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Systemic sclerosis induced by CNS stimulants for ADHD: A case series and review of the literature

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ABSTRACT

Introduction: Methylphenidate (Ritalin) is a CNS stimulant, and is a common treatment for children and adults with ADHD. It has been associated with Raynaud's phenomenon (RP) but not with Systemic Sclerosis (SSc). We report a case series of patients pointing out the connection between Methylphenidate and SSc.

Cases: We identified three patients in a single Rheumatology clinic in Israel, who developed SSc following treatment with CNS stimulants for ADHD. All three cases had Raynaud's phenomenon, skin changes, pathological capillaroscopy and positive ANA. Symptoms appeared and worsened over months following the use of methylphenidate and subsided after its cessation.

Conclusion: This is the first report in the literature of a causative relation between methylphenidate and the development of SSc, a serious, life-threatening condition. Patients treated with CNS stimulants should be followed closely for side-effects such as RP and skin changes.

1. Introduction

Raynaud's phenomenon (RP) is a clinical syndrome characterized by recurrent episodes of vasospasm involving peripheral small vessels, triggered by exposure to physical, chemical or emotional stress [1]. RP is very common in young adults with a prevalence of 3–5% in the general population [2,3]. Abnormalities of the blood vessel wall, of neural control mechanisms and of circulating factors are known to interact in the pathogenesis of RP [2].

RP is often referred to as primary or secondary depending on whether it occurs as an isolated condition with no associated cause (primary RP) or is associated with an underlying condition (mainly connective tissue diseases), or other causes of vasospasm in the blood vessels (secondary RP) [4].

Some drugs and toxic substances with a vasoconstrictor effect are associated with the development of RP [1,4,5]. Drug-induced RP is attributed mainly to chemotherapy drugs, cyclosporin, estrogens, sympathetic mimetic agents, non-selective beta blockers, etc.

Cases of RP induced by central nervous system (CNS) stimulants have been reported [5–10]. Medications used to treat attention deficit hyperactivity disorder (ADHD) cause central stimulation of the dopaminergic and noradrenergic system which is responsible for the peripheral release of catecholamines leading to vasoconstriction [5]. The largest study that investigated whether these ADHD medications were associated with the development of RP, was a retrospective case-control study by Goldman et al. in 2008 [7]. The authors enrolled 32 children with RP and compared them to a group of 32 matched controls without RP. A significant association between the presence of RP and past or current use of ADHD stimulants was found.

A retrospective chart review by Coulombe et al. identified high incidence of exposure to ADHD stimulants among children diagnosed with abnormal sensitivity to cold, but the rates of RP specifically were low and similar between groups [11]. None of the patients in these series and case reports was subsequently diagnosed with a connective tissue disease.

Systemic sclerosis (SSc) is a chronic connective tissue disease (CTD) characterized by inflammation and fibrosis of the skin, vascular abnormalities, visceral damage, and production of autoantibodies [12]. SSc is the CTD most frequently associated with RP (96%) [13–15], which is often the first clinical manifestation of SSc.

Some case reports about drug-induced SSc have been published [16–18] but none was secondary to the use of CNS stimulants to treat ADHD. Cocaine, an addictive stimulant, has been implicated in SSc and scleroderma-like disorders [19]. In reports of drug-induced sclerodermiform diseases, the lack of RP, capillaroscopic abnormalities or scleroderma-specific autoantibodies helped differentiate these conditions from SSc [20].

We describe a case series of 3 patients followed in a rheumatology

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clinic in a single center in Israel, that were diagnosed with SSc following treatment with CNS stimulants.

2. Cases

The first patient is a 41-year-old-female. She has had RP since around the age of 12 years. She was first prescribed methylphenidate (the most common CNS stimulant for ADHD) during her university studies, and at the age of 23 years, started taking the instant release formulation (Ritalin). Six months later, her RP worsened but she had no ulcers or skin changes. At the age of 26 years, she began adding the extended release form of methylphenidate (Concerta) intermittently and at the age of 37, began using it daily. At that time ANA was negative. After 10 months of daily use, a significant worsening of her RP appeared, while serologic tests revealed seroconversion of ANA and strongly positive anti-centromere. Over the following three years, she developed puffy fingers, sclerodactyly, telangiectasis, pathologic capillaroscopy and GERD, and by the age of 40 years was diagnosed with limited SSc. Following the diagnosis, she stopped using all forms of methylphenidate, which resulted in some improvement in RP but autoantibodies remained positive. Pulmonary function tests were normal, but serial echocardiograms demonstrated stable, mild pulmonary hypertension of 30–40 mmHg. Coronary CT and high-resolution CT of chest were normal. She is currently treated with proton pump inhibitors (PPI) and calcium channel blockers (CCB). She has had no pitting scars or ulcers so far and has no respiratory symptoms. Her modified Rodnan skin score (mRSS) is currently 4. She also has had premenstrual syndrome for the past 10 years.

The second patient is a 19-year-old-female. At the age of 10 she was diagnosed with ADHD and started taking the extended release form of methylphenidate (Concerta). She was otherwise a healthy young girl without concurrent use of medications or other substances. After a year of use she developed mild RP, but ANA was negative at the time. Over the next three years her RP symptoms worsened and she developed digital ischemia with pitting ulcers, sclerodactyly, weight loss and pathologic capillaroscopy. At that time, ANA became positive (1/640 titer, in a nucleolar pattern) but specific SSc serologies, as well as all other serologies were negative. She was then diagnosed with limited SSc and methylphenidate was stopped, resulting in some clinical improvement. Four months later, a trial to take the instant release formulation (Ritalin) resulted in immediate worsening of RP and digital ulcers. She stopped Ritalin after 2 months, and RP remained mild for 2 years, without digital ulcers. Then, a third trial of psychostimulant therapy (lisdexamfetamine) resulted in clinical worsening of RP and was stopped after 3 months. Currently, she also has GERD and telangiectasis. Her mRSS score is 4. She has no respiratory symptoms; pulmonary function tests and cardiac echo were normal. She was treated with PPI, iloprost, hydrochloroquine and CCB. She also has migraines.

The third patient is a 38-year-old female. Past medical history was significant for hypothyroidism diagnosed at the age of 28 years. At the same age, she was prescribed the instant release formulation (Ritalin) of methylphenidate for ADHD. About 9 months later, she developed RP, sclerodactyly and positive ANA and was diagnosed with limited SSc. During the following year, she had digital ulcers and was treated with iloprost. Arthralgia was treated with hydroxychloroquine and methotrexate alternately. Her mRSS score was 18 and capillaroscopy was pathologic. She discontinued the drug after 14 months of use with some improvement of her symptoms, and mRSS decreased to 8. Pulmonary function tests demonstrated mildly decreased DLCO but serial cardiac echo tests were normal. Recent echo revealed mild pulmonary hypertension. Chest imaging was normal and she has no respiratory complaints. She was also diagnosed with migraines. Eight years after discontinuing the drug, ANA was negative, and the patient restarted Ritalin but stopped after 5 months due to worsening of RP. Her mRSS score is currently 4.

3. Discussion

ADHD affects around 3% to 4% of children and adolescents [21] and often continues into adulthood [22,23]. Methylphenidate, a CNS stimulant, is the first-line and most common pharmacological treatment for ADHD [24]. Known adverse events include decreased appetite, growth retardation and sleep disturbance, although most are transient [25].

CNS stimulants are sympathomimetics that cause vasoconstriction and have been associated with RP [5–10]. A review of literature did not reveal any reported cases of SSc induced by CNS stimulants used for ADHD.

In the last decade, we have recognized an increasing number of patients in our rheumatology clinic with RP who were recently treated with CNS stimulants for ADHD. The patients described above developed RP, as well as full-blown SSc after the use of methylphenidate.

Goldman et al. [7] reported an association between the presence of RP and use of CNS stimulants but the timing of the appearance of RP in relation to the drug use was not specified. Notably, in the six cases of RP associated with ADHD medication use, there were no other signs of SSc or other CTD.

Andreussi et al. recently described two cases of SSc associated with cocaine use, with predominantly vascular involvement, including multiple ulcers and SRC [19]. Interestingly, the signs and symptoms of the disease appeared after years of drug abuse.

In contrast to these reports, in the current case series, signs and symptoms of SSc appeared sooner - after only several months of treatment. In the first patient, Ritalin aggravated the known RP, and in the two other cases, RP appeared for the first time after months of treatment. In all three cases, cessation of methylphenidate resulted in clinical improvement. The two latter patients tried to renew therapy with CNS stimulants but symptoms reappeared even earlier with second and third exposures. Furthermore, all 3 cases subsequently developed skin changes and pathological capillaroscopy. Based on these findings, we deduced that methylphenidate treatment in susceptible patients might cause RP and SSc within months.

Patients described in most of the above-mentioned case reports of drug-induced SSc did not have specific auto-antibodies. In our study, the first patient had positive ANA and anti-centromere, while the other two had ANA only, without specific scleroderma-related antibodies. Moreover, in the first two cases, in conjunction with exacerbation of symptoms, the previously negative ANA turned positive, a fact that strengthens our belief that the CNS stimulant, methylphenidate unveils an autoimmune predisposition in some patients.

Migraine is considered a vasospastic condition and is strongly associated with RP [3]. Two of our patients developed migraine headaches, another possible clue to their microvascular vulnerability.

Our findings suggest a causative relation between methylphenidate and the development of SSc. These are the first three cases reported of this serious side-effect of CNS stimulants. Physicians should be aware that in patients with underlying RP, symptoms may worsen with these medications, and in rare cases they may even develop SSc.

These potential side-effects should be discussed with patients, especially if there are other signs of autoimmune or vasospastic conditions, such as migraines. Furthermore, once RP or skin changes appear, the medication should be stopped immediately and the patient must be followed closely.

Larger studies are needed to evaluate the risk of RP and SSc among patients treated with CNS stimulants, as well as to explore associations with specific formulations and doses.

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Declaration of Competing Interest

None.

References

[1] Prete M, Fatone MC, Favoino E, Perosa F. Raynaud's phenomenon: from molecular pathogenesis to therapy. Autoimmun Rev 2014;13:655–67. https://doi.org/10.1016/j.autrev.2013.12.001.

[2] Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol 2012;8:469–79. https://doi.org/10.1038/nrrheum.2012.96.

[3] Garner R, Kumari R, Lanyon P, Doherty M, Zhang W. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. BMJ Open 2015;5. https://doi.org/10.1136/bmjopen-2014-006389. (e006389–e006389).

[4] Ratchford EV, Evans NS. Raynaud's phenomenon. Vasc Med 2015;20:269–71. https://doi.org/10.1177/1358863X15579122.

[5] Khouri C, Blaise S, Carpentier P, Villier C, Cracowski J-L, Roustit M. Drug-induced Raynaud's phenomenon: beyond β-adrenoceptor blockers. Br J Clin Pharmacol 2016;82:6–16. https://doi.org/10.1111/bcp.12912.

[6] Syed RH, Moore TL. Methylphenidate and dextroamphetamine-induced peripheral vasculopathy. J Clin Rheumatol 2008;14:30–3. https://doi.org/10.1097/RHU.0b013e3181639aaa.

[7] Goldman W, Seltzer R, Reuman P. Association between treatment with central nervous system stimulants and Raynaud's syndrome in children: a retrospective case-control study of rheumatology patients. Arthritis Rheum 2008;58:563–6. https://doi.org/10.1002/art.23301.

[8] Yu ZJ, Parker-Kotler C, Tran K, Weller RA, Weller EB. Peripheral vasculopathy associated with psychostimulant treatment in children with attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 2010;12:111–5. https://doi.org/10.1007/s11920-010-0093-y.

[9] Bayram Ö, Hergüner S. OROS-methylphenidate-induced Raynaud's phenomenon: a dose-related side effect. J Child Adolesc Psychopharmacol 2015;25:521–2. https://doi.org/10.1089/cap.2015.0033.

[10] Iglesias Otero M, Portela Romero M, Bugarín González R, Ventura Victoria MA. Metilfenidato y fenómeno de Raynaud secundario. Semer - Med Fam 2013;39:330–4. https://doi.org/10.1016/j.semerg.2012.07.011.

[11] Coulombe J, Powell J, Hatami A, Mccuaig C, Renet S, Marcoux D. Diseases of abnormal sensitivity to cold in children on psychostimulant drugs. J Cutan Med Surg 2015;19:121–4. https://doi.org/10.2310/7750.2014.14052.

[12] Scherlinger M, Guillotin V, Truchetet M-E, Contin-Bordes C, Sisirak V, Duffau P, et al. Systemic lupus erythematosus and systemic sclerosis: all roads lead to platelets. Autoimmun Rev 2018;17:625–35. https://doi.org/10.1016/j.autrev.2018.01.012.

[13] Guiducci S, Giacomelli R, Cerinic MM. Vascular complications of scleroderma. Autoimmun Rev 2007;6:520–3. https://doi.org/10.1016/J.AUTREV.2006.12.006.

[14] Meier FMP, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR scleroderma trials and research group database. Ann Rheum Dis 2012;71:1355–60. https://doi.org/10.1136/annrheumdis-2011-200742.

[15] Thiebaut M, Launay D, Rivière S, Mahévas T, Bellakhal S, Hachulla E, et al. Efficacy and safety of rituximab in systemic sclerosis: French retrospective study and literature review. Autoimmun Rev 2018;17:582–7. https://doi.org/10.1016/j.autrev.2017.12.010.

[16] Haustein UF, Haupt B. Drug-induced scleroderma and sclerodermiform conditions. Clin Dermatol 1998;16:353–66.

[17] Graham JR. Drug-induced localized systemic scleroses. Trans Am Clin Climatol Assoc 1981;92:122–32.

[18] Verdelli A, Antiga E, Bonciolini V, Bonciani D, Volpi W, Caproni M. Drug induction in connective tissue diseases. G Ital Dermatol Venereol 2014;149:573–80.

[19] Andreussi R, Silva LMB, da Silva HC, Luppino-Assad AP, Andrade DCO, Sampaio-Barros PD. Systemic sclerosis induced by the use of cocaine: is there an association? Rheumatol Int 2019;39:387–93. https://doi.org/10.1007/s00296-018-4227-6.

[20] Ferreli C, Gasparini G, Parodi A, Cozzani E, Rongioletti F, Atzori L. Cutaneous manifestations of scleroderma and scleroderma-like disorders: a comprehensive review. Clin Rev Allergy Immunol 2017;53:306–36. https://doi.org/10.1007/s12016-017-8625-4.

[21] Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015;56:345–65. https://doi.org/10.1111/jcpp.12381.

[22] Simon V, Czobor P, Bálint S, Mészáros Á, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry 2009;194:204–11. https://doi.org/10.1192/bjp.bp.107.048827.

[23] van Lieshout M, Luman M, Twisk JWR, van Ewijk H, Groenman AP, Thissen AJAM, et al. A 6-year follow-up of a large European cohort of children with attention-deficit/hyperactivity disorder-combined subtype: outcomes in late adolescence and young adulthood. Eur Child Adolesc Psychiatry 2016;25:1007–17. https://doi.org/10.1007/s00787-016-0820-y.

[24] Golmirzaei J, Mahboobi H, Yazdanparast M, Mushtaq G, Kamal MA, Hamzei E. Psychopharmacology of attention-deficit hyperactivity disorder: effects and side effects. Curr Pharm Des 2016;22:590–4.

[25] Groenman AP, Schweren LJS, Dietrich A, Hoekstra PJ. An update on the safety of psychostimulants for the treatment of attention-deficit/hyperactivity disorder. Expert Opin Drug Saf 2017;16:455–64. https://doi.org/10.1080/14740338.2017.1301928.