Brain Natriuretic Peptide as a Biomarker of Asymptomatic Clozapine-Related Heart Dysfunction: A Criterion for a More Cautious Administration

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Abstract

Clozapine-related pericarditis is a rare side effect of the drug. We reported the clinical cases of two women, aged 22 and 28 years, affected by schizophrenia with pericarditis symptoms related to clozapine treatment of 200 mg/day. Clozapine was discontinued in both patients, resulting in normalization of the ECG changes, and echocardiography confirmed the progressive disappearance of the pericardial effusion. Interestingly, while inflammatory indices and pro-brain natriuretic peptide (pro-BNP) plasma levels were high in both patients, only one of them showed tachycardia, subjective chest pain, shortness of breath and dyspnea, with a clinical symptomatology suggesting a cardiac involvement. BNP is a vasoactive peptide synthetized by the ventricular myocardium which splits in two fragments: BNP and the N-terminal (pro-BNP). Both are considered valuable biomarkers in clinical practice for the prediction of disease state and prognosis in patients with suspected heart failure. Pro-BNP acts as a key regulator in the homeostasis of water and salt excretion and in the maintenance of blood pressure, mainly by inhibiting the renin-angiotensin-aldosterone axis and blocking the sympathetic nervous activity. In our cases, pro-BNP plasma levels proved to be a profitable way to identify subjects with asymptomatic cardiac impairment who could benefit from a therapy preventing progression to heart failure.

Key Words: Schizophrenia, Clozapine, Heart Dysfunction, Brain Natriuretic Peptide

Introduction

Despite clozapine being a valuable treatment in psychotic patients, it is associated with several cardiovascular side effects (1), such as tachycardia and orthostatic hypotension, whose higher incidence have a clinical relevance only in a few cases (2). The increasing number of life-threatening complications related to drug administration is causing concern, particularly the adverse reactions such as myocarditis, cardiomyopathy, pericarditis and heart failure (3), which are reported to occur in less than 1% of treated patients (4). Wehmeier et al. and others (5, 6) report a high mortality rate despite the low incidence for these clozapine-related diseases. Diagnosis of cardiotoxicity is made only in the occurrence of severe clinical symptoms and marked depression of left ventricular function (7).

Clozapine-related pericarditis represents a rare side effect within a clinical picture presenting heart-related symptoms whose origin may be also due to different factors (8, 9). Literature reports that clozapine may cause pericardial effusion from 9 days to 7 years after its initiation (5, 9, 10), but with a higher probability during titration phase and in the first 5 weeks from its initiation (11, 12).

Eosinophilia is observed in clozapine-related pericarditis (13), although its diagnosis derives from other symptoms—not always concurrent—such as tachycardia, slight increase in body temperature, subjective chest pain, progressive shortness of breath and dyspnea. In addition, C-reactive

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protein (CRP), troponin T blood levels, electrocardiogram and echocardiogram might be of great use to make a diagnosis. Eosinophilia is often delayed after the peak in troponin T for a lapse of time up to 8 days (14); echocardiography often shows a pericardial effusion suggestive of a cardiac tamponade and signs of heart failure.

> *Kropp et al. state that pro-BNP may represent a more accurate marker of early cardiac dysfunction than BNP.*

Toxic doses of clozapine are already acknowledged to cause cardiac arrhythmias, but also therapeutic doses may be associated with heart failure (15). Heart failure can result from both pericarditis and myocarditis, as the systemic inflammatory response in both cases is similar (12); Layland et al. (16) suggest measuring brain natriuretic peptide (BNP) levels to detect early and asymptomatic cardiac dysfunctions. BNP is a vasoactive peptide synthetized by the ventricular myocardium, which acts as a key regulator in the homeostasis of water and salt excretion and in the maintenance of blood pressure, mainly by inhibiting the renin-angiotensin-aldosterone axis and blocking the sympathetic nervous activity. Its synthesis and secretion as pro-BNP are activated by myocyte stretch; it splits in two fragments—BNP and the N-terminal (pro-BNP)—both considered as valuable biomarkers in clinical practice for the prediction of disease state and prognosis in patients with suspected heart failure (17). Sensitivity to identify patients with decreased left ventricular ejection fraction (LVEF) is 91%, specificity is 73% (7), but very few studies ascertain its diagnostic value in patients with suspected myocarditis or pericarditis. In particular, Kropp et al. (18) state that pro-BNP may represent a more accurate marker of early cardiac dysfunction than BNP.

Up to now we lack decisive data on the pro-BNP plasma concentration relevance prior to clozapine introduction, and its significance as a predictor of heart dysfunctions is yet unrecognized.

Methods

We report the clinical cases of 2 women, aged 22 and 28 years, whose body weight was 91 kg (BMI: 37.9) and 65 kg (BMI: 25.4). The two patients and their caregivers were informed, and gave consent to measure BNP plasma levels. They both suffered from an early-onset schizophrenia (paranoid subtype), showing persecutory and reference delusions, auditory hallucinations (commenting voices with a hostile tone) and aggressive behavior. Treated for several years with first-generation (haloperidol) or second-generation antipsychotics (olanzapine, paliperidone) at therapeutic doses, they reported only occasional ameliorations, usually followed by a worsening of their clinical picture, with a clear tendency to a chronic course and considerable social, relational, and occupational dysfunctions. Therefore, the two patients were frequently hospitalized over the years and, given their resistance to other typical and atypical antipsychotics, the initial treatment (haloperidol in the first patient and paliperidone in the second) was gradually tapered down and then discontinued.

Clozapine was gradually introduced up to a dose of 200 mg/day, associated with diazepam (30 mg/day) or delorazepam (2 mg/day), showing no previous evidence of pericarditis prior to its introduction. The co-treatment with benzodiazepines aimed to control patients' agitation and aggression.

We used the 18-item Brief Psychiatric Rating Scale (BPRS) (19) to assess clinical efficacy both before the initiation of clozapine therapy and every week during the first 16 weeks of treatment. Clinical response was established as a minimum of 20% improvement of the BPRS global score (20) and, in both cases, a clinical improvement was registered.

After about one month, the first patient was nearly asymptomatic, displaying only high CRP, pro-BNP and troponin I values: 16.9 mg/dl, 1,004 pg/ml and 0.14 ng/ml, respectively. The second patient, however, showed a complex clinical picture, with several symptoms as tachycardia, subjective chest pain, progressive shortness of breath and dyspnea. In addition, fibrinogen plasma levels (517 mg/dl), VES and CRP were increased (36 mm and 10.5 mg/dl, respectively), WBC and ANC counts ranges were 9.93×10^3–11.40×10^3/mm^3 and 7.10×10^3–8.39×10^3/mm^3, respectively, and pro-BNP levels were high (164.1 pg/ml).

Other laboratory values were normal and the tests for antinuclear antibodies, C3, C4, procalcitonin and urine toxicology screen were negative. In both cases, no eosinophilia emerged, and ECG showed only a sinus tachycardia.

Despite the absence of symptomatology in the first patient, due to the high pro-BNP plasma levels and the sinus tachycardia we did an echocardiography, which showed a normal ejection fraction and a pericardial effusion suggestive of a cardiac tamponade, similar to what occurred to the symptomatic subject. Both patients were then transferred to the coronary emergence unit.

The clinical assessment and the Naranjo Adverse Drug Reaction Probability Scale (an algorithm to ascertain the likelihood of whether an adverse drug reaction is actually due to a drug rather than a combination of other factors) suggested a probable relationship between clozapine treatment and pericarditis with effusion (21).

Results

Multiple clinical consultations were made to explore the possible triggers of pericarditis with pericardial effusion. No clinical evidence of infection was present as displayed with urine analysis, hepatitis profile, thyroid/liver/kidney function tests, serum electrolytes, chest x-ray, and full abdomen echography all within normal limits. Medical and immunological consultations found no evidence of any systemic illness.

Interestingly, in both patients, pro-BNP returned to normal plasma levels after clozapine cessation.

Clozapine was discontinued in both patients and 75 mg/day indomethacin treatment was initiated, and then increased to 150 mg/day, until resolution of the tachycardia. Echocardiography confirmed the progressive resolution of the pericardial effusion. Interestingly, in both patients, pro-BNP returned to normal plasma levels after clozapine cessation. Specifically, pro-BNP plasma concentration fell from 1,004 to 13 pg/ml in a few days in the first patient. Clozapine was replaced by quetiapine 300 mg/day in the first patient and haloperidol 6 mg/day in the second, with a worsening in their psychopathological picture. For both patients, loss of treatment efficacy emerged in the thought disorder subtotal score (20) and in the hostility-suspiciousness subtotal score (17). At three-month follow-up, there was no accumulation of pericardial fluid, and transthoracic echocardiography showed a complete resolution of pericardial effusion.

Discussion

The presentation of clozapine-induced pericarditis may range from a nearly asymptomatic clinical picture characterized only by a flu-like syndrome and an elevation of pro-inflammatory indices up to a fulminating cardiomyopathy resulting in death. On the other hand, there may also appear a subclinical clozapine-mediated cardio-toxic effect (7), which is underestimated. Therefore, it is advisable to maintain a high level of suspicion when treating patients who take clozapine and who develop cardiac symptoms. As we reported, one of our patients was nearly asymptomatic, apart from the increase of pro-inflammatory indices and pro-BNP plasma levels. Troughton et al. (22) maintain that in patients with left ventricular systolic impairment and symptomatic heart failure, drug treatment that encompasses the monitoring of pro-BNP concentrations reduces the number of cardiovascular diseases more effectively than a treatment based only on clinical judgment.

Plasma pro-BNP concentrations might help to reveal symptomatic cardiac impairment but, as we suggested, also to predict clozapine-related adverse effects. The measurement of the pro-BNP concentration both at baseline and after the beginning of antipsychotic treatment might help to diagnose an increased risk of cardiovascular diseases in patients with no specific symptomatology.

Annamraju et al. (23) recommend pro-BNP plasma levels as a diagnostic marker of both symptomatic and asymptomatic heart failure, thus offering a means of monitoring clozapine-treated patients to detect early and initially asymptomatic myocarditis before clinical signs of heart failure (2). Moreover, the systemic inflammatory response is similar in myocarditis and pericarditis, which may lead to heart failure if not recognized (12).

Mechanisms of clozapine-induced cardiotoxicity, though yet unexplained, may cause an imbalance in autonomic nervous system, which might explain clozapine-related rest tachycardia and QT interval prolongation (24). Considering pro-BNP involvement in the sympathetic activity and increased noradrenaline plasma levels correlation with left ventricular dysfunction, new evidence suggests that catecholamines may contribute to cardiac pathology (16). When clozapine treatment is discontinued (25), left ventricular impairment becomes reversible, and cardiac function improves overtime, with the pro-BNP levels within the normal range indicating an improvement of heart function (23).

The measurement of pro-BNP concentration both at baseline and after the beginning of clozapine treatment revealed a promising method to identify patients with an increased risk of cardiovascular side effects due to antipsychotics. Some studies show considerable immunomodulatory effects of clozapine (26, 27). Clozapine-mediated inflammatory response appears mainly during the first month of treatment through an increase of pro-inflammatory cytokines; Pollmächer et al. (28) found a significant increase in TNF-α while Maes et al. (29) in IL-6 levels during the first 6 weeks of clozapine treatment. These immunologic mechanisms could be triggered by clozapine treatment in the onset of myocarditis, pericarditis, serositis and hyperthermia (27).

Pro-BNP plasma levels appear to be a valuable laboratory biomarker to identify patients with asymptomatic cardiac impairment who might benefit from a therapy preventing progression to heart failure. It would be interesting to ascertain whether early treatment with ß-blockers and ACE-inhibitors might prevent progression to heart dysfunction in patients still receiving clozapine but presenting mild signs of cardiac toxicity.

Further studies, conducted in large populations and controlled environments, might confirm or reject this hypothesis, which remains, at the moment, purely speculative.

Conclusions

- Clozapine-related pericarditis could be early identified by pro-BNP plasma levels elevation.

- Measurement of pro-BNP plasma levels appears to be an interesting screening test to identify subjects with asymptomatic cardiac impairment. Treatment with ß-blockers and ACE-inhibitors may allow the continuation of therapy despite mild signs of cardiac toxicity due to clozapine.

- Further research is needed to clarify the real importance of pro-BNP in early detection of clozapine-related pericarditis.

Consent

Written informed consent was obtained from the patients for publication of this Case Report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

List of Abbreviations

BNP: brain natriuretic peptide; CRP: C-reactive protein; LVEF: left ventricular ejection fraction; BMI: body mass index; BPRS: Brief Psychiatric Rating Scale; VES (ESR): erythrocyte sedimentation rate; WBC: white blood count; ANC: absolute neutrophil count; ECG: electrocardiogram; TNF-α: tumor necrosis factor-α; ACE: angiotensin converting enzyme.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Vincenzo Prisco performed the conception of the study, preparation of the manuscript, interpretation, editing and revising in collaboration with the other authors.

References

1. Lieberman JA, Kane JM, Johnes CA. Clozapine: guidelines for clinical management. J Clin Psychiatry 1989;50(9):329-338.

2. Layland JJ, Liew D, Prior DL. Clozapine-induced cardiotoxicity: a clinical update. Med J Aust 2009;190(4):190-192.

3. Markovic J, Momcilov-Popin T, Mitrovic D, Ivanovic-Kovacevic S, Sekuli S, Stojsic-Milosavljevic A. Clozapine-induced pericarditis. Afr J Psychiatry (Johannesbg) 2011;14(3):236-238.

4. Merril DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. J Clin Psychopharmacol 2005;25(1):32-41.

5. Wehmeier PM, Heiser P, Remschmidt H. Myocarditis, pericarditis and cardiomyopathy in patients treated with clozapine. J Clin Pharm Ther 2005;30(1):91-96.

6. Kelly DL, McMahon RP, Liu F, Love RC, Wehring HJ, Shim JC, et al. Cardiovascular disease mortality in patients with chronic schizophrenia treated with clozapine: a retrospective cohort study. J Clin Psychiatry 2010;71(3):304-311.

7. Rostagno C, Domenichetti S, Gensini GF. Does a subclinical cardiotoxic effect of clozapine exist? Results from a follow-up pilot study. Cardiovasc Hematol Agents Med Chem 2012;10(2):148-153.

8. Rathore S, Masani ND, Callaghan PO. Clozapine-induced effuso-constrictive pericarditis. Case report and review of the literature. Cardiology 2007;108(3):183-185.

9. Raju P, Rao GK, Davis G. Pericardial effusion in patients with schizophrenia: are they on clozapine? Emerg Med J 2008;25(6):383-384.

10. Catalano G, Catalano MC, Frankel Wetter RL. Clozapine induced polyserositis. Clin Neuropharmacol 1997;20(4):352-356.

11. Cadeddu G, Deidda A, Stochino ME, Velluti N, Burrai C, Del Zompo M. Clozapine toxicity due to a multiple drug interaction: a case report. J Med Case Rep 2015;9:77.

12. De Berardis D, Campanella D, Serroni N, Rapini G, Olivieri L, Fornaro M, et al. Clozapine-related pericarditis during titration phase in a patient with resistant schizophrenia and concomitant valproate treatment: a case report. J Clin Psychopharmacol 2014;34(5):649-651.

13. Kortner K, Neuhaus AH, Schurer F, Dettling M. Eosinophilia indicating subclinical clozapine-induced pericarditis. J Clin Psychiatry 2007;68(7):1147-1148.

14. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust N Z J Psychiatry 2011;45(6):458-465.

15. Koren W, Kreis Y, Duchowiczny K, Prince T, Sancovici S, Sidi Y, et al. Lactic acidosis and fatal myocardial failure due to clozapine. Ann Pharmacother 1997;31(2):168-170.

16. Layland JJ, Liew D, Prior DL. Clozapine-induced cardiotoxicity: a clinical update. Med J Aust 2009;190(4):190-192.

17. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362(9380):316-322.

18. Kropp S, Kern V, Lange K, Degner D, Hajak G, Kornhuber J, et al. Oxidative stress during treatment with first- and second-generation antipsychotics. J Neuropsychiatry Clin Neurosci 2005;17(2):227-231.

19. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799-812.

20. Kane JM, Honigfeld G, Singer J, Melzer HY. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789-796.

21. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):293-245.

22. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic (N-BNP) concentrations. Lancet 2000;355(9210):1126-1130.

23. Annmraju S, Sheitman B, Saik S, Stephenson A. Early recognition of clozapine-induced myocarditis. J Clin Psychopharmacol 2007;27(5):479-483.

24. Walker NL, Cobbe SM, Birnie DH. Tachycardiomyopathy: a diagnosis not to be missed. Heart 2004;90(2):e7.

25. Hobbs RE. Using BNP to diagnose, manage and treat heart failure. Cleve Clin J Med 2003;70(4):333-336.

26. Liu F, Mahgoub N, Ferrando S. Leukocytosis associated with clozapine treatment: a case report. Psychosomatics 2011;52(5):488-491.

27. Røge R, Møller BK, Andersen CR, Correll CU, Nielsen J. Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? Schizophr Res 2012;140(1-3):204-213.

28. Pollmächer T, Hinze-Selch D, Mullington J. Effects of clozapine on plasma cytokine and soluble cytokine receptor levels. J Clin Psychopharmacol 1996;16(5):403-409.

29. Maes M, Bosmans E, Kenis G, De Jong R, Smith RS, Meltzer HY. In vivo immunomodulatory effects of clozapine in schizophrenia. Schizophr Res 1997;29(2-3):221-225.