Overweight is a risk factor for NTD. It is known that atypical antipsychotics cause weight gain, and low serum folate levels, along with overweight, may put infants of women with clozapine at high risk for NTD. Amount of overall weight gain during pregnancy and serum folate levels are not available for this patient. Maternal diabetes is also a risk factor for NTD. This case had no diabetes before conception and was diagnosed to have gestational diabetes at the third trimester.

Clozapine is less studied in pregnancy or animal studies. NTD may be an effect of clozapine interfering in organogenesis. Clinicians must be vigilant about such cases. Further prospective studies are warranted to determine the safety of clozapine in pregnancy. Clozapine should be used only in difficult cases and in such situations, monitoring should be ensured.

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There are no conflicts of interest.

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Comorbid Bipolar Disorder and Benign Joint Hyper Mobility Syndrome (BJHS): More than a Mere Coincidence?

Sir,

Benign Joint Hypermobility Syndrome (BJHS) is thought to be an inherited connective tissue disorder with an autosomal dominant pattern, clinically characterized by hypermobility and pain in multiple joints in the absence of systemic rheumatologic
There is no consensus on whether this as an independent disorder or a milder variant of well-known Ehler-Danlos syndrome (type-III). Although perceived as a rare condition, BJHS is common, with a prevalence of 5%-38% depending on age, sex, and race. The syndrome appears to be due to an abnormality in collagen or the ratio of collagen subtypes. Mutation in the Fibrillin gene has also been identified in families with BJHS, and recently, mutations in a non-collagenous molecule, Tenascin-X, have also been identified in a subset of patients with BJHS. An increased prevalence of psychological disturbances, such as anxiety, depression, agoraphobia, panic disorder, and attention deficit hyperkinetic disorder (ADHD) has been found in patients with BJHS. Here, we describe a young male with BJHS comorbid with bipolar affective disorder (BPAD). To the best of our knowledge, BPAD comorbidity in BJHS has not been reported till date.

We report a 29-year-old male patient, an unmarried graduate, referred by the neurologist who was treating him for pain in multiple joints for more than a year. The patient had the first episode of depression at 21 years of age, followed by another episode within 4 years. Recently, he had manic episode followed again by depression and was treated with lithium carbonate 800 mg/day, olanzapine 5 mg/day, and escitalopram 2.5 mg/day. He was referred to us due to a partial response to the current treatment with persistent social withdrawal, suspiciousness, and reduced sleep and appetite. Mental status examination revealed referential and persecutory delusions, thought broadcasting, and depressed affect. His physical examination had several significant findings. He had marfanoid habitus such as tall stature, upper segment less than lower segment (<0.89 ratio) and arm span to height ratio of 1.20 (normal value is <1.05). He had hypermobile joints with a Beighton score of 6 [Figures 1-4]. Neurological and cardiovascular examinations were within normal limits. He was diagnosed with BJHS according to Brighton criteria: Beighton score of >4 and arthralgia for longer than 3 months in four or more
various psychiatric disorders is not yet clear. This could
without BJHS. Studies have observed a higher
disorder found hypermobile joints in 41% of the sample,
somatic phenotype of BPAD with co-morbid anxiety
amplification.

This case illustrates the co-occurrence of BPAD with
psychotic features in the presentation and BJHS in a
male with a family history of BPAD but not of
connective tissue disorders. Our patient had a significant
disability due to the BJHS that he seldom played with
friends and rather stayed back at home most of the time
during his adolescent age. He presented with a history
of predominantly depressive episodes with a single
manic episode and responded well to a combination
of lithium and olanzapine.

BJHS has a well-known association with psychological
problems. A recent meta-analysis exploring the
relationship between BJHS and psychological distress
found greater perceptions of fear and more intense fear
among patients with BJHS. Furthermore, they have
a higher probability of demonstrating agoraphobia,
anxiety, depression and panic disorders than those
without BJHS. Studies have observed a higher
prevalence of autism spectrum disorders, BPAD, ADHD,
depression and attempted suicide among patients with
hypermobility syndromes (including different variants
of Ehler-Danlos syndrome) when compared with
matched controls. A relationship was determined
between five potentially pathophysiologically linked
domains: anxiety disorders, joint laxity, chronic
pain disorders, immune dysfunction, and mood
disorders. A recent study exploring psychiatric and
somatic phenotype of BPAD with co-morbid anxiety
disorder found hypermobile joints in 41% of the sample,
and it was significantly associated with somatosensory
amplification. The commonly used medications for
these symptoms, such as antidepressants for anxiety
symptoms and steroids for pain symptoms, can have
a negative impact on the course of BPAD. Hence,
clinicians need to be careful in managing patients with
BJHS at risk for BPAD.

The pathophysiology by which BJHS precipitates
various psychiatric disorders is not yet clear. This could
partly be due to the fear and anxiety associated with
potential re-injuries. Moreover, the disease load in BJHS
can contribute to poor quality of life and an increased
risk of depression and suicide attempt. However, such
explanations could not clarify the association between
BJHS and BPAD, a progressive, chronic, and episodic
psychiatric disorder with multifactorial etiology and
strong heritability. BPAD occurring in association
with BJHS may be attributed to psychosocial stressors
secondary to BJHS or maybe a chance association.

Another possible etiological link between BJHS and
BPAD seems to be genetic. Recent evidence suggests
that BPAD arises not merely due to neurotransmitter
imbalances — rather, it is the result of an impaired
synaptic modulation and neural plasticity in crucial
pathways that mediate cognitive and affective
functions. It can be hypothesized that mutation in the
fibrillin gene may predispose patients with
BJHS to neurodevelopmental abnormalities which
may manifest as psychiatric disorders such as BPAD.
A recent genome-wide association study based on
single-nucleotide polymorphisms also indicated that
polymorphic FBN1 increases the susceptibility to
BPAD. Though BJHS is not considered primarily an
inflammatory condition, a recent analysis of electronic
medical records showed its association with autoimmune/
inflammatory disorders. As neuroinflammation
is being recognized as an important mediator of the
etiopathogenesis of BPAD, the possibility of a shared
inflammatory process needs consideration.

In conclusion, our case highlights the co-morbidity of
BJHS with BPAD. Such co-occurrences of heritable
disorders help us to further understand the neurobiology
of both the disorders, especially the role of genes
associated with BJHS and the role of connective tissue
proteins, in the pathophysiology of BPAD.

Declaration of patient consent
The authors certify that they have obtained all
appropriate patient consent forms. In the form the
patient(s) has/have given his/her/their consent for his/
her/their images and other clinical information to be
reported in the journal. The patients understand that
their names and initials will not be published and
due efforts will be made to conceal their identity, but
anonymity cannot be guaranteed.

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