lower in the group with BD compared to the general population: 1.28 ± 0.688 µIU/ml versus 1.83 ± 1.06 µIU/ml, p = 0.02 indicating deficiency of central origin [41].

This hypothesis was confirmed by the dynamic tests with assay of the TSH response at 20 and 60 minutes after an injection of TRH. The response in the group with BD was significantly lower than in the group of healthy controls (TSH at 20 minutes: 9.63 ± 5.3 µIU/ml versus 15.29 ± 0.33 µIU/ml, p=0, 03 and TSH at 60 minutes: 8.4 ± 4.89 µIU/ml versus 11.07 ± 5.23 µIU/ml, p=0.05) confirming the pituitary origin of thyroid hormone deficiency [41].

- The study of Karakus S et al, performed in 43 patients with BD of both sexes and different ages had not shown significant differences for all thyroid biologic tests (fT4 and TSH) compared to two groups controls: subjects with systemic lupus erythematosus and healthy subjects matched for age and sex. On the other hand, the T3 level was significantly higher in the Behçet group compared to healthy subjects (p1=0.002) and those with systemic lupus erythematosus (p2=0.006) while remaining within the normal range for all patients and had no clinical impact [40]. In the Behçet group, no statistically significant difference was observed for the various thyroid hormones measured (T3, fT4 and TSH) according to the active or inactive status of the disease or whether or not there was severe visceral involvement of the disease, especially ocular [40].

### c. Mechanisms of thyroid involvement in BD

Involvement of the thyroid gland during BD can result from two main mechanisms [21]:

- Specific direct attacks: leukocytoclasticvasculitis of the thyroid arteries (thyroid involvement by thyroid vasculitis),

- Autoimmune disease: associated autoimmune thyroiditis because of the dysimmuneprofile that presents the BD.

### d. A direct damage of the thyroid gland by BD vasculitis

The thyroid as a richly vascularized organ may be a preferred target during vasculitis of Behçet's disease [21,44] whereas thyroid involvement is rarely studied in this pathology [21,44]. Exceptionally some sporadic cases of functional disorders (hypo- or hyper-thyroidism) have been reported during BD [45,46] as well as some cases of thyroid cancer, and more rarely some morphological abnormalities (nodules and goiter) [21, 47-50].

Thus, the 13th International Conference on Behçet's Disease (13th ICBD) held in Austria in 2008 had recognized thyroid gland involvement as a possible rare event in BD; the various thyropathies mentioned were: Graves' disease, Hashimoto's thyroiditis, thyroid nodule (s) and diffuse goiter [51].

The significant decrease in fT4 levels during BD compared to the general population in the Cebeci F et alseries, and the absence of any thyroid immunological abnormalities, is suggestive of a direct thyroid parenchymal involvement by the vasculitic process [21].

Morphological changes in the thyroid gland can be seen during BD, without having any impact on the hormonal functioning of the gland; this again testifies to the vasculitic mechanism of thyroid glandular involvement during BD [21]. The authors recommend the morphological and hormonal investigations of the thyroid during BD rather than the thyroid immunological test, which does not seem to have any diagnostic or prognostic implications [21].

### e. An association between two dysimmune diseases

The Lockwood CM et al study, once again, suggests the major role of auto-reactive T cells in the pathogenesis of BD [52]. This mechanism represents another hypothetical pathway that can explain, in part, the thyroid dysfunction during BD, since the role of these lymphocytes is well documented in the pathogenesis of thyroid autoimmune thyroiditis [53] mainly via "thyroglobulin-reactive T cells"[54].

Indeed, the experimental study of Kolypetri P et al, had demonstrated that self-reactive T cells are required both for the development and maintenance of spontaneous autoimmune thyroiditis (Spontaneous Autoimmune Thyroiditis, SAIT): It is the epitope p2549-2560 of thyroglobulin which contains thyrosin at position 2553 (T4p2553), which induces a strong specific response of self-reactive T cells generating autoimmune thyroiditis in NOD.H2(h4) mice [55].

From another meaning, the study by Soy M et al, seeking to catalog systemic diseases, particularly those of dys-immune mechanism, in association with autoimmune thyropathies, had objectified a frequency of 18% of recurrent aphtosis stomatitis (a major sign of BD) in subjects with autoimmune hypothyroidism [56]. Similarly, the study by Arnaout MA et al, Seeking to quantify the prevalence of abnormalities of thyroid tests in patients followed for connective tissue diseasesand systemic vasculitis (including BD), had objectified :subclinical and/or overt hypothyroidism in two/24 patients with BD (8.3%), and positive antithyroid antibodies, independent of the clinical presentation of underlying thyropathy, in two patients/24 with BD (8.3%) [43].

### f. Iatrogenic association between BD and thyroid dysfunction

The association of thyropathy with BD may be iatrogenic: Some therapies used during BD may influence thyroid function, as such:

The treatment of BD with CAMPATH-1H, a humanized anti-CD52 that causes lymphocyte depletion, may be the cause of primary hypothyroidism. The Lockwood CM et al study, reporting 18 patients with active BD requiring treatment with a single course of CAMPATH-1H at 134 mg to achieve remission in 72% of cases, noted the appearance of primary hypothyroidism in two patients(11% of cases) [52].

Similarly, the study by Mohammad AJ et al, conducted in patients with refractory BD requiring the use of Alemtuzumab® (anti-CD52), reported subclinicalautoimmune thyropathies as a complication of this treatment in 25% of patients[57].

Interferon biotherapy, which is increasingly used in severe forms of BD [58,59], may be the cause of autoimmune hypothyroidism particularly in patients who already have asymptomatic antithyroid antibodies[59,60]. It should also be recalled that cases of Behçet induced by treatment with interferon-

α2a and interferon-ϒ have been reported [60]. The possible induction of thyropathy and BD by recombinant interferon suggests a dys-immune origin common to these two conditions (predisposing dys-immune profile that will subsequently be amplified and maintained by this molecule) [ 60].

Finally, it should be noted that long-term corticosteroid therapy, a treatment frequently prescribed during BD, may also influence thyroid biological tests [41].

### g. Other anecdotic thyropathies associated to BD

Certain conditions, which are far from rare in BD, particularly depression and schizophrenia, may alter or rather influence thyroid tests [41]; in fact, these manifestations are frequent during the course of BD with neurological involvement (neuro-Behçet) which is seen in 2.5 to 49% of cases [61,62]. Depression is particularly frequent during BD: the study of Ishchenko DA et al, had objectified it in 40% of patients with BD (28.3% of recurrent depressive disorders and 11.7% of mild to moderate depressive episodes) [63]. Its prevalence can reach 86% at the beginning of the disease according to some authors [64]. As for schizophrenia, it is much rarer during BD [65].

Finally, there are two anecdotal cases of thyroid damage during BD:

- Chung SY et al, reported an original case of tuberculous thyroiditis in a woman with BD [66]. As a result, the possibility of infectious thyroiditis must always be kept in mind since BD is an immunosuppressive condition with often long-term systemic corticosteroids and immunosuppressive therapy.

- Similarly, another anecdotal case of "Black thyroid" associated with a hyalinizing trabecular tumor has been reported in a 42-year-old patient with an underlying BD, without giving any idea about the values of thyroid tests [67].

These various possible disorders of the thyroid gland during Behçet's disease and their mechanisms are summarized in Figure 1 (Figure.1).

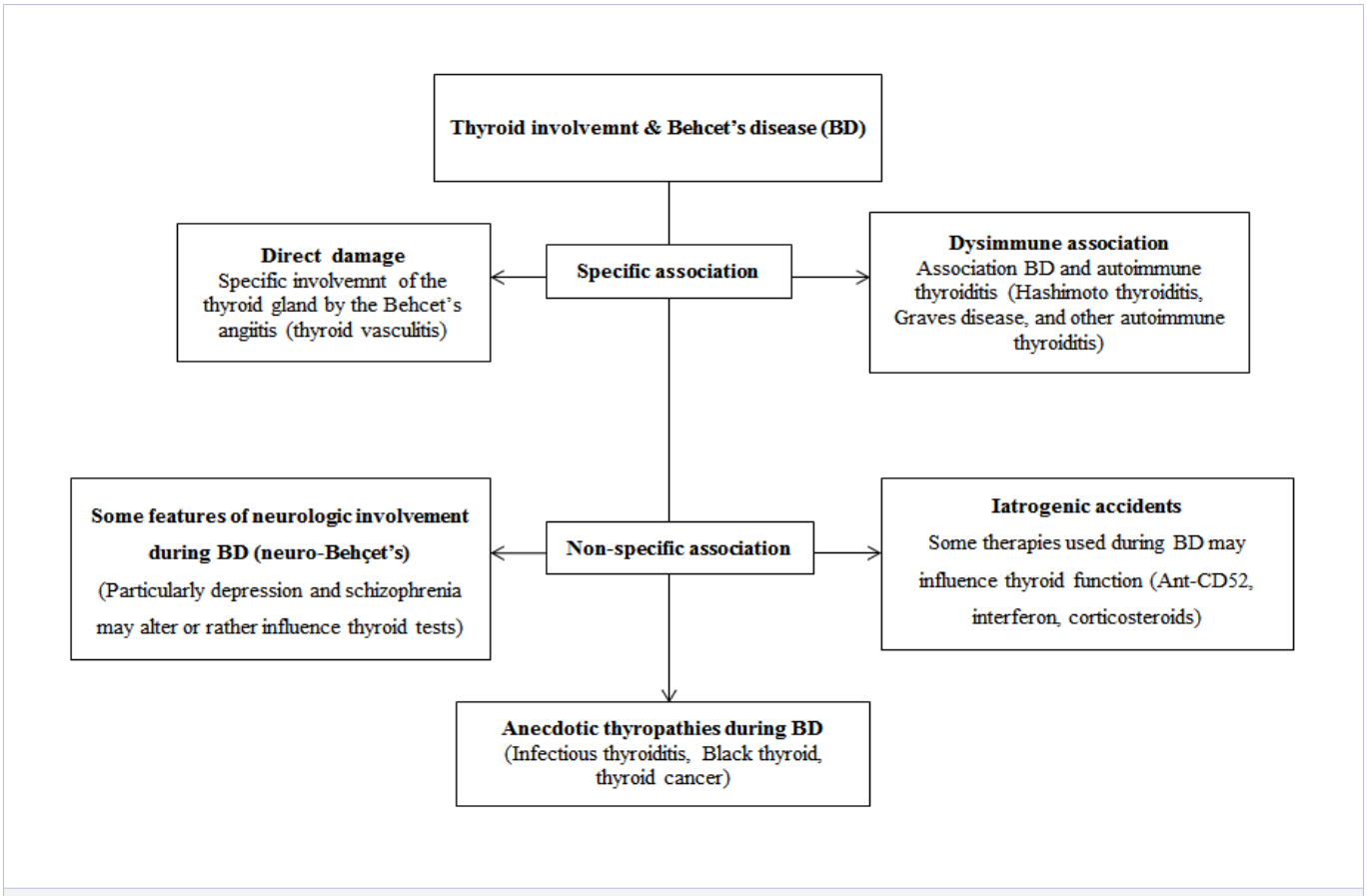


**Figure 1:** Schematic summary of the various possible involvement of the thyroid gland during Behçet's disease, and their mechanisms

## Conclusion

Affection of the thyroid gland during the BD seems to be far from a mere coincidence. Several findings of temporal and evolutionary concordance argue in favor of a causal association. Autoimmunity plays a major role in this association, suggesting a common immunological mechanism involved in the genesis of these two conditions (autoimmune thyoiditis and BD). Direct and specific thyroid involvement of BD seems much rarer (thyroid vasculitis). The possibility of thyroid cancer must also be evoked and sought after because of the proven carcinogenicity of BD.

Thyroid injury during BD can sometimes be severe and condition the prognosis hence the particular interest of a systematic screening, recommended by several authors, with static thyroid tests and thyroid imaging in any patient having a BD.

The early detection of these lesions makes it possible to take care of them adequately and in time thus improving the prognosis of this systemic vasculitis which can be fatal.

## References

1. Zaccarelli-Marino MA, Saldiva André CD, Singer JM. Overt Primary Hypothyroidism in an Industrial Area in São Paulo, Brazil: The Impact of Public Disclosure. Int J Environ Res Public Health. 2016;13(11).
2. Escribano-Serrano J, Mancera-Romero J, Santos-Sánchez V, Payá-Giner C, Méndez-Esteban MI, García-Bonilla A et al. Prevalence of Hypothyroidism in Andalusia, Spain, Determined by Thyroid Hormone Comsumption. Rev Esp Salud Publica. 2016;90:e1-e12.
3. Unnikrishnan AG, Kalra S, Sahay RK, Bantwal G, John M, Tewari N. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. Indian J Endocrinol Metab. 2013;17(4):647-52. doi: 10.4103/2230-8210.113755
4. Murthy MB, Jain SS, Ramteke KB, Raparti GT. Thyroid: Disorders, disruptors and drugs. Int J NutrPharmacolNeurol Dis. 2013;3(2):87-95.
5. Almandoz JP, Gharib H. Hypothyroidism: etiology, diagnosis, and management. Med Clin North Am. 2012;96(2):203-221.
6. Kasagi K, Takahashi N, Inoue G, Honda T, Kawachi Y, Izumi Y. Thyroid function in Japanese adults as assessed by a general health checkup system in relation with thyroid-related antibodies and other clinical parameters. Thyroid. 2009;19(9):937-44.
7. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev. 2015;14(2):174-180. doi: 10.1016/j.autrev.2014.10.016
8. Watad A, Mahroum N, Whitby A, Gertel S, Comaneshter D, Cohen AD et al. Hypothyroidism among SLE patients: Case-control study. Autoimmun Rev. 2016;15(5):484-486. doi: 10.1016/j.autrev.2016.01.019
9. Bouomrani S, Ben Hamad M, Regaïeg N, Belgacem N, Trabelsi S. Endocrine involvement in granulomatosis with polyangiitis. Res Rev Insights. 2018;2(2):1-3. doi: 10.15761/RRI.1000131
10. Rothe HM, Siegmund J, Müller H, Wopperer J. Association of ANCA-positive vasculitis with thyroid disease. Nephrol Dial Transplant. 2008;23(6):2107. doi: 10.1093/ndt/gfn030
11. Tanaka A, Maeda K, Sawai K, Okuda J, Sugawara A, Kuwahara T. Concealed hypothyroidism in patients with myeloperoxidase antineutrophili cytoplasmic autoantibodies- (MPO-ANCA) positive renal disease. ClinNephrol. 1999;52(2):91-95.
12. Ghorbel IB, Feki NB, Salem TB, Hamzaoui A, Khanfir M, Lamloum M et al. Microscopic polyangiitis associated with primary biliary cirrhosis, Sjogren's syndrome and Hashimoto's thyroiditis. Saudi J Kidney Dis Transpl. 2015;26(2):359-362.
13. Fallahi P, Ferrari SM, Ruffilli I, Elia G, Giuggioli D, Colaci M et al. Incidence of thyroid disorders in mixed cryoglobulinemia: Results from a longitudinal follow-up. Autoimmun Rev. 2016;15(7):747-751.
14. Fallahi P, Ferrari SM, Giuggioli D, Corrado A, Fabiani S, Marchi S et al. Mixed cryoglobulinemia and thyroid autoimmune disorders. Clin Ter. 2013;164(4):e337-41. doi: 10.7417/CT.2013.1598
15. Bouomrani S. Thyroid Disorders in Systemic Angiitis: Myth or Reality?. EC Endocrinology and Metabolic Research. 2018;3(3):133-135.
16. Oner A, Demircin G, Tinaztepe K, Akinci A, Tezic T. Henoch-Schonlein nephritis associated with subacute thyroiditis. Turk J Pediatr. 1996;38(1):131-135.
17. Bouomrani S, Trabelsi S, HalwaniCh, Ben Hamad M, Regaïeg N, Belgacem N, et al. Thyroid Involvement in Takayasu's Disease. Rep Thyroid Res. 2018; 2(1):105-109.
18. Schneider I, Pályi I, Dobos J. Cutaneous benign polyarteriitisnodosa. Simultaneous occurrence with autoimmune hyperthyreosis. DermatolMonatsschr. 1981;167(7):418-424.
19. Shih G, Shih WJ, Huang WS, Milan PP. Hashimoto thyroiditis and Takayasuaortitis: visualization of the thyroid gland and ring appearance of the mediastinum on F-18-FDG PET. Clin Nucl Med. 2008;33(5):377-379.
20. Aksu K, Oksel F, Keser G, Ozgen AG, Ynal V, Kabalak T et al. Thyroid functions in Behçet's disease. ClinEndocrinol (Oxf). 1999;50(3):406-407.
21. Cebeci F, Onsun N, Pekdemir A, Uras AR, Kayataş K. Thyroid autoimmunity and Behçet's disease: is there a significant association? ScientificWorldJournal. 2013;2013:956837.
22. Wiseman P, Stewart K, Rai GS. Hypothyroidism in polymyalgia rheumatica and giant cell arteritis. BMJ. 1989;298(6674):647-648.
23. Stewart I, Ridway J. Hypothyroidism and thyroid antibodies in polymyalgia rheumatica. Br J Rheumatol. 1992;31(3):214.
24. Bowness P, Shotliff K, Middlemiss A, Myles AB. Prevalence of hypothyroidism in patients with polymyalgia rheumatica and giant cell arteritis. Br J Rheumatol. 1991;30(5):349-351.
25. Holl-Ulrich K. Vasculitis: New nomenclature of the Chapel Hill consensus conference 2012. Z Rheumatol. 2014;73(9):823-833. doi: 10.1007/s00393-014-1477-x
26. Behcet H. Uberrezidivierende, aphtose, dürchein Virus verursachteGeshwure am Munde, am Auge und an den Genitalien. DermatologischeWochenschrift 1937;36:1152-1157.
27. Bouomrani S, Hammami S, Braham R, Mahjoub S. Ciclosporin-associated cerebral tumor-like location of Behçet's disease. Rev Neurol (Paris). 2010;166(10):849-854. doi: 10.1016/j.neurol.2010.01.010
28. Bouomrani S, Baïli H, Beji M. Fatal bilateral pulmonary aneurysm in Behçet disease. Research fr. 2016;3:1545.

29. Hammami S, Barhoumi A, Bouomrani S, Harzallah O, Mahjoub S. Double etiology of recurrent thrombophlebitis: Behçet's disease and inferior vena cava agenesis. AnadoluKardiyolDerg. 2009;9:428-429.
30. Yazici H, Seyahi E, Hatemi G, Yazici Y. Behçet syndrome: a contemporary view. Nat Rev Rheumatol. 2018;14(2):107-119. doi: 10.1038/nrrheum.2017.208
31. Bouomrani S, Belgacem N, Rekik F, Baïli H, Trabelsi S, Lassoued N, Beji M. Bilateral Synchronous Retrobulbar Optic Neuritis Inaugural of Behçet's Disease. EC Ophthalmology 5.4 (2017): 141-144.
32. Bouomrani S, Farah A, Bouassida N, Ayadi N, Béji M. Orbital inflammatory pseudotumor with optic neuritis in Behçet's disease. J Fr Ophtalmol. 2012;35:439.e1-6. doi: 10.1016/j.jfo.2011.08.018
33. International Study Group for Behçet's disease: criteria for diagnosis of Behçet's disease. Lancet 1990;335(8697):1078–1080.
34. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28(3):338-47. doi: 10.1111/jdv.12107
35. Labib M, Haddon A, Delamere J. Behçet's disease and hypopituitarism: a possible link. Ann ClinBiochem. 1994;31(Pt 5):506-507.
36. Ozhan O, Sezer K. Behcet's Disease and Endocrine System. Patholog Res Int. 2012. doi: 10.1155/2012/827815
37. Otsuka F, Amano T, Ogura T, Ota Z. Diabetes insipidus with Behçet's disease. Lancet. 1995;346(8988):1494-1495.
38. Khiari K, Cherif L, Hadj Ali I, Abderrahim E, Turki S, Ben Abdallah N. Etiologic and therapeutic aspects of acquired central diabetes insipidus. Ann Endocrinol (Paris). 2004;65(3):213-220.
39. Mont'Alverne AR, Yamakami LY, Gonçalves CR, Baracat EC, Bonfá E, Silva CA. Diminished ovarian reserve in Behçet's disease patients. ClinRheumatol. 2015;34(1):179-183.
40. Karakuş S, Nar A, Toprak SK, Atalay F, Özcebe Oİ. An Evaluation of Hormone Levels in Behçet's Disease. Arch Rheumatol. 2012;27(3):158-164. doi: 10.5606/tjr.2012.027
41. Akdeniz S, Colak S, Tuzcu AK, Bahceci M, Harman M. Baseline and stimulated thyroid functions in Behçet's disease. J EurAcadDermatolVenereol. 2006;20(7):878-879.
42. Muderrisoglu IH, Sivri B, Kansu E, Telatar F. Thyroid Functions in Behçet's Disease. Journal of Islamic Academy of Sciences. 1988;1:40-42.
43. Arnaout MA, Nasrallah NS, el-Khateeb MS. Prevalence of abnormal thyroid function tests in connective tissue disease. Scand J Rheumatol. 1994;23(3):128-132.
44. Ersoy R, Ersoy O, Tatlıcan S, Yayar Ö, Gümüş M, Çakır B. The Thyroid in Behcet's Disease: Hormonal and Ultrasonographic Findings. Turk J EndocrinolMetab. 2007;11:70-72.
45. Abro AH, Abdou AMS, Saleh JA, Ustadi AM, Younis NJ, Doleh WF. Behcet's disease associated with hyperthyroidism: A case report and literature review of Behcet's Disease. Pak J Med Sci. 2010;26(2):464-469.
46. Gönül M, Hızlı P, Gül U. Half-and-half nail in Behçet's disease. Int J Dermatol. 2014;53(1):e26-7. doi: 10.1111/j.1365-4632.2012.05471.x
47. Zhang Y, Sun A, Zhang B, Zhong Y, Dong R, Fan D. The clinical electrophysiology and pathological characteristics of 15 cases of vasculitic neuropathy. ZhonghuaNeiKeZaZhi. 2014;53(5):384-389.
48. Lin Y, Li G, Zheng W, Tian X, Zhang F. Behcet's disease associated with malignancy: a report of 41 Chinese cases. Int J Rheum Dis. 2014;17(4):459-465. doi: 10.1111/1756-185X.12269
49. Ahn JK, Oh JM, Lee J, Koh EM, Cha HS. Behcet's disease associated with malignancy in Korea: a single center experience. Rheumatol Int. 2010;30(6):831-835.
50. Kaklamani VG, Tzonou A, Kaklamanis PG. Behçet's disease associated with malignancies. Report of two cases and review of the literature. ClinExpRheumatol. 2005;23(4 Suppl 38):S35-41.
51. Dejaco C, Duftner C, Calamia KT, Schirmer M. 13th International Conference on Behçet's Disease, May 24-27, 2008, Pörtschach am Wörthersee, Austria. J Rheumatol. 2009;36(6):1312-1317.
52. Lockwood CM, Hale G, Waldman H, Jayne DR. Remission induction in Behçet's disease following lymphocyte depletion by the anti-CD52 antibody CAMPATH 1-H. Rheumatology (Oxford). 2003;42(12):1539-1544.
53. Allen EM, Thupari JN. Thyroglobulin-reactive T lymphocytes in thyroiditis-prone BB/Wor rats. J Endocrinol Invest. 1995;18(1):45-49.
54. Kong YM, Brown NK, Morris GP, Flynn JC. The Essential Role of Circulating Thyroglobulin in Maintaining Dominance of Natural Regulatory T Cell Function to Prevent Autoimmune Thyroiditis. HormMetab Res. 2015;47(10):711-720. doi: 10.1055/s-0035-1548872
55. Kolypetri P, Carayanniotis K, Rahman S, Georghiou PE, Magafa V, Cordopatis P et al. The thyroxine-containing thyroglobulin peptide (aa 2549-2560) is a target epitope in iodide-accelerated spontaneous autoimmune thyroiditis. J Immunol. 2014;193(1):96-101. doi: 10.4049/jimmunol.1400561
56. Soy M, Guldiken S, Arikan E, Altun BU, Tugrul A. Frequency of rheumatic diseases in patients with autoimmune thyroid disease. Rheumatol Int. 2007;27(6):575-577.
57. Mohammad AJ, Smith RM, Chow YW, Chaudhry AN, Jayne DR. Alemtuzumab as Remission Induction Therapy in Behçet Disease: A 20-year Experience. J Rheumatol. 2015;42(10):1906-1913. doi: 10.3899/jrheum.141344
58. Kötter I, Zierhut M, Eckstein AK, Vonthein R, Ness T, Günaydin I et al. Human recombinant interferon alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis. Br J Ophthalmol. 2003;87:423-431.
59. Krause L, Altenburg A, Pleyer U, Köhler AK, Zouboulis CC, Foerster MH. Longterm visual prognosis of patients with ocular Adamantiades-Behçet's disease treated with interferon-alpha-2a. J Rheumatol. 2008;35(5):896-903.
60. Raanani P, Ben-Bassat I. Immune-mediated complications during interferon therapy in hematological patients. Acta Haematol. 2002;107(3):133-144.
61. Kürtüncü M, Tüzün E, Akman-Demir G. Behçet's Disease and Nervous System Involvement. Curr Treat Options Neurol. 2016;18(5):19. doi: 10.1007/s11940-016-0405-6

62. Davatchi F, Chams-Davatchi C, Shams H, Nadji A, Faezi T, Akhlaghi M et al. Adult Behcet's disease in Iran: analysis of 6075 patients. Int J Rheum Dis. 2016;19(1):95-103. doi: 10.1111/1756-185X.12691
63. Ishchenko DA, Veltishchev DY, Alekberova ZS, Lisitsyna TA, Kovalevskaya OB, Seravina OF et al. Psychotraumatic factors and anxiety-depressive spectrum disorders in Behcet's disease: the interdisciplinary study. ZhNevrolPsikhiatrIm S SKorsakova. 2014;114(11):14-9.
64. de Oliveira Ribeiro NP, de Mello Schier AR, Pessoa TM, Pereira VM, Machado S, Arias-Carrión O et al. Depression as a comorbidity in Behcet's syndrome. CNS NeurolDisord Drug Targets. 2014;13(6):1041-1048.
65. De Berardis D, Serroni N, Campanella D, Olivieri L, Marini S, Moschetta FS et al. Safety and efficacy of combined clozapine-azathioprine treatment in a case of resistant schizophrenia associated with Behçet's disease: a 2-year follow-up. Gen Hosp Psychiatry. 2013;35(2): 213.e9-213.e11.
66. Chung SY, Oh KK, Chang HS. Sonographic findings of tuberculous thyroiditis in a patient with Behçet's syndrome. J Clin Ultrasound. 2002;30(3):184-188.
67. Kang SW, Hong SW, Yeon PJ, Jeong JJ, Sung TY, Lee SC et al. A case of black thyroid associated with hyalinizing trabecular tumor. Endocr J. 2008;55(6):1109-1112.