Clozapine-induced reversible Brugada Syndrome

Jun Hua Chong and Franz Eversheim

Abstract— **We describe a case of reversible Brugada Syndrome in a patient on Clozapine for schizophrenia, highlighting the risk of antipsychotics causing a variety of phenotypic expressions of predisposing sodium channelopathy.**

Keywords- Clozapine; Brugada Syndrome; Sodium channelopathy; Antipsychotics

I. Clinical Case Report

Our patient was a 49 year old male with a background of schizophrenia diagnosed in February 2004. His condition was poorly controlled on Zuclopenthixol injections commenced in May 2006. He was subsequently commenced on Clozapine in 2009 with improvement in schizophrenia control. However, an electrocardiogram (ECG) performed post commencement of Clozapine revealed an incomplete right bundle branch block and ST elevations in V1 to V3, suggestive of Brugada Syndrome. This raised the concern of the risk of sudden cardiac death whilst on Clozapine.

Clozapine was withheld and a thorough cardiac assessment was performed. The patient reported no previous personal history of angina, palpitations, pre-syncope or syncope. There was no known family history of sudden cardiac death. His other past medical history included hypertension and hypertension-related ventricular hypertrophy.

His medications included Chlorpromazine hydrochloride 200mg nocte, Chlopromazine hydrochloride 50mg nocte PRN, Enalapril/Hydrochlorothiazide 20mg/6mg daily, Budesonide/Eformoterol 400/12 micrograms 2 puffs BD and Simvastatin 40mg daily.

An echocardiogram performed on 31st March 2009 showed normal diameters of all 4 heart chambers, concentric left ventricular hypertrophy with no signs of heart failure or myocarditis. There was no change to his previous echocardiogram. A troponin was sent which was negative hence making myocarditis unlikely. Holter monitoring was performed which revealed sinus rhythm with no significant arrhythmias detected.

Novartis Cardiologist was contacted and it was thought that Clozapine was responsible for a Brugada Syndrome pattern on the patient's ECG. Clozapine can interfere with sodium channels and Brugada Syndrome ECG changes can be brought out in a patient so predisposed. The consensus opinion was for Clozapine to be ceased. Should rechallenge with Clozapine be required for control of schizophrenia symptoms, this should occur in an inpatient setting with daily ECG monitoring.

Electrophysiological studies would be indicated particularly if there was a family history of premature sudden death. Clozapine therapy would be contraindicated should recurrent Brugada Syndrome-like changes develop.

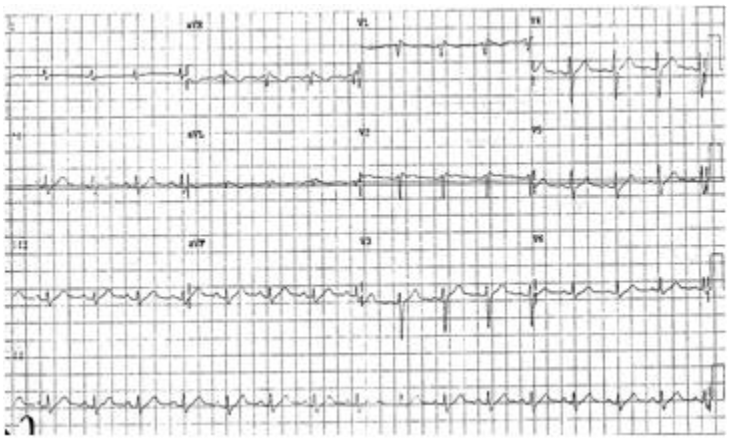

Figure 1. ECG prior to Clozapine

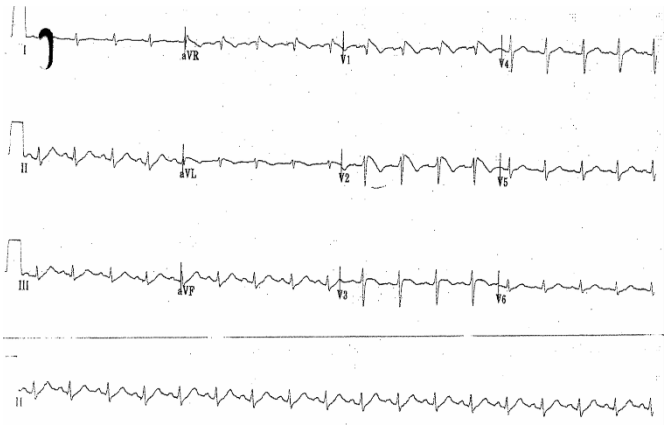

Figure 2. ECG post Clozapine

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II. Discussion

Schizophrenia has a lifetime prevalence of 0.55% and an annual incidence of about 0.015% [1]. The disease can be a distressing and debilitating condition for the sufferer.

Clozapine is a useful atypical antipsychotic for schizophrenia symptoms that are refractory and has been shown to reduce suicide rates in patients [2]. Commonly described cardiovascular side-effects of Clozapine include myocarditis, with cardiomyopathy and pericarditis also being described [2]. Whilst existing literature have alluded to the potential that sodium channel blocking agents like Clozapine can induce Brugada syndrome [3], there have been no case reports published to date on actual clinical cases.

Brugada Syndrome is inherited as an autosomal dominant condition with incomplete penetrance [4] but can also be associated with use of tricyclic antidepressants and neuroleptics [5]. Brugada Syndrome can cause ventricular arrhythmias like ventricular tachycardia and fibrillation in structurally normal hearts, leading to sudden cardiac death in about 20% of untreated patients [5].

The point prevalence of the Brugada Syndrome ECG pattern in the healthy population has been estimated at 1–5 per 10,000 people throughout the world [6].

Drugs described with the potential to cause Brugada Syndrome include Lithium, and possibly other mood stabilizers that block sodium channels (e.g., carbamazepine, oxcarbazepine, valproate, lamotrigine) [7]. Other psychiatric medications such as tricyclic antidepressants (e.g., amitriptyline, desipramine), clozapine, and selective serotonin reuptake inhibitors (e.g., fluoxetine), also affect the activity and function of cardiac sodium channels [7]. Hence, these medications may also increase the risk of developing symptomatic Brugada Syndrome [7].

Mutations in the SCN5A gene with resultant gain-of-function can cause Long QT type 3 Syndrome through overactive cardiac sodium channels leaking sodium and causing prolongation of the action potential [8]. Loss-of-function mutations in the SCN5A gene can cause Brugada Syndrome through underactive sodium channels [8]. Both clinical conditions tend to present with nocturnal sudden cardiac death, and families exist where the same genetic mutation can result in both of these conditions being present in different family members [8].

Several mechanisms through which Clozapine induces Brugada Syndrome can be postulated. Clozapine can induce a sodium channelopathy [3], which is the pathogenesis of Brugada Syndrome. Sodium channelopathy selectively affecting the epicardium results in a transmural voltage discrepancy between the epicardium and the endocardium [4].

There is inhomogeneous repolarization in different areas of the right ventricular epicardium leading to phase 2 re-entry [4]. This in turn gives rise to closely coupled extrasystoles which can trigger ventricular tachycardia or fibrillation [4]. Other factors that can affect the size of the voltage discrepancy include the testosterone effect of the male gender [4]. The Brugada Syndrome phenotype is more commonly observed in males than females due to the presence of more prominent transient outward current channels in males than females [5].

In the case of our patient, whilst Brugada Syndrome was thought to be a direct effect of Clozapine use, it was also postulated that Clozapine use could have unraveled the Brugada Syndrome ECG phenotype in the patient who was genetically predisposed. Lithium causing phenotypic expression of Brugada syndrome has been described in current literature [7]. Certainly, in another case of a 42 year old man with syncope on Lithium, provocation testing with ajmaline in the patient who was taken off Lithium demonstrated ST segment elevations in the anterior chest leads [7]. Whilst the patient denied personal or family history of sudden death or syncope, ajmaline testing clearly unraveled predisposing sodium channelopathy [7].

At the molecular level, it has been proposed that the cardiac voltage-gated sodium channel ($Na_v1.5$) may be part of a complex of proteins that are regulated by anchoring proteins, modifying enzymes and modulating proteins [9]. Phenotypic SCN5A disease has been found to be related to mutations in genes encoding these regulatory proteins [9]. Consideration should be given to the pathogenic potential of mutations in these regulatory proteins in the context of drug-induced Brugada Syndrome as well. It has also been postulated that various $Na_v1.5$ channel complexes consists of different proteins and are regulated differently depending on their location within the cell membrane compartments [9]. This could explain why a certain medication can result in 2 different phenotypes (Long QT or Brugada Syndrome) depending on the concentration, distribution and location of various $Na_v1.5$ channels within the cell.

A subgroup of familial sudden cardiac death syndrome has been identified in which a Brugada Syndrome phenotype is seen in combination with a short QT interval (QT interval (corrected) $\leq$ 360 ms) [5]. In these patients, gene mutations affecting the calcium channel have been found to be the underlying cause [5]. These include loss-of-function missense mutations in CACNA1C (A39V and G490R) gene and CACNB2 (S481L) gene encoding the a1-subunits and b2b-subunits of the L-type calcium channel [5]. This development may pave the way for the discovery of other ion channelopathies apart from $Na_v1.5$ that might contribute to the Brugada Syndrome phenotype and its various subtypes. Indeed, it can be postulated that the interaction of psychotropic drugs with various ion channels apart from $Na_v1.5$ may even help explain drug-induced Brugada Syndrome phenotype seen in individual cases.

In conclusion, it is important to be aware of the typical signs of Brugada Syndrome in psychiatric patients being treated with psychotropic medications. Baseline ECG

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monitoring in these patients is paramount to pre-empting serious cardiac sequelae. Just as the same genetic mutation in the SCN5A gene (or $Na_v1.5$ regulatory proteins genes) can result in either Long QT Syndrome or Brugada Syndrome in different individuals [9], it appears that Clozapine can induce either Long QT Syndrome or Brugada Syndrome in different patients on this medication. Whilst focus has been placed on the role of sodium channelopathy in drug-induced Brugada Syndrome, new paths of discovery could involve other ion channelopathies and their role in the pathophysiology of Brugada Syndrome subtypes. Whilst research literature exists on the observed effect of Clozapine-induced QT prolongation [10], more research needs to be done on the prevalence, pathogenesis and molecular pathology of Clozapine-induced Brugada Syndrome.

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