Review Article

Antipsychotics as a probable cause of Leukocytoclastic Vasculitis: A Systematic Review

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ABSTRACT

Abstract: Leukocytoclastic vasculitis (LCV) is a skin condition that is a result of unregulated immune activation. The exact causes have to date not been established. The studied causes tend to have a higher probability of causing LCV. This raises concerns about a deep-seated causal relationship and the tendency of an individual for the development of LCV. Antipsychotics are a class of drug mainly used for psychiatric disorders including schizophrenia, schizophreniform disorder, or even depressive disorder with psychotic features. These drugs target the dopamine receptors in the central nervous system to exert their effects. They are classified as typical or the older antipsychotics and atypical or the newer antipsychotics. Prevalent in the current literature are the reported cases of LCV with antipsychotic medications. We carried out a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) protocol to find out previously reported cases on LCV due to antipsychotic medication administration from inception till current date. Our study aims to check and in turn, discuss the causal relationship of antipsychotics with LCV.

Keywords: Leukocytoclastic Vasculitis, Adverse Drug Reactions, Systematic Review, Typical antipsychotics, Atypical antipsychotics.

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INTRODUCTION

Leukocytoclastic Vasculitis (LCV) is an immunologic condition involving cutaneous blood vessels including small arterioles, capillaries and post capillary venules [1]. The incidence of LCV has been increasing to 4.5 per 100,000 person years (95% CI: 3.5 - 4.5) according to a population-wide study [2]. According to the Dermatologic Addendum to International Chapel Hill Consensus Conference (CHCC) 2012, cutaneous small-vessel vasculitis could be (1) skin component of systemic vasculitis; (2) a skin limited or dominant expression or a variant of systemic vasculitis; (3) a single organ vasculitis that differs with regard to clinical,

laboratory and pathologic features from recognized systemic vasculitis [3]. Its presentation can be limited to the skin of a specific part, or it can be secondary to an ongoing systemic condition. Due to the varied presentation, its diagnosis becomes a challenge. The prognosis of LCV is comparatively better if it is an isolated skin presentation [4], if there is the involvement of lungs, heart, or kidneys, prompt treatment is required for better outcomes. To date, there have been numerous proposed causes of LCV out of which the secondary causes are thought to be rare ones. Secondary LCV can occur after drug exposure, underlying infection, or malignancy. Numerous drugs have been proposed which have the potential to cause LCV.
Antipsychotics are a class of drugs used to treat psychotic conditions like Schizophrenia and its spectrum of disorders and delusional disorders. Also, it can be used in various neurotic disorders like major depression with psychotic features, bipolar mood disorder, and obsessive-compulsive disorder to name a few. Apart from these conditions, they are also used for various other conditions like personality disorders, autism, Tourette syndrome, and agitation related to dementia and encephalopathies [5]. In recent times, there have been cases reported of LCV after antipsychotic drugs. We intend to carry out a systematic review to dig deep into the individual patient demographics, the pathogenesis in each specific case, and to rule out any underlying culprit if any. We aim to add to the current literature depicting the association of antipsychotics with LCV.

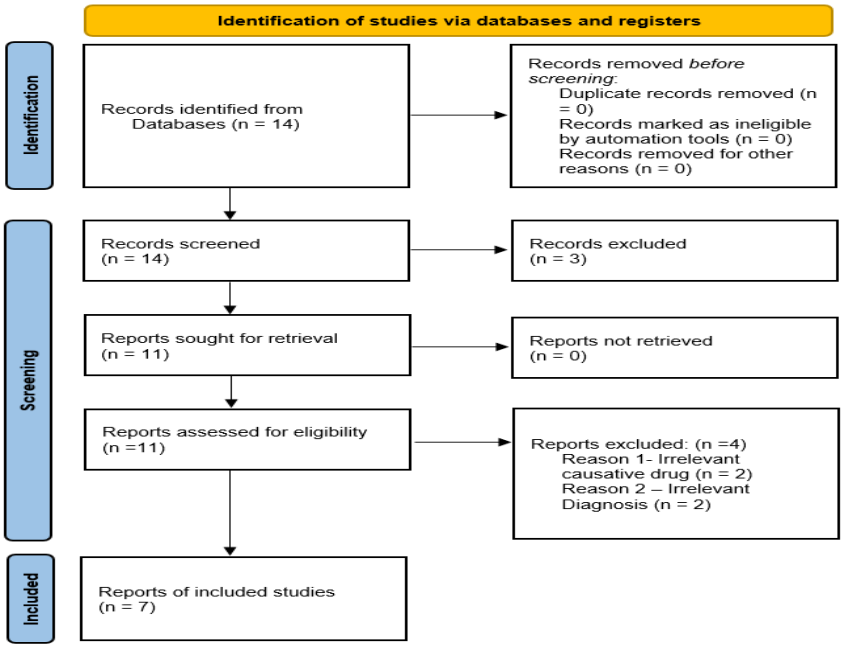
METHODOLOGY OF CONDUCTING THE REVIEW

Search strategy: We used PubMed as the sole database, from inception till current date, a systematic search with keywords (antipsychotics OR typical antipsychotic OR atypical antipsychotic AND Leukocytoclastic Vasculitis) was carried out revealing 14 case reports. After a detailed review of the full-length articles, we finally included 7 case reports for our systematic review. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines were followed for the screening of the articles[6]. (Figure 1).

Pathophysiology:
Leukocytoclastic vasculitis refers to the inflammation of small vessels including the cutaneous arterioles and venules. It is thought to be mediated by Immune complex deposition secondary to an inciting agent or disease [7]. To date, the most common culprits are thought to be underlying Hepatitis B and C virus or even it could be a manifestation of a larger picture like rheumatoid arthritis, Sjogren Syndrome, or Systemic lupus erythematosus [8].
The immune complexes deposition in the cutaneous blood vessel walls activates the downstream signalling of the immune system. This activation leads to the expression of adhesive molecules locally and releases of chemokines systemically. This cumulatively leads to the recruitment of neutrophils and eosinophils at the local site. These activated white blood cells activate the inflammatory cascade which is the cause for the localized symptoms of edema, pain, itching and systemic symptoms like fever. Locally, this leads to sluggish blood flow and vasodilation to fulfil the white cell count demand created by the chemokines [9].
Once around the vessel, these neutrophils, and eosinophils degranulate and release proteolytic enzymes including elastases and collagenases, generate reactive oxygen species, and also activate the complement system to form the membrane attack complex. Collectively, this further damages the endothelial cells and the surrounding tissues [10]. Also, the classical presentation of LCV in the lower extremities, palms, and the dependent areas of the body can be explained by the gravitational pull and relatively sluggish venous return from these areas. Once the immune chaos sets in, it leads to the emergence of non-blanchable purpura due to the cut-off of blood supply to the skin supplied by the involved blood vessel. This could sometimes be severe enough to cause necrosis of the supplied skin and even lead to superadded infections.

Demographics: 7 case reports with 1 patient each (N=7), were included in the total for the systematic review. All these 7 patients were on antipsychotic medication due to a psychiatric condition, acute encephalopathic presentation, or were recently switched to an antipsychotic medication from another one prior to the onset of dermal symptoms. Of these, there were 4 males and 3 females. The age of these patients lied anywhere between 40-90 years

Figure 1: Screening of studies according to PRISMA protocol



Clinical Presentation: Taking into consideration the administration of antipsychotics, the patients reported had some form of schizophrenia spectrum disorder including schizoaffective disorder, or acute psychotic episodes due to an underlying encephalopathy. Also, they have been the medication of choice for bipolar disorder and major depressive disorder with psychotic features. The initial dermal symptoms appeared within 5 to 21 days of initiation of the inciting agent. Another similarity noted among these patients was the emergence of cutaneous symptoms after initiation or change of a current therapeutic drug. These symptoms either appeared solo or were associated with systemic symptoms like arthralgia and myalgia as described by Mukherjee and others [11].

The cutaneous symptoms ranged from confluent, non-blanching, palpable purpura which may or may not be associated with pruritus, swelling, and in severe cases necrotic patches of the skin. This could be a nidus to localized infection and sepsis warranting timely diagnosis and treatment. The initial appearance of the rash was on the most dependent body parts like legs and buttocks, after which it progressed to less dependent body parts like knees, arms, palms, and sometimes severe enough to cover the whole body.

Diagnosis: Almost all these included cases were diagnosed as LCV with its definitive testing of biopsy of the lesion. LCV was a diagnosis of exclusion in all these cases, once a detailed examination and investigations revealed no specific cause. Once these lesions were suspected to be LCV, a standard workup included the following [4]

- Complete Blood count
- Comprehensive metabolic panel
- Erythrocyte sediment rate (ESR)
- Serum Cryoglobulins
- Serum Complement levels
- Antineutrophil cytoplasmic antibodies
- Hepatitis B and C
- Human Immunodeficiency Virus (HIV)
- Coagulation panel with Prothrombin time (PT), activated Partial thromboplatin time (aPTT), and International Normalised Ratio (INR)

This was the basic protocol for investigation and establishing a cause of such a presentation. To date, HIV and hepatitis B and C have been associated with various forms of vasculitis. Hence it becomes important to

rule out such factors. The initial set of differential diagnoses included various autoimmune disorders and infectious aetiologies like:

- Churg- Strauss syndrome
- Wegener's granulomatosis
- Microscopic polyarteritis
- Mixed cryoglobulinemia
- Henoch-Schonlein Purpura
- Rocky Mountain spotted fever

All these conditions were ruled out based upon the above-mentioned investigations.

The association between the drug and LCV was assessed by Naranjo Adverse Drug Reaction (ADR) Probability Scale (Table 2) [18]. It comprises a set of questions that need to be answered prior to establishing the fact that the untoward event under evaluation is an adverse reaction due to a drug that was recently administered or recently changed from one class to the other.

Table 2: Naranjo Adverse drug reaction assessment questionnaire

Question	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse events appear after the suspected drug was given?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given?	+1	0	0
Did the adverse reaction appear when the drug was readministered?	+2	-1	0
Are there alternative causes that could have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

Based upon the answers to these questions, a score was generated which depicted the association of the adverse reaction with the drug. A score of ≥ 9 suggested a definite ADR, 5-8 probable ADR, 1-4 possible ADR, and a score of 0 suggested doubtful ADR. While this scale was a standard to assess for the association of a drug with an observed reaction, some authors had a different perspective.

Lee and other [17], and colleagues had a different approach to diagnosing the condition. The causative agent in their patient was haloperidol which was used to reduce the altered mental status past the diagnosis of metabolic encephalopathy. They carried out intradermal and oral haloperidol provocation tests, which led to the appearance of rash with a similar histologic picture.

A similar approach was noted in the case report by Duggal and others [15], they tried the trial and error method to find the culprit. The rash appeared 8 days after olanzapine treatment for behavioural disturbances. The patient also had a history of pulmonary embolism for which she was on chronic warfarin. They thought

warfarin could be associated with erythematous skin lesions. On further investigation, the International Normalised Ratio (INR) was found to be in a normal range. All the non-essential medications of the patients were discontinued, and warfarin was switched to subcutaneous enoxaparin, yet there was no improvement noted in the lesions. The lesions started healing once Olanzapine was switched to Risperidone. But, when olanzapine was restarted due to excessive dizziness experienced by the patient, similar rashes started appearing. This, in retrospect, established olanzapine as a cause of the LCV in their patient. Olanzapine was also reported as a causative agent in the case reported by Papaioannides and others [14], and they had a much similar approach to the previous one.

Treatment and Outcomes: Once they discovered the causative agent, the first and foremost thing was to discontinue the drug. Secondly, supportive treatment with non-steroidal anti-inflammatory drugs and local ointments would help reduce the associated symptoms of pruritus and pain, if present.
Discontinuation of the inciting agent halted the progression of LCV or initiated the healing of the same. In some of the cases, steroids were required to suppress the immune chaos and initiate healing. Mukherjee and others [11] and colleagues, had their patient on hydroxyzine once the diagnosis was established. It nearly took 2 months for complete resolution for the lesions. Methylprednisolone 16 mg/day administered orally for 5 days and gradually tapered to 4mg on day 15 and discontinued on the 21st day, a few days after which complete resolution of the rash was observed by Papaioannides and colleagues [12]

CONCLUSION

After having discussed the fact with the supporting evidence, antipsychotics are a class of medication that has the potential to cause immune activation and lead to LCV. From the current literature, we can see that the number of cases of LCV reported are mostly associated with atypical antipsychotics. This could be due to reduction in use of typical antipsychotics, or it could also imply the increased incidence of LCV with atypical antipsychotics. This necessitates further research into this topic to exactly identify what exactly causes LCV after administration of antipsychotics.

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