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Should C-Reactive Protein and Troponin Be Monitored for Early Diagnosis of Clozapine Induced Myocarditis? An Assessment Within the Framework of Two Cases

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SUMMARY

Clozapine is an important treatment option in patients with treatment-resistant schizophrenia and bipolar disorder. Clozapine has multiple systemic side effects with myocarditis and cardiomyopathy being considered as serious cardiovascular outcomes. Although the aetiology of myocarditis is still unknown, its frequent occurrence in the early stages of clozapine use suggests that type 1 drug hypersensivity may underlie. Although rare, the cardiovascular side effects can be life-threatening and must be recognized and treated promptly. The non-specific clinical presentation of these conditions makes risk evaluation and identification of the affected patients difficult. A consensus has not yet been formed on following up the patients without the suspected clinical cardiac symptoms.

In this article we presented two cases of myocarditis associated with clozapine. We aimed to emphasize that C-Reactive Protein and troponin monitoring, in accordance with the current clozapine guidelines, was practical and useful for early detection of myocarditis in asymptomatic patients. We also wanted to draw attention to the factors that may increase the cardiovascular risk such as polypharmacy and concomitant use of lithium and valproate with clozapine.

Keywords: Clozapine, myocarditis, drug monitoring

INTRODUCTION

Clozapine is an important management option in patients with treatment-resistant schizophrenia and bipolar disorder (Shivakumar et al. 2018). Clozapine has multiple systemic side effects with myocarditis and cardiomyopathy being considered as serious cardiovascular outcomes (Kilian et al. 1999, Bellissima et al. 2018).Although development of myocarditis after clozapine use was first reported 40 years ago (Vesterb et al. 1980), the incidence of 1/500 myocarditis in the first month of clozapine treatment was presented as the strong evidence to draw attention to the subject some twenty years later (Kilian et al. 1999).

Although the aetiology of clozapine related myocarditis is still unknown, its frequent occurrence in the early stages of clozapine use suggests that type 1 drug hypersensivity may underlie these effects (Kilian et al. 1999).To the best of our knowledge, there have been only two studies conducted on mice and rats on the aetiology of myocarditis (Wang et al. 2008, Nair et al. 2019).

Having limited knowledge on the aetiology and epidemiology of myocarditis causes difficulties in the follow-up, diagnosis and treatment of this serious and life-threatening side effect. In this article, the cases of two patients necessitating stopping clozapine treatment on grounds of suspected myocarditis will be presented and following up the C-protein (CRP) and troponin levels or eosinophil counts as a routine practice for early diagnosis of myocarditis, similarly to the procedure of assessing agranulocytosis risk by neutrophil counts, will be discussed.

CASE 1

The 42-year-old, married male blue-collar worker using lithium (1200 mg/day), sodium valproate (1500 mg/day) and levothyroxine (75 mcg/day) consulted with complaints

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of increased preoccupation with religion, insomnia and suspiciousness. He was admitted to the hospital with the diagnosis of "Bipolar Disorder Manic Episode with Psychotic Features".

During his psychiatric examination the patient was conscious, oriented and cooperative with apparent normal self care, dysphoric mood, angry affect, accelerated associations and increased amount of talking. He had mystical delusions and auditory hallucinations. His judgmental skills were inadequate, whereas his abstract thinking skills were maintained. He lacked insight.

Relapsing despite maintaining therapeutic levels of serum lithium and valproate, not having responded to the various antipsychotics and mood stabilisers used in the past and failure to achive prophylaxis, the patient was diagnosed with treatment resistant bipolar disorder and clozapine treatment was planned to be started as of 28.02.2019. Clozapine treatment was started at a dose of 25 mg/day, scheduled to be increased by 25-50 mg every other day, in addition to biperiden(4 mg/day), haloperidol (20 mg/day), lithium (900 mg/day), valproate (1000 mg/day) and levothyroxine (75 mcg/day). The patient reported nausea and vomiting on 11.03.2019, while on treatment with 175 mg/day clozapine. Investigations showed serum CRP raised to 45 mg/L and a pulse of 120/min with normal respiratory rate, fever and blood pressure. Subsequently, the infectious diseases unit was consulted with and no focus of enfection was detected. The cardiac markers of the patient who reported chest pain on 18.03.2019 were examined. His troponin I value was 256 pg/ml (his concurrent respiratory rate, fever, blood pressure and pulse were in the normal range). The cardiology department was consulted with. No cardiac pathology was considered by the cardiology department, but due the fact that eosinophil value was 5510 µg/L, the cardiology unit was consulted with once more on suspicion of myocarditis due to clozapine. Myocarditis was not considered since the echocardiographic assessment of ejection fraction (EF) was within normal limits. However, clozapine therapy was terminated with the possibility of clozapine induced ''eosinophilic myocarditis". The patient's treatment was continued on olanzapine (20 mg/day), quetiapine (200 mg/day), lithium (900 mg/day) and valproate (1500 mg/day). On 01.04.2019 test results on CRP (19 mg/L), troponin (5,2 pg/ml), eosinophil level (1120 µg/L), creatine kinase-MB (CK-MB-23 IU/L) and lactic dehydrogenase (LDH-223 U/L) had approached normality (Figure1 and Figure 2). The patient was discharged on grounds of partial clinical recovery.

CASE 2

The 36-year-old single male factory employee who has not used any medication regularly for the past year, was hospitalized with the preliminary diagnosis of schizophrenia on grounds of his complaints of insomnia, self isolation in a room and suspiciousness.

In his mental examination, the patient was conscious, oriented and cooperative. His self care was average, mood dysphoric, affect blunt. His spontaneous speech was reduced and associations were loose. He did not describe hallucinations, but had persecutory and grandiose delusions. His skills of judgment and abstract thinking were inadequate. He lacked insight. Treatment was started with haloperidol (20 mg/day), biperiden (10 mg/day) and quetiapine (100 mg/day), followed with haloperidol (20 mg/day), olanzapine (30 mg/day), amisulpride (1200 mg/day) by giving adequate treatment period when his delusions did not regress. He was diagnosed with treatment resistant schizophrenia and it was planned to start clozapine treatment as of 04.11.2019, starting with a dose of 25 mg/day, to be titrated with 25-50 mg every other day, in addition to biperiden (4 mg/day), quetiapine (100 mg/day) and amisulpride (1200 mg/day). A routine weekly follow up on haemogram, CRP and troponin was started as planned in our clinic for clozapine treament after the observations made on case 1 reported here. On 20.11.2019 while the patient was on 425 mg/day clozapine, test results indicated the levels of the white blood cells (WBC) at 11500 µg/L, eosinophil at 5300 µg/L, CRP at 244.19 mg/L and troponin of 100.3 pg/mL. Clozapine treatment was terminated with suspected clozapine induced myocarditis although the patient did not have any complaints and his vital signs at normal limits. Cardiology unit was consulted. Echocardiography showed normal left ventricular function. Electrocardiography (ECG) showed a right bundle branch block indicating troponin follow up although emergent cardiac pathology was not expected. Consulting the infectious diseases unit with results of urinary and biochemical tests and pulmonary x-ray imaging tests did not detect a focal infection. Controls requested on 20.11.2019 showed WBC level was at 10800 µg/L, eosinophil at 6300 µg/L, CRP at 209.44 mg/L and troponin at 71.9 pg/mL. On 21.11.2019 repeated controls showed WBC at 12400 µg/L, eosinophil at 7700 µg/L, CRP at 212.09 mg/L, troponin at 23.9 pg/mL, CK-MB at 15 U/L, LDH at 289 U/L, sedimentation rate at 46 mm/hour. The vital signs were within normal limits. ECG showed normal sinus rhythm. Possible malignity or pulmonary embolism were eliminated by normal tumour marker and D-dimer levels. On 25.11.2019 the test results showed CRP level at 21.24 mg/L, CK-MB at 17 U/L, LDH at 223 U/L, troponin at I 4.5 pg/ml and eosinophil at 9100 µg/ml (Figure 1 and Figure 2). The patient's continued therapy with paliperidone resulted with improvement of the affective participation and delusions. The patient was discharged with clinical recovery on 12 mg/day paliperidone, and a plan of using the long-acting form during the follow-up period.

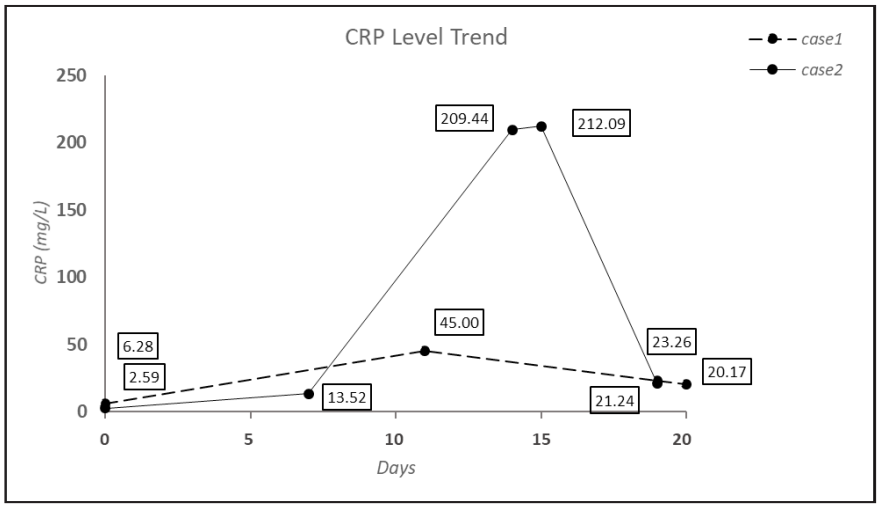

Figure 1. C-Reactive Protein Levels in the Treatment Process of the two cases
Crp: C-reactive protein

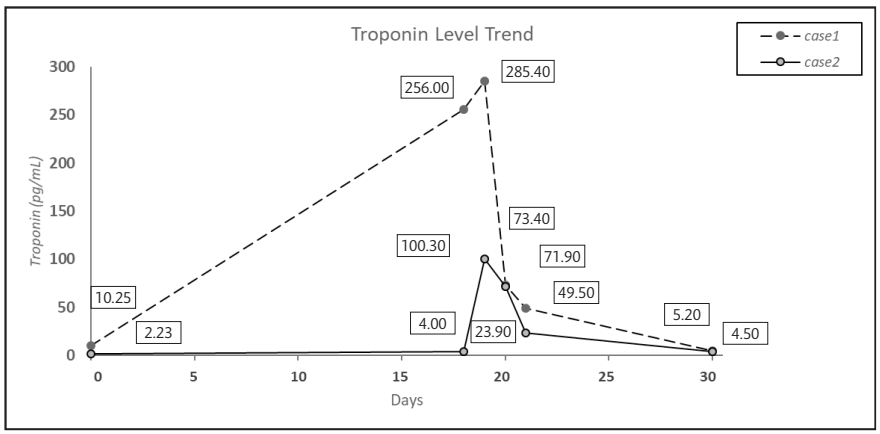

Figure 2. Troponin Levels in the Treatment Process of the two cases

DISCUSSION

Despite being a fatal side effect, there is still not a standard follow-up protocol similar to the recommendations made for agranulocytosis. Investigation showed that clozapine induced myocarditis developed between the 14th and the 21st day of the clozapine treatment in 83% of the cases and weekly troponin and CRP follow-up was recommended within the first month (Ronaldson et al. 2011). In case 1 and case 2 discussed here, myocarditis was suspected on the 18th and the 16th days of treatment, respectively. Although myocarditis can develop at any stage of clozapine treatment, our observations support the reports that the highest risk is in the first three weeks (Knoph et al. 2018).

A review article on 359 possible cases of clozapine-related myocarditis showed that myocarditis developed within the first month of clozapine treatment in 87% of the patients on a clozapine dose of 250 mg/day, with a median age of 30 years and the most common symptoms of respiratory distress (67%), fever (67%), and tachycardia (58%) which started in the first 14 days in half of the cases. The cardiac markers were found to have increased in 87% of the cases (n: 54), in which the cardiac markers were evaluated (Bellisima et al. 2018). It is noteworthy that in case 1 discussed here the nonspecific myocarditis symptoms of nausea and vomiting started on the 11th day of clozapine treatment. The appearance, 7 days later, of the more specific symptoms of respiratory distress, fever and chest pain raised the suspicion of myocarditis and the ensuing cardiological evaluations lead a delay in the diagnosis of myocarditis. On the other hand, in case 2, myocarditis was suspected in the absence of any clinical signs or symptoms on the basis of routine CRP and troponin follow-up results.

It has been reported that advanced age, rapid titration of clozapine dose, use of comorbid psychoactive substances, addition of lithium or valproate to clozapine treatment and metabolic side effects may increase the risk of cardiac side effects during clozapine use (Ronaldson et al. 2012, Anıl Yağcıoğlu et al. 2019). Others have also reported increased risk of myocarditis by adding to clozapine therapy valproate, lithium, phenothiazine group antipsychotics, antidepressants including sertraline, fluvoxamine, amitriptyline and imipramine, as well as multiple antipsychotics or polypharmacy including other psychotropes (Berardis et al. 2012, Berardis et al. 2018). In the treatment of both patients discussed in this report, clozapine titrations were made in accordance with the guideline recommendations. The

patients were not elderly and did not have a history of using psychoactive agents. In case-1 treatment history included lithium and valproate in addition to the clozapine use and, in case-2, polypharmacy was in effect with the use of more than one psychoactive agent, despite exclusion of valproate, lithium and phenothiazine type of agents. These observations draw attention to the factors that could inscrease the risk of myocarditis.

There are reports in the literature on 1/500 incidence of clozapine related myocarditis in the first month of treatment (Kilian ve ark. 1999) and on the variation between 0.01% and 0.19% of the absolute risk of developing the pathology,which numerically seems lower than the 1.3% risk reported for agranulocytosis, but has significance given the 10-48% mortality risk in myocarditis or cardiomyopathy (Citrome ve ark. 2016). Determination of myocarditis in both cases discussed here in similar time periods, especially in the absence of symptoms in case-2, raises the question on the presence of a higher than the currently predicted risk of myocarditis. The incidence of myocarditis diagnosis in 38 patients put on a follow up protocol was 11.3% (n=8), in comparison to 1.4% (n=1) among 33 patients not followed up (Yağcıoğlu et al. 2019), indicating that successful diagnosis of clozapine induced myocarditis is determined by a follow up procedure for signs of the pathology.

There are not clear diagnostic criteria for the diagnosis of clozapine induced myocarditis. Stiıpulation of diagnostic criteria was seen to create the risks of exaggerated or missed diagnoses of the pathology, on the argument that whereas myocarditis diagnosis rests on clinical and investigative data on ECG, cardiac imaging and biochemical test in the established cardiology practice (Patel et al. 2019), only 65% of the clozapine related myocarditis cases meet the diagnostic criteria given in the current guidelines (Goodison et al-2015). In the present report, we have determined that the diagnostic criteria were met only in case 1 on the 11th day of the clozapine treatment.

Although there is not a consensus on the follow-up parameters to be used for the early diagnosis of myocarditis, there are some follow-up protocols recommended in the literature for the early diagnosis of clozapine-induced myocarditis (Ronaldson et al. 2011, Knoph et al. 2018). The sensitivity of the cardiac parameters, namely the left ventricular hypokinesia, low ejection fraction, abnormalities in the ECHO and the CK or CK-MB levels, used in early diagnosis were found not to exceed 40-50% (Annamraju et al. 2007). Evaluation of the literature on the use of eosinophil count in follow-up of clozapine treatment as a diagnostic parameter indicates limitations to its specificity in that it does not increase in all cases, it can increase in non-myocarditis cases, and more importantly, its increase in clozapine-induced myocarditis cases is observed only after the first week of the clozapine treatment (Ronaldson et al. 2011, Knoph et al. 2018). Since the clinical signs and symptoms of tachycardia, respiratory distress, fever and chest pain suggesting myocarditis may not be detected, as seen in the case-2 reported here, and nonspecific gastrointestinal tract signs such as diarrhea and nausea or flu-like symptoms may also occure, as observed in the case-1, follow-up of clinical signs and symptoms have not been regarded as adequate for early diagnosis of clozapine induced myocarditis (Bellisima et al. 2018). Transthoracic echocardiography, cardiac magnetic resonance imaging and endomyocardial biopsy, the gold standard mehtod for the diagnosis of myocarditis, although recommended for use when necessary, are costly to be routine follow-up services for early detection of clozapine-induced myocarditis, as well as being difficult to apply to every patient (Patel et al. 2019).

Troponin, a protein found mainly in the myocardium and in small amounts in the skeletal muscle, is currently used as a marker of cardiac damage and as an assessment tool in cardiac ischemia and inflammation. Serum troponin levels are expected to increase in myocarditis and if accompanied with a cardiac symptom, myocarditis should definitely be included in the differential diagnosis (Patel et al. 2019). Although CRP is an iflammatory marker not specific to myocarditis, it is reported to be increased in the early period of myocarditis ahead of any change in serum troponin levels and levels above 100 mg/L should be considered as a sign of the pathology (Ronaldson et al. 2011, Fehily et al. 2016). Hence, following up troponin and CRP levels together would increase the sensitivity of monitoring myocarditis. Considering the normal ECHO and nonspecific ECG results and the delayed increase of the eosinophil counts observed in both the case 1 and case 2 discussed here, CRP and troponin values have been more significant in warning and guidance of early diagnosis.

Despite the lack of a consensus, the predominantly recommended method of follow up for early diagnosis of myocarditis during clozapine treatment in the literature includes troponin and CRP tests, ECG examination and, if possible, ECHO examination on the first day of clozapine therapy; daily screeening for symptoms of chest pain, fever, dyspnea, myalgia, cough, headache, nausea-vomiting throughout the first month; hemodynamic evaluations of pulse, fever, blood pressure, respiratory rate every other day and CRP and troponin tests once a week. It has been recommended that clozapine treatment be discontinued if troponin level increases more than two fold or if CRP level increases above 100mg/L (Patel et al. 2019). Although the cardiology department did not confirm myocarditis in either case 1 or case 2, we decided to discontinue clozapine treatment upon strong suspicion of myocarditis, and observed the troponin and CRP levels decrease to the normal ranges, supporting our decision (Figure1 and Figure 2).

In conclusion, although a commoınly accepted follow-up method is not given in the current guidelines, the clinicians should follow up, as a life saving practice, the development of myocarditis during clozapine treatment which curently the most effective approach for managing treatment-resistant schizophrenia. The sooner myocarditis is diagnosed and the earlier clozapine is discontinued, the more reversible this life threatening clinical status will be. More care is required when starting clozapine therapy in patients already on medications such as lithium and valproate or when adding clozapine to conditions of polypharmacy. Based on the cases of the two patients discussed here and the relevant data in the literature, we believe that it is very important to monitor, especially within the first month of clozapine therapy, CRP and troponin levels together with the weekly WBC counts.

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