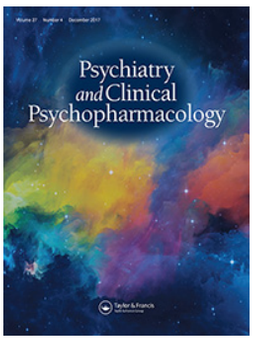

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CASE REPORT

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Bipolar disorder with Marfan syndrome: a case illustration based on possible involvement of TGF-β1 in the common etiopathogenesis

Possible neurobiological underpinnings of co-occurrent bipolar disorder and Marfan Syndrome

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ABSTRACT

Marfan syndrome (MFS) is mainly characterized by the pathological connective tissue. The mutant fibrillin protein in MFS misleads the constitutive pathways of various tissues through inappropriate transforming growth factor beta (TGF-β) signalling. Bipolar disorder (BPD) is believed to arise as a result of impaired synaptic modulation and neural plasticity in crucial pathways that mediate cognition and affection. TGF-β was linked with neurogenesis and developmental neural remodelling. Altered TGF-β functions with pleiotropic effects to the brain could increase susceptibility to psychiatric disorders such as BPD. Disrupted circuits of molecular signalling chains cause improper synapse formation, synaptic transmission, and synaptic plasticity that ultimately may end up with BPD. Here, we report a 26-year-old male who was diagnosed with MFS and BPD. This case report aimed to argue probable impaired neuroprotective mechanisms which may lead to such comorbidity. We may inspire later studies on possible shared etiopathogenesis via defective microfibrillar proteins of both disorders.

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Bipolar disorder; Marfan syndrome; neurodevelopment; neuroinflammation; neuroprotection; TGF-β1

Introduction

Marfan syndrome (MFS) is an autosomal dominant systemic disorder, mainly characterized by the pathological connective tissue architecture with predominant manifestations in various organ systems. The estimated worldwide incidence of MFS is about 2–3 per 10,000 [1]. The fibrillin-1 gene (*FBN1*), located on chromosome 15q21.1, encodes the microfibril *fibrillin*, an extracellular structural matrix glycoprotein, and its mutation is related with MFS. The mutant gene is suggested to mislead several constitutive pathways of connective tissue, and inappropriate *transforming growth factor beta (TGF-β)* signalling is attributed to deranged *fibrillin* as a consequence of such mislead pathways [2]. Distorted tissue architecture specifically manifests in cardiovascular, skeletal, and ocular systems. Despite genetic analysis being noteworthy in MFS, due to the absence of mutant *FBN1* in many cases, accurate clinical diagnosis requires detailed history, physical examination, and imaging studies. One major involvement plus identified mutation or two major system involvements without mutation are required for the diagnosis according to Ghent nosology [1]. Major entities are pectus carinatum, lens dislocation, aorta pathologies, and dural ectasia. In 2010, revised Ghent nosology has published with seven new criteria, requiring at least one for the diagnosis [3]. These are: in the absence of family history, ectopic lens and *FBN1* mutation with known aorta pathology or aortic root *Z*-score ≥2 with ectopic lens or *FBN1* mutation or >7 points of systemic scores; in the presence of family history, ectopic lens or aortic root *Z*-score ≥2 or >7 points of systemic scores. Bipolar disorder (BPD) is a progressive, chronic, and episodic psychiatric illness associated with functional impairment and increased suicidal risk. The estimated worldwide lifetime prevalence of BPD is 2.4%. BPD is believed to have strong heritability among psychiatric disorders; however, a multifactorial model is more fit for the aetiology, with the various combinations of susceptible/preventive genetic profiles and environmental interactions. As recognized, BPD arises as a result of impaired synaptic modulation and neural plasticity in crucial pathways that mediate cognitive and affective functions. Therefore, BPD is accepted as a disorder of altered synaptic and neuronal circuits rather than being caused by neurotransmitter imbalance [4]. Literature scarcely reports cases of psychiatric comorbidity in MFS; mostly and particularly schizophrenia was demonstrated, and a few reviewed neuropsychological manifestations. To the best of our knowledge, BPD comorbidity in MFS has been reported once [5], but

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without arguing possible underlying mechanisms. In this report, we aimed to present a previously diagnosed MFS case with BPD with arguing probable underlying neurobiological underpinnings.

Case

We report a 26-year-old male patient, who was single, graduated primary school, and working as a caretaker. He was previously diagnosed with MFS according to the Ghent criteria at age 23, based on his cardiovascular abnormalities (having aortic root dilatation requiring surgical repair) and lens dislocation with the shown mutation in chromosome 15. The patient's first psychiatric admission was at age 18 with a manic episode and diagnosed with BPD. Since then, manic, hypomanic, and depressive episodes had been revealed. It was documented that none of those mood episodes were accompanied by psychotic features. He was admitted to our outpatient clinic with suicidal thoughts, anhedonia, and sleeplessness with attempting suicide two weeks ago with high-dose warfarin, requiring intensive care. These complaints had been presented for two months despite having been under per oral medication with olanzapine 10 mg/day and lithium carbonate 900 mg/day. The patient was hospitalized as required. His physical examination had several significant findings. A height of 6 feet 2 inches and marfanoid face with a sternal surgical scar were recorded. Arm span to height ratio of 1.20 (normal ratio < 1.05) and positive thumb and wrist sign were observed. X-ray imaging showed arachnodactyly in bilateral hands and feet. His neurological examination was normal and ophthalmological evaluation revealed ectopic lens. In his mental examination, he appeared his age and self-care was slightly decreased. Depressed affect and dysphoric mood were recorded. Psychomotor activity, speech output, and speed were decreased without any psychotic symptoms. He had reasoning and insight. Cognitive evaluation was normal. The Montgomery–Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HDRS) scores were 32 and 31, respectively. He had no history of drug or alcohol abuse. He had an uncle and an aunt diagnosed with schizophrenia. He did not have any relative with MFS. No abnormality was detected in his routine biochemistry and hemogram screen. We raised olanzapine up to 20 mg/day and lithium carbonate up to 1200 mg/day per oral. Brief cognitive and behavioural interviews were implemented regularly. His suicidal thoughts were improved with the treatment. His MADRS and HDRS scores decreased to 16 and 9, respectively. Soon after his blood lithium level reached 0.92 mEq/l, he was discharged with olanzapine 20 mg/day and lithium carbonate 1200 mg/day per oral, suggesting admission to the outpatient clinic regularly.

Discussion

It has been hypothesized that defects on the genes encoding microfibrillar proteins such as *fibrillin* and related impaired growth factor signalling may predispose to neurodevelopmental abnormalities which could explain neuropsychiatric manifestations as the phenotype of MFS. *TGF-β* was affiliated with neurogenesis and developmental neural remodelling in animal studies [6]. Altered *TGF-β* functions with its pleiotropic effects to the brain were linked with liability to psychotic disorders. A mutation in *FBN1* and hyperactivation of *TGF-β* could cause both the symptomatology of MFS and an increased susceptibility to schizophrenia; that susceptibility was attributed to defective proliferation and differentiation in the hippocampus and the nasal epithelium [7]. Increased peripheral levels of *TGF-β receptor-2 mRNA* were also considered as a potential state marker for schizophrenia [8]. Despite our patient's long-term clinical course has not linked with psychotic symptomatology, both psychotic disorders and mood disorders have been frequently implied to have a convergent genetic basis in the aetiology. For example, population-based studies have recently shown that many alleles such as *CACNA1C*, *TENM4*, and *NCAN*, involving polygenic risk of BPD, also partly overlap with schizophrenia [9]; however, *FBN1* has not been implied in those studies. Genetically varied or disrupted molecular pathways including microtubule regulation and cytokine modulation attract the authors to define neurodevelopmental processes in BPD. Microtubule and microfibril-related mechanisms need to remain stabilized in order to provide accurate neuronal migration and function; disrupted circuits of molecular signalling chain in the brain may cause improper synapse formation, synaptic transmission, and synaptic plasticity that ultimately may end up with BPD [10]. A recent genome-wide association study based on single-nucleotide polymorphisms indicated that polymorphic *FBN1* leads to susceptibility to BPD [11].

Growing body of studies also focused on immune dysfunction in BPD that influences the affective and cognitive functions, with suggesting biomarkers such as cytokines to reflect proinflammatory status in BPD. Studies regarding association of *TGF-β* and BPD lack, one of the most intriguing was post-mortem sampling from frontal cortex investigating *TGF-β1* mRNA via RT-PCR and was found to be down-regulated in BPD which may reveal *TGF-β1's* specific role as a neuroprotector [12]. Unlikely, a recent meta-analysis showed no significant differences between BPD patients and healthy controls for the levels of *TGF-β1* [6]. Two recent studies have not demonstrated elevated *TGF-β1* plasma levels in BPD [13,14]. In contrast, another has found *TGF-β1* and *IL-23* plasma levels significantly higher in BPD [15] (Table 1). Such controversial findings may be attributed to low sensitivity of peripheral levels of

Table 1 . Studies of peripheral *TGF-β1* levels in BPD.

Author, year	Subjects, *n*	Age	Assay	Sample	Result
Kim et al., 2004	Mania = 70	32.9 ± 12.2	ELISA	Plasma	Lower in patients ($p = .001$)
	Control = 96	30.3 ± 10.1			
Li et al., 2015	Mania = 41	37.5 ± 13.6	ELISA	Plasma	Higher in patients ($p < .001$)
	Control = 36	36.9 ± 6.3			
Fiedorowicz et al., 2015	Mania = 15	36 ± 13	ELISA	Plasma	No significance between any group ($p > .05$)
	Depression = 9	44 ± 13			
	Euthymia = 13	41 ± 14			
	Control = 29	41 ± 13			

any biomarker that shows neuroinflammatory status. From another perspective, *TGF-β1* may be considered as a negative regulatory factor in peripheral blood that may compensate and help to relieve the inflammation status in BPD; unlikely decreased expression of *TGF-β1* in the brain tissue famishes the anti-inflammatory and neuroprotective ability as a psychoimmunological mediator. The mutant *FBN1* gene in MFS misleads the *TGF-β* signalling and may disrupt its roles in neuroprotectional and neurodevelopmental processes. As concurrence of MFS with any affective disorder has been rarely published yet, our report could pave the way for different neurobiological arguments and perspectives on BPD comorbidity in MFS. Despite this kind of co-occurrence is likely to concur coincidentally, whether both diseases share a common genetic aetiology via defective microfibrillar proteins, roles of growth factors, and connective tissue proteins in neurodevelopment and physiopathology of BPD will be remarkably inspiring for later studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

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