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Letter to the Editor / Editöre Mektup

Hypomanic Episode in CADASIL Syndrome

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Dear Editor,

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a systemic disease associated with mutation of the Notch 3 gene on chromosome 19p13.1 (1). Deposition of granular osmiophilic material (GOM) in the tunica media of small cerebral arteries which can be seen under an electron microscope is pathognomonic for the disease (2). Neurological signs of the disease, such as migraine, transient ischemic attacks, lacunar infarcts, cognitive declines and dementia, are often comorbid with psychiatric symptoms (1,3). With this, the age of onset and clinical presentations are multifactorious. Attacks of migraine with aura are the first clinical manifestation in 20-30% of patients (4). Mood disorders, anxiety disorders, psychotic disorders, adjustment disorders, behavioral disorders, personality disorders, drug addiction, and substance abuse are main psychiatric diagnoses in CADASIL patients (2). In this paper, we report a patient having mood disturbance while being diagnosed with CADASIL.

Our case was a 27-year-old, primary school graduate, single male patient. He was admitted to the Neurology clinic with complaints of headache, puffiness at the left temporal artery region and forgetfulness ongoing for last two to three years. He was examined by psychiatric consultant because of depressive symptoms. He and his family were told that he had migraine attacks without aura during childhood. He had feeling of pins and needles in his arm two times in last 5 years. Additionally, two years ago, he had a depressive episode that continued for nearly 6 months and ended spontaneously without psychiatric treatment. He had no family history of psychiatric disorders, though his grandmother, mother, uncle and elder brother had stroke episodes at young ages.

The psychiatric evaluation revealed that he was having a new depressive episode. He scored 24 points from both the Beck Depression Inventory and Mini-Mental State Examination (MMSE). His neurological examination was normal. Escitalopram 10mg was begun as antidepressant therapy. Routine biochemical tests, full blood count, liver function tests, thyroid

function test and microbiological tests were normal. Transthoracic echocardiography, bilateral carotid vertebral doppler ultrasound and electroencephalography examinations were normal. Pathologic intensity changes with hyper intense features, sometimes forming confluence at the bilateral periventriculer-supraventriculer white matter regions, were seen in cerebral magnetic resonance imaging (MRI). Initially, these findings were attributed to demyelinating disease or vasculitis. However, his mother's and elder brother's cerebral MRIs showed similar lesions. NOTCH 3 mutation, which was reported to be diagnostic for CADASIL was positive. 300mg acetylsalicylic acid was included in medical treatment for reducing risk of cerebrovascular accident.

Two months later during his follow-up psychiatric examination, he reported decreased need of sleep, irritability, insistency, impatience, and increased talkativeness that was more than usual. The Young Mania Rating Scale (YMRS) score was 21 points. Escitalopram treatment was stopped and risperidone 1mg/day recommended. One month later, he declared feeling nervous, so dosage of risperidone was increased to 2mg/day. Subsequently, mood elation decreased over approximately two weeks (YMRS: 7 points).

Commencing symptoms of CADASIL according to age are common but migraine and transient ischemic attacks are the most reported (5). The history of our case was congruent with the data as his complaints started with migraine. Cognitive declines and dementia are usually the other noted clinical forms. Cognitive declines are generally insidious and subsist before transient ischemic attacks or strokes. Cross-sectional studies showed that attention and executive functions were impaired at early phases of the disease and 90% of the patients between 35-50 years old were affected (4). As our case is a young man, he had no cognitive decline, however he did obtain a borderline score with the MMSE form (24/30). Cognitive decline in bipolar disorder is proportionate with hyperintensity frequently reflected in cerebral MRI (6). It is known that cerebral imaging studies usually exhibit certain abnormalities for risky people before appearance of bipolar disorder's clinical hallmarks and symptoms (7).

Mood disturbances are the most common (9-41%) psychiatric disorders and seem to be associated with executive dysfunction in CADASIL (4). The onset of psychiatric disorder was a depressive episode in our case. It is thought that depression episodes seen in a CADASIL course present with melancholic-type symptoms. Psychic somatization and anxiety can be perceived by patients (1). Mood disturbance comorbidity with neurologic symptoms and having no family history of mood disorders made us consider an organic etiology in our case. One CADASIL case presented as a mood disorder was reported from our country previously (8). Deep brain hyperintensities at the white matter seen in elderly depression and bipolar disorder patients have some similarities with lesions in CADASIL cases (9). It has been demonstrated that pathways associated with the NOTCH gene cause white matter changes with bipolar disorder (10).

NOTCH 3 is expressed exclusively from smooth muscle cells located at arterial walls and mutations in the NOTCH 3 gene bring about degeneration of vascular smooth muscle cells and multiple small infarcts at the white matter and deep gray matter (4,11). How the NOTCH 3 gene engenders arteriopathy is unknown. Yet, it is shown that dysfunction of NOTCH 3 receptors affects certain pathways of cell functions, such as growth, differentiation and apoptosis (9).

In experimental studies, mutant NOTCH 3 develops vascular alterations specific for CADASIL and disturbances in autoregulation of vascular blood flow (11). Reduced relaxation or induced resistance in cerebral vessels is apparent from the data (4). By way of addition of highly reduced relaxation-affiliated flowing, highly induced myogenic tone demonstrates vascular structure disturbance (12).

Although antidepressant effects on developing hypomania is unknown in our case, and should be acceded as restrictiveness, absence of bipolar disorder family history and comorbid neurologic symptoms suggested a relationship between cerebral vascular diseases and mood disorders. Our case supports the argument of the role of ischemic subcortical lesions at the onset of mood disturbances by a destructive effect on cortical-subcortical cycles.

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