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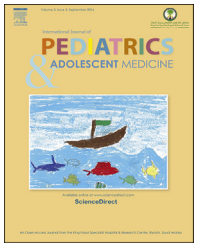

Original Research Article

Coexistence of endocrinopathies in children with rheumatic diseases

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Serum 25-hydroxyvitamin D

Abstract *Background and objectives:* To examine the frequency of endocrinopathies in children with systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA).
Design and setting: A cross-sectional study.
Patients and methods: A study was conducted in Saudi children with SLE and JIA who were seen at King Faisal Specialist Hospital and Research Centre, Riyadh, between September 2013 and April 2015. All enrolled patients completed the clinical evaluation, which included information about family history of autoimmune disease, growth parameters and tanner stage, as well as the following assessments: vitamin D profile (parathyroid hormone and 25-OH vitamin D levels), TSH, FT4 and total T3, thyroglobulin antibodies, thyroperoxidase antibodies, random blood sugar, Hb_{A1C}, IGF_1, IGF_{BP-3}, LH, and FSH.
Results: A total of 42 patients, 22 with JIA and 20 with SLE, were included in the study. The mean participant age was 12.2 ± 5.3 years with a mean disease duration of 3.2 ± 3.4 years. Female gender was predominant (17 SLE, 13 JIA) in the patient population. Fifteen patients (35.7%) presented with a family history of autoimmune disease. The most frequently detected endocrinopathies were vitamin D insufficiency (35%) and thyroid disease (31%). Eight JIA patients and 7 SLE patients exhibited low vitamin D levels; 10 patients presented with hyperparathyroidism. Thyroid dysfunction was observed in 13 patients (8 SLE, 5 JIA), and 2 patients were found to be euthyroid (normal TSH, FT4) with positive thyroid autoantibodies. Furthermore, 7 patients presented with subclinical hypothyroidism (high TSH, normal FT4), and 4 patients presented with overt hypothyroidism (high TSH, low FT4). Seven patients (4 SLE and 3 JIA) presented with short stature due to growth hormone insufficiency (low IGF_1, IGF_{BP-3}). Two patients exhibited delayed puberty accompanied by low LH levels. Diabetes mellitus was more frequently observed in patients with JIA (4 patients) than in patients with SLE (1 patient).
Conclusion: Our findings demonstrated that coexistence of endocrinopathies is not uncommon in children diagnosed with JIA and SLE. Abnormal thyroid function occurs frequently and at a

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similar rate in children diagnosed with SLE and JIA. Thus, screening for endocrinopathies, namely thyroid disease, during the assessment of childhood SLE and JIA is worth consideration.

1. Introduction

Autoimmunity plays a role in many inflammatory disorders including rheumatic diseases. Although the exact etiology of systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA) remains undefined, multiple etiologic factors including genetic, environmental, and hormonal factors might contribute to immune dysregulation and pathogenesis [1]. Growing evidence has indicated that vitamin D deficiency may be associated with an increased susceptibility of developing autoimmune diseases [2]. Furthermore, patients who have been diagnosed with autoimmune disorders have a higher probability of being affected by a second autoimmune disorder. Endocrinopathies have been frequently described in patients with autoimmune rheumatic diseases such as SLE and Sjögren's syndrome [3–5]. Interestingly, there is evidence suggesting that JIA shares many susceptibility loci with other autoimmune diseases [6].

Autoimmune endocrinopathies frequently overlap with autoimmune rheumatic diseases; the prevalence of various autoantibodies in patients with SLE and rheumatoid arthritis is not uncommon, indicating the importance of screening patients with SLE and systemic rheumatic diseases for the coexistence of other autoimmune diseases [7,8]. The presence of endocrinopathies in patients with autoimmune diseases has primarily been described in adult patients. Reports of the coexistence of endocrinopathies and childhood autoimmune diseases, namely childhood SLE and JIA, are scarce. Interestingly, some of the associated autoimmune disorders occur at a subclinical level, and the appearance of clinical manifestations may emerge late in the disease course [9,10].

In this study, we examined the frequency of selected endocrinopathies in children with SLE and JIA. We compared the results from children diagnosed with SLE to children diagnosed with JIA. We elucidated the impact of endocrinopathies on disease activity of childhood SLE.

2. Patients and methods

A cross-sectional study was conducted on Saudi children diagnosed with SLE and JIA who were followed at King Faisal Specialist Hospital and Research Centre, Riyadh, between September 2013 and April 2015. All enrolled patients were 14 years or younger. All SLE patients met the criteria of SLE diagnosis according to the Systemic Lupus International Collaborating Clinic classification criteria for systemic lupus erythematosus, and all patients diagnosed with JIA met the diagnostic criteria of the International League of Associations for Rheumatology [11,12]. All patients were assessed for demographic data and disease duration. Patients completed a clinical assessment that addressed family history of autoimmune disease, growth parameters, and tanner stage. They were evaluated for the following laboratory values: vitamin D profile (parathyroid hormone and 25-OH vitamin D levels), TSH, FT4 and total T3, thyroglobulin antibodies (TgA), thyroperoxidase antibodies (TPOA), random blood sugar, Hb_{A1C}, IGF_1, IGF_{BP-3}, LH, FSH, and Celiac disease panel. We considered vitamin D insufficiency to be an autoimmune disease regardless of the underlying cause, coexistence with endocrinopathies, the sequence of the disease, or the current treatment. The standard range in Saudi Arabia for total 25-OH vitamin D levels established by liquid chromatography-tandem mass spectrometry is 13–76 nmol/l, and the optimal concentration should exceed 75 nmol/l. We diagnosed patients with vitamin D insufficiency if the 25-OH vitamin D level was below 75 nmol/l. Additionally, we considered patients to have diabetes mellitus if the Hb_{A1C} value was greater than 0.065.

Complement (C3, C4) levels, anti-double-stranded DNA (anti-ds DNA) antibody and anti-nuclear antibody (ANA) were included in the analysis of patients with SLE. We also calculated the disease activity score using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [13].

All collected data were handled anonymously, and patient confidentiality was protected. Additionally, all collected data were acquired through routine clinical care. Informed consent was obtained from the parents of pediatric patients. The proposal was approved by the Research Affairs Council at KFSHRC.

3. Statistical methods

SAS 9.2 (SAS Institute Inc., Cary, NC, USA) software was used for statistical analysis. The variables were compared using 2-sample *t*-tests, chi-square tests, and Fisher's exact tests. The results are expressed as the mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Regression analysis was carried out to examine the influence of the variables on outcome measures. A P value of $<.05$ was considered statistically significant.

4. Results

A total of 42 Saudi children, 22 with JIA, and 20 with SLE, were included in the current study. The mean age was 12.2 ± 5.3 years with a mean disease duration of 4.2 ± 5.4 years. Female gender was predominant (17 SLE, 13 JIA). All SLE patients presented with multiple organ involvement and a mean SLEDAI score of 6 ± 5.6. Overall, nephritis (61%) was the most frequently detected major organ condition; none of the SLE patients exhibited renal impairment.

Patients exhibited an elevated ANA with a mean value of 965 (normal range: <40) and an elevated anti-ds DNA level with a mean value of 784 (normal range: 0–20). Ten patients presented with low C3 and C4 levels with mean values of 0.6 and 0.8 (normal range: 0.9–1.8 and 0.1–0.4), respectively. The JIA patient group was composed of 13 patients with polyarticular subtype JIA, 4 patients with oligoarticular subtype JIA and 5 patients with systemic onset subtype JIA. All SLE patients were treated with glucocorticoids, hydroxychloroquine, and immunosuppressive medications including cyclophosphamide, azathioprine, and mycophenolate mofetil. In contrast, JIA patients were treated with glucocorticoids, methotrexate, and biologic agents including TNF-inhibitors (either etanercept or adalimumab) or IL-6 inhibitors (tocilizumab). The mean dose of glucocorticoids for all patients was 0.5 ± 0.2 mg/kg/day.

Table 1 presents the spectrum of endocrinopathies in Saudi children with SLE and JIA.

Fifteen patients (35.7%) reported a family history of autoimmune disease. The most common autoimmune disease among family members was hypothyroidism; other diseases included hyperthyroidism, myasthenia gravis, SLE, rheumatoid arthritis, diabetes mellitus, vitiligo, and psoriasis.

The most frequently detected endocrinopathies were vitamin D insufficiency (35%) and thyroid disease (31%). Fifteen (8 JIA, 7 SLE) patients exhibited vitamin D insufficiency with a mean level of 51.1 ± 33.6 nmol/l; out of these patients, 10 had been diagnosed with secondary hyperparathyroidism, but none had been diagnosed with hypoparathyroidism.

Thyroid dysfunction was detected in 13 patients (8 SLE, 5 JIA); 2 patients were identified as euthyroid with positive thyroid autoantibodies (TgA ± TPOA) and normal TSH and FT4. Furthermore, 7 patients were diagnosed with subclinical hypothyroidism as manifested by high TSH and normal FT4. In contrast, 4 patients presented with overt hypothyroidism characterized by high TSH and low FT4. None of the patients in the current study exhibited thyrotoxicosis.

Nineteen patients (11 SLE, 8 JIA) presented with short stature for their age and gender; 7 patients (4 SLE and 3 JIA) exhibited growth hormone insufficiency as confirmed by low levels of IGF_1 and IGF_{BP-3}. Interestingly, one JIA patient presented with celiac disease confirmed by histopathology.

Two patients were diagnosed with delayed puberty via clinical assessment and low LH levels. The diagnosis of diabetes mellitus was confirmed by an elevated Hb_{A1C} value (>6.5%) and was more frequently detected in patients with JIA (4 patients) compared to SLE (1 patient); 2 patients were taking low doses of glucocorticoids.

Sixteen SLE patients were found to have an active form of the disease, characterized by a mean SLEDAI score of 6 ± 5.6. The levels of 25-OH vitamin D were inversely correlated with SLEDAI scores, but the correlation was not statistically significant (*P* values > .05). Other variables associated with endocrinopathy were not correlated with the SLEDAI score.

Table 1 Endocrinopathies in children with SLE and JIA.

	SLE	JIA
Total	20	22
Age	12.1	12.4
Gender (F:M)	17:3	13:9
Family history	7	8
Thyroid disease	8	5
Euthyroid	2	0
Subclinical hypothyroidism	4	3
Overt hypothyroidism	2	2
Vitamin D insufficiency	7	8
Growth hormone insufficiency	4	3
Diabetes mellitus	1	4
Delayed puberty	1	1

5. Discussion

The presence of an additional autoimmune disease is common in patients diagnosed with an autoimmune disorder characterized by multi-organ involvement and massive autoantibody production such as SLE. The majority of reports of endocrinopathies in children with SLE and JIA have focused on thyroid diseases, perhaps due to the ease in measuring thyroid hormones and thyroid antibodies. Previous reports demonstrated variable frequencies of autoimmune thyroiditis among children diagnosed with autoimmune diseases ranging between 5% and 44% [5,14,15]. In contrast, other endocrinopathies such as diabetes mellitus, delayed puberty, and short stature can be attributed to different factors and are not commonly studied.

In the current study, we examined the frequency of several endocrinopathies in 42 children diagnosed with SLE and JIA. One-third of our patients had relatives who had been diagnosed with an autoimmune disease. As previously reported, the prevalence of autoimmune diseases in the relatives of children with SLE and JIA is high, indicating that different autoimmune diseases may share common susceptibility genes [16,17]. Vitamin D insufficiency is commonly seen in children with chronic autoimmune diseases. In this study, children with SLE and JIA are equally affected; this observation confirms and supports findings from previous studies [18,19]. Remarkably, the frequency of vitamin D insufficiency is comparable to the frequency of thyroid disease in this cohort, which might indicate that vitamin D insufficiency is not simply related to glucocorticoid administration and may be associated with an increased incidence of autoimmune disease [2,20]. The serum concentration of 25-OH vitamin D was inversely correlated with SLE disease activity, which is consistent with previous reports [19,21]. Ten patients were diagnosed with hyperparathyroidism secondary to vitamin D deficiency, which improved after vitamin D treatment.

Thyroid dysfunction was frequently detected in patients in the current study, which was also described in previous reports [8,10]. Short stature and delayed puberty are known comorbidities of chronic inflammatory disease due to different causes. However, in the current study, short stature and delayed puberty were associated with hormone insufficiency, supporting the coexistence of

endocrinopathies in SLE and JIA patients. This study revealed a higher frequency of diabetes mellitus among patients diagnosed with JIA compared to SLE patients; this might be related to the presence of shared common susceptibility loci between JIA and diabetes mellitus [6]. Unfortunately, HLA typing was not performed in our patients.

Few studies have demonstrated an association between childhood SLE or JIA and celiac disease [22]. However, in the current study, we identified one JIA patient with celiac disease confirmed by histopathology.

6. Conclusion

In conclusion, our findings demonstrate that the coexistence of endocrinopathies is not uncommon in children diagnosed with JIA and SLE. Vitamin D insufficiency and abnormal thyroid function occur frequently and at similar rates in children diagnosed with SLE and JIA. Thus, careful screening for possible endocrinopathies, namely thyroid disease, during assessments of patients with childhood SLE and JIA is worth consideration.

Conflict of interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

[1] Molokhia M, McKeigue P. Systemic lupus erythematosus: genes versus environment in high-risk populations. Lupus 2006;15:827—32.
[2] Cutolo M. Vitamin D and autoimmune rheumatic diseases. Rheumatology (Oxford) 2009;48:210—2.
[3] Tagoe C, Zezon A, Khattri S. Rheumatic manifestations of autoimmune thyroid disease: the other autoimmune disease. J Rheumatol 2012;39:1125—9.
[4] McCoy S, Crowson C, Gabriel S, Matteson E. Hypothyroidism as a risk factor for development of cardiovascular disease in patients with rheumatoid arthritis. J Rheumatol 2012;39:954—8.
[5] Mihailova D, Grigorova R, Vassileva B, Mladenova G, Ivanova N, Stephanov S, et al. Autoimmune thyroid disorders in juvenile chronic arthritis and systemic lupus erythematosus. Adv Exp Med Biol 1999;455:55—60.
[6] Hinks A, Martin P, Flynn E, Eyre S, Packham J, Barton A, et al. Investigation of type 1 diabetes and coeliac disease susceptibility loci for association with juvenile idiopathic arthritis. Ann Rheum Dis 2010;69:2169—72.
[7] Lazúrová I, Benhatchi K, Rovenský J, Kozáková D, Wagnerová H, Tajtáková M, et al. Autoimmune thyroid disease and autoimmune rheumatic disorders: a two-sided analysis. Ann N Y Acad Sci 2009;1173:211—6.
[8] El-Sherif W, ElGendi S, Ashmawy M, Ahmed H, Salama M. Thyroid disorders and autoantibodies in systemic lupus erythematosus and rheumatoid arthritis patients. Egypt J Immunol 2004;11:81—90.
[9] Cooper G, Stroehla B. The epidemiology of autoimmune diseases. Autoimmun Rev 2003;2:119—25.
[10] Stagi S, Giani T, Simonini G, Falcini F. Thyroid function, autoimmune thyroiditis and coeliac disease in juvenile idiopathic arthritis. Rheumatology 2005;44:517—20.
[11] Petri M, Orbai A, Alarcón G, Gordon C, Merrill J, Fortin P, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinic classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677—86.
[12] Petty R, Southwood T, Baum J, Bhettay E, Glass D, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991—4.
[13] Brunner H, Silverman E, To T, Bombardier C, Feldman B. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. Arthritis Rheum 2002;46:436—44.
[14] Alpigiani M, Cerboni M, Bertini I, d'Ammuzio G, Haupt R, Lester A, et al. Endocrine autoimmunity in young patients with juvenile chronic arthritis. Clin Exp Rheumatol 2002;20:565—8.
[15] Unsal E, Oren O, Salar K, Makay B, Abaci A, Ozhan B, et al. The frequency of autoimmune thyroid disorders in juvenile idiopathic arthritis. Truk J Pediatr 2008;50:462—5.
[16] Prahalad S, Shear E, Thompson S, Giannini E, Glass D. Increased prevalence of familial autoimmunity in simplex and multiplex families with juvenile rheumatoid arthritis. Arthritis Rheum 2002;46:1851—6.
[17] Huang C, Yang Y, Chiang B. Different familial association patterns of autoimmune diseases between juvenile-onset systemic lupus erythematosus and juvenile rheumatoid arthritis. J Microbiol Immunol Infect 2004;37:88—94.
[18] Mok C, Wong S, Ma K. Childhood-onset disease carries a higher risk of low bone mineral density in adult population of systemic lupus erythematosus. Rheumatology (Oxford) 2012;51:468—75.
[19] AlSaleem A, AlE'ed A, AlSaghier A, Al-Mayouf SM. Vitamin D status in children with systemic lupus erythematosus and its association with clinical and laboratory parameters. Clin Rheumatol 2015;34:81—4.
[20] Bonakdar Z, Jahanshahifar L, Jahanshahifar F, Gholamrezaei A. Vitamin D deficiency and its association with disease activity in new cases of systemic lupus erythematosus. Lupus 2011;20:1155—60.
[21] Bogaczewicz J, Sysa-Jedrzeiowska A, Arkusewska C, Zabek J, Kontny E, McCauliffe D, et al. Vitamin D status in systemic lupus erythematosus patients and its association with selected clinical and laboratory parameters. Lupus 2012;21:477—84.
[22] Robazzi T, Adan L, Pimentel K, Magalhaes Fiho J, Toralles M, Rolim A. Autoimmune endocrine disorders and coeliac disease in children and adolescents with juvenile idiopathic arthritis and rheumatic fever. Clin Exp Rheumatol 2013;3:310—7.