Original Article

Serum sickness-like reaction to a second generation antipsychotic drug

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ABSTRACT

Introduction: Serum sickness is a type III hypersensitivity reaction. Immune complex deposition activates complement pathways resulting in fever, vasculitic rash, arthritis and lymphadenopathy. Medications are known to trigger serum sickness-like reactions which clinically resemble serum sickness, however, are not thought to involve circulating immune complexes. The full pathophysiology is not clear. Risperidone is an atypical antipsychotic drug commonly used in the paediatric population.

Aim: To describe the diagnosis, disease course and outcome of a patient who developed serum sickness-like reaction secondary to risperidone.

Methods: Review of patient chart and medical interview in accordance with institutional research ethics board approval.

Results: The patient, a 7 year old male with Attention Deficit Hyperactivity Disorder, was started on risperidone 0.25 mg once daily. Within a week the dose was increased to 0.5 mg once daily. During the third week after initiation of medication, the patient developed generalized purpuric, confluent, maculopapular rash. Although the patient did not have any signs and symptoms of a viral illness, he was diagnosed with viral-induced exanthema and continued on risperidone. On day 28, he developed significant, bilateral swelling of upper and lower extremities, facial angioedema, lymphadenopathy, arthralgia and arthritis in ankles, knees, hands and elbows without fever. Investigations showed normal complement C3 and C4 levels. C1 esterase inhibitor, anti-nuclear antibody and urinalysis were normal. Erythrocyte sedimentation rate, C-reactive protein and leukocyte levels were elevated. The diagnosis of serum sickness-like reaction to risperidone was made and the patient subsequently treated with cetirizine, hydrocortisone, and prednisone for 1 week with significant improvement. Skin biopsy was declined by the patients' parents and therefore was not performed. Provocative oral challenge to risperidone was not considered because of clear suggestive history and ethical consideration.

Conclusion: Psychotropic medications are known to cause cutaneous eruptions. Serum sickness-like reactions can happen upon exposure to risperidone. Clinicians should be aware of this potential adverse reaction that can develop weeks after therapy initiation, and be encouraged to discontinue risperidone when the suggestive symptoms emerges.

Statement of novelty: We describe a case of serum sickness-like reaction to risperidone in a paediatric patient. To our knowledge, this is the first case of serum sickness-like reaction to risperidone.

Introduction

Serum sickness is a type III hypersensitivity reaction, which requires the presence of an antigen and antibodies directed against the antigen, leading to formation of antigen-antibody or immune complexes (Alissa 2018). The deposition of immune complexes in tissues activates complement pathways that can trigger

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an inflammatory response (Alissa 2018). Hence, patients with serum sickness can present with fever, rash, arthritis, and lymphadenopathy (Alissa 2018). Medications that are known to trigger serum sickness-like reactions, in which immune complexes are not found, include penicillin, sulfonamides, thiouracils, and phenytoin (Solensky and Khan 2010). This case report details a rare case of risperidone-induced serum sickness-like reaction. To our knowledge, this is the first report that describes a case of risperidone-induced serum sickness-like reaction in a paediatric patient.

Case presentation

History of present illness

A 7 year old male with Attention Deficit Hyperactivity Disorder (ADHD) was started on risperidone 0.25 mg once daily. Within 1 week, the dose of risperidone was increased to 0.5 mg once daily to optimize therapeutic effect. In the third week, the patient developed right ankle erythematous rash associated with itchiness and irritability. The rash extended to his lower and upper extremities and to the chest and back within 6 hours. The rash was subjectively described as round, erythematous papules that evolved into edematous lesions with central dusky color associated with an outer dark red inflammatory zone; most lesions measured 1–3 cm. There were no gastrointestinal symptoms, joint pain or fever at this time. The patient was advised to take diphenhydramine given the impression of viral induced exanthema. The patient continued risperidone as allergic reaction to this medication was less likely deemed to be the cause of rash. Our patient received his regular risperidone and 2 doses of diphenhydramine within a period of 10 days after consultation with the primary care physician.

In the fourth week, the patient developed periorbital edema, swelling of dorsum of his hands and feet. In addition, he experienced arthralgia in knees, ankles, elbows, and hands. Due to arthralgia, he developed difficulty with ambulating. The rash progressed to central purpura associated with subcutaneous petechial bleeding in lower and upper extremities, chest and back. The rash was associated with new onset abdominal pain at this time. He denied fever, respiratory symptoms, or skin exfoliation. There were no apparent mucosal involvements.

The patient was brought into hospital due to difficulty ambulating and admitted for angioedema, arthralgia and tactile fever. Review of systems during admission was negative for conjunctivitis, photophobia, oral or genital ulcer, mucositis, blister or vesicular rash, abdominal pain, shortness of breath or gastrointestinal symptoms.

Risperidone was discontinued at the time of admission. Inpatient treatment consisted of 1 dose of IV hydrocortisone, which significantly improved the generalized edema overnight. The patient was able to ambulate the following day and discharged with prednisone 50 mg orally once daily for a total of 5 days and cetirizine 10 mg orally once daily for a total of 3 months. The generalized edema and arthralgia significantly improved after finishing the full course of prednisone. It took the rash almost 2 weeks to completely disappear. Two weeks post discharge, the patient was seen in the paediatric clinic and was free of all the initial symptoms experienced since the prior month.

Allergy, medications and immunization

There were no known drug or food allergies. The patient was started on methylphenidate 15 mg once daily for ADHD 2 weeks after being discharged from the hospital. He was on no other medications other than those summarized above. His immunizations were up to date.

Past medical history including developmental history

The patient was born following a pregnancy complicated by drug and alcohol use. Medical history was notable for aggressive behavior along with ADHD. He had no surgeries or hospitalizations other than those summarized above. The details of family history are not available.

Investigations

Admission labs showed white blood count: 13.1×10^9/L, neutrophil count: 11.0×10^9/L, lymphocyte count 1.45×10^9/L, eosinophil count 0.1×10^9/L, hemoglobin: 118 g/L, platelets: 518×10^9/L, INR: 1.4, PTT: 35 seconds, creatinine: 32 mmol/L, AST: 29 U/L, ALT: 23 U/L, and creatinine kinase: 78 IU/L. Immunology work up revealed IgE: 2007 µg/L, IgG: 10.3 g/L, IgA: 2.19 g/L, IgM: 1.04 g/L, C3: 1.28 g/L, C4: 0.34 g/L, and C1 esterase inhibitor: 0.37 g/L. Rheumatology work up included antinuclear antibody titer (ANA): (1:80) with speckled pattern, erythrocyte and sedimentation rate (ESR): 11 mm/hr. C-reactive

protein (CRP) trended down from 73 to 2.9 mg/L. Thyroid Stimulating Hormone (TSH), anti-double stranded DNA antibodies, and rheumatoid factor were within normal limits.

Abdominal ultrasound was unremarkable with no hepatomegaly or abnormality in kidneys. Urine analysis was normal. The patient refused skin biopsy.

Physical examination

The patient was assessed and examined in the paediatric clinic 2 weeks after being discharged from the hospital. Weight was 44.5 kg, and height 127 cm. Head and neck examination revealed normal tympanic membranes bilaterally, normal oropharynx, and 129 normal conjunctiva. No oral ulcers, nasal ulcers or facial rashes. No cervical lymphadenopathy was noted.

On cardio pulmonary exam, heart sounds were normal and no murmurs appreciated. Lung was clear to auscultation; no extra sounds such as crackles, rhonchi or wheezing heard. Abdomen was soft and non-tender; no hepatosplenomegaly or masses palpated. Genitalia appeared normal. Musculoskeletal examination revealed full range of motion in all joints; no effusion, enthesitis or tenosynovitis were noted. Examination of the skin revealed faint macule and occasional clusters of petechiae that were non palpable and non blanchable, most prominently on buttocks and lower limbs. No angioedema detected on face or extremities.

Discussion

Type III immune complex reactions typically present with fever, rash, urticaria, lymphadenopathy, and arthralgia 1–3 weeks after starting use of the offending agent (Solensky and Khan 2010). Classic serum sickness results from the formation of immune complexes due to immunization of a human host with a foreign protein (Alissa 2018). The reaction requires antigen and antibodies against the antigen to form antigen-antibody or immune complexes. Immune complexes are usually cleared by phagocytic system, however in case of excess immune complex load, they deposit in tissues such as joints (fenestrated synovial endothelium). The deposition of immune complexes in parenchymal tissues triggers formation of complement fragments, including C3a, and subsequent inflammatory responses. Immune complexes deposition in tissues can directly interact with Fc-gamma-receptors on neutrophils, mast cells, and phagocytes and activates an inflammatory response even in the absence of complement activation (Sylvestre and Ravetch 1994; Clynes et al. 1998; Ravetch and Bolland 2001).

Serum sickness-like reactions refer to a constellation of signs and symptoms resembling classic serum sickness but typically caused by reaction to a variety of drugs (Wener 2018). Even though the pathogenesis of these reactions may not depend on circulating immune complexes or complement activation, the mechanism behind serum sickness-like reactions is not fully understood (Wener 2018).

Our patient had the characteristic signs and symptoms of serum sickness-like reaction associated with exposure to risperidone. There was a clear temporal relationship between the start of this medication and development of adverse events (Solensky and Khan 2010).

One of the differential diagnoses is Drug Rash with Eosinophilia and Systemic Symptoms (DRESS). Characteristic features of DRESS include various cutaneous eruptions, fever, high eosinophil count in most cases, hepatic dysfunction, renal involvement, and enlarged lymph nodes. The reaction develops usually 2–8 weeks after initiation of culprit medication and symptoms may worsen even after drug discontinuation. The patient did not develop any eosinophilia (eosinophil count ranged between 0.1 and 0.3×10^9/L throughout illness). The patient's laboratory investigations and imaging did not reveal any renal or hepatic abnormalities. The patient improved after discontinuation of risperidone and initiation of steroids.

Another differential diagnosis in this case could be Henoch–Schonlein purpura, as the features of purpuric generalized rash, abdominal pain and arthralgia are consistent with this possibility. However, the degree of angioedema in our patient is not typical of this small vessel vasculitis (Roberts et al. 2007).

A third possible working diagnosis was drug-induced urticarial vasculitis. This condition requires the presence of both urticaria and histopathological evidence of leukoclastic vasculitis (Brewer and Davis 2018). Even though our patient had dermatological findings compatible with urticarial vasculitis, arthralgia is more likely to present in serum sickness than primary

vasculitis (Wener 2018). A skin biopsy would have been beneficial in terms of providing a confirmatory diagnosis and ruling out vasculitis. Unfortunately our patient refused skin biopsy.

On laboratory evaluation during admission, CRP and WBC were elevated. This is compatible with the inflammatory process that occurs in serum sickness-like reactions. Elevated IgE is also consistent with an allergic reaction. ANA was positive; even though ANA is a marker of autoimmune disease, its positivity in allergic reaction is well documented in other studies (Grygiel-Gorniak et al. 2017). The remainder of the rheumatology work up, such as anti-double stranded DNA antibodies, TSH, and rheumatoid factor, were normal, making our patient's presentation unlikely to be part of a rheumatological disorder.

In serum sickness-like reactions, complement levels can remain normal due to complement independent mechanisms or immune complex independent pathophysiology. The fact that complements remained normal in our patient argues in favour of serum sickness-like reaction due to medications as opposed to other diagnoses (Sylvestre et al. 1996; Ravetch and Bolland 2001).

Once a drug is identified as a potential source of allergy, the next step is withdrawing the offending agent (Celik et al. 2014). In this case report, risperidone was stopped upon the patient's admission to the inpatient unit, as this medication was thought to be contributing to his allergic reaction. The next step is introduction of supportive therapy and consideration of how the incriminating drug should be substituted. The recommended treatment for serum sickness and serum sickness-like reactions is administration of systemic corticosteroids and antihistamines (Solensky and Khan 2010). This is the exact treatment regimen that was prescribed to our patient with an excellent response. Our patient was switched to methylphenidate after risperidone was thought to be the culprit behind his allergic reaction.

The prognosis for complete recovery from a serum sickness-like reaction is excellent. However symptoms may last several weeks (Solensky and Khan 2010). Our patient had an excellent recovery from his allergic reaction and his symptoms were almost resolved 2 weeks post discharge from the hospital.

Conclusion

Psychotropic medications are known to cause cutaneous eruptions, however, this is the first case report that describes a serum sickness-like reaction to risperidone. Once serum sickness develops, reintroduction of the same drug can result in subsequent allergic reaction within shorter time frame. Hence, once serum sickness is diagnosed, the responsible drug should be avoided (Wener 2018).

This case report serves to raise awareness to clinicians on the rare but possible occurrence of serum sickness-like reaction to risperidone. Clinicians should be aware of the potential allergic reaction that can develop with initiation of risperidone. Upon slight development of allergic symptoms, discontinuation of risperidone and substitution with other agents should be considered as the first line of treatment.

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