Kluver-Bucy and Frontal Syndromes Following Meningoencephalitis in a Young Boy: Pathophysiological and Clinical Considerations

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ABSTRACT
We describe the clinical picture and one-year follow-up in a 55-month-old boy who developed a constellation of behavioral/emotional symptoms with sudden onset following meningoencephalitis. He was given the diagnosis of Kluver-Bucy and frontal syndrome. His behavioral symptoms responded to the combination of methylphenidate and risperidone better than either medication alone. Herein, we discuss the clinical and pathophysiological aspects in this case. (Archives of Neuropsychiatry 2012;49: 163-166)

Key words: Kluver-Bucy syndrome, frontal syndrome, children

Introduction
Kluver-Bucy syndrome (KBS), a rare neurobehavioral syndrome, was first described in 1939 by Kluver and Bucy in rhesus monkeys after the removal of greater portions of both temporal lobes and rhinencephalon (1). In human beings, KBS was first reported after bilateral temporal lobectomy (2). Subsequently, KBS has been observed in several neurological disorders, such as meningoencephalitis, cerebrovascular accidents, epilepsy, intracranial lesions or cerebral traumas, which lead predominantly to destruction or dysfunction of the bilateral temporal lobes (3,4,5,6). KBS is characterized by: (1) visual agnosia, i.e. psychic blindness with inability to recognize objects without loss of gross visual discrimination; (2) excessive oral tendencies, i.e. strong urge to examine all objects by mouth; (3) hypermetamorphosis, i.e. excessive attentiveness to visual stimuli with tendency to take notice of and touch every such stimulus (4); placidity with loss of normal fear and anger (5); altered sexual behaviour manifesting mainly as prominent and indiscriminate hypersexuality (6) and changes in dietary habits usually manifested as hyperphagia (7).

Frontal lobe syndromes may present with different clinical pictures varying according to the affected part of the lobe. The orbitofrontal (disinhibited) syndrome includes disinhibited and impulsive behaviors, inappropriate affect, euphoria, puerility, emotional lability, poor judgment, distractibility, increased energy, aggression, and violence (8). Frontal lobe damage has also been reported to be associated with mania, depression, confabulation, catatonia, perseveration and obsessive compulsive behaviors (9).
Here, we present a 55-month-old boy who developed a constellation of distinctive behavioral symptoms following meningoencephalitis and related cerebrovascular accident. We aimed to discuss the unusual clinical picture, possible etiological factors, management of behavioral symptoms with combination of risperidone (RIS) and methylphenidate (MPH), and the one-year clinical follow-up in this case.

**Case**

A 55-month-old boy presented with his biological parents. The main complaint of the parents was a sudden onset of behavioral and emotional symptoms that have been present for the last two months.

The parents reported that the child was quite well until he was admitted to hospital following a generalized tonic-clonic seizure five months ago at 50 months of age. He was conscious, cooperative and had no significant neurological deficits at the time of hospitalization. After admission, his clinical picture deteriorated as the boy lost his consciousness and cooperativeness gradually and started to display left hemiparesis one week later. Cerebrospinal fluid (CSF) analysis revealed white blood cell count of 35 cells/L and protein level of 80 mg/dL. The patient was eventually diagnosed with meningoencephalitis and the related cerebrovascular accident. His T1-weighted axial images demonstrated right temporal hypointensity and contrast enhancement due to occlusion of the inferior division of the right middle cerebral artery at subacute stage in magnetic resonance imaging (MRI) taken on the tenth day of hospitalization (Figure 1). His detailed laboratory investigations (including screening for metabolic disorders and polymerase-chain reaction (PCR) for Herpes viruses) did not reveal any other abnormalities. Sequential evaluation of CSF specimens from the patient indicated decreasing cell counts and protein levels after using broad-spectrum antibiotics.

After one month of hospitalization, the patient was discharged with carbamazapine (CBZ) 200 mg/day treatment for seizure control and was scheduled for a physical rehabilitation program for his neurological deficits including left hemiparesis and inability to sit unaided. His motor deficits improved remarkably within a month. After one month of discharge, the boy started to have complex partial seizures 5-10 times a day, and the dose of CBZ was increased to 400 mg/day. His follow-up cranial MRI at age 53-months revealed large hyperintense area in the right cerebral hemisphere prevalent in the right temporal lobe at the chronic stage of the disease on T2-weighted axial images (Figure 2). Since the seizures did not respond well to CBZ 400 mg/day, valproate 150 mg/day was added. At the third day of this combination treatment, the patient started to display a constellation of behavioral and emotional symptoms such as hyperactivity, irritability, aggression towards peers, inappropriate sexual behaviors, excessive talking and asking, increased appetite and food consumption, and fearless behaviors. Although valproate was discontinued 15 days later, behavioral/emotional symptoms continued, but the boy remained seizure-free.

During the interview, it was observed that the patient had significant hyperactivity, excessive talking and asking (usually in the form of verbal perseveration), increased attentiveness to visual stimuli around him and a need to touch most of the things he saw, asking for hand shaking (in the form of motor perseveration) or for a kiss frequently, and using the phrase “my love” towards young women. Upon questioning, the parents reported aggressive and impulsive behaviors especially towards his peers, hyperphagia and excessive oral tendencies (i.e. finger sucking or putting objects into his mouth), loss of previously existing fears (i.e. loss of fear of cats and darkness, and approaching even big barking dogs), changes in affective state frequently during the day, and talking with unfamiliar people in a friendly manner. The parents noted that the child did not have any of these symptoms previously at all.

His prenatal, postnatal and developmental history was unremarkable. He had no previous history of neurological (including epilepsy) or serious medical illnesses, hospitalization or head trauma. There was no family history of neurological or psychiatric disorders. The Denver developmental screening test (Denver II) revealed normal premorbid developmental milestones.

Given his clinical picture, recent history of neurological
disorder and findings on neuroimaging studies, we made a provisional diagnosis of KBS and frontal lobe syndrome. He was started on haloperidol 0.5-1 mg/day for behavioral control. Because his behavioral symptoms did not improve, haloperidol was discontinued two weeks later and RIS 0.25-0.75 mg/day was started. The patient showed a mild improvement on RIS and tolerated medication quite well. Three weeks later, we further added MPH 5-20 mg/day to his treatment. He showed much-to-very much improvement, except for hyperactivity and excessive talking, with this combination (RIS 0.75 mg + MPH 20 mg/day) during the subsequent month. Because we interpreted this improvement to be due to adding MPH, we decided to cease RIS gradually to continue as MPH monotherapy. However, the behavioral symptoms worsened during MPH 20 mg/day monotherapy for three weeks. We added RIS 0.5-0.75 mg/day again and the behavioral symptoms showed much improvement on this combination. As the patient tolerated medications well, we increased the MPH dose up to 30 mg/day. Behavioral symptoms showed further improvement, including hyperactivity and excessive talking, without any significant side effects. Although his three follow-up electroencephalograms (EEGs) showed diffuse abnormalities in the right hemisphere, particularly on the temporal region, the boy did not have clinical seizures during the follow-up. His cranial SPECT analysis at age 66-months with a two-week medication-free period revealed nonperfusion in the right inferior temporal and frontal lobes and in the right parietooccipital and left middle frontal regions as well as massive hypoperfusion in the right middle frontal region (Figure 3). His behavioral symptoms gradually remerged with the previous severity during the two-month medication-free period with a similar response to the combination treatment of MPH 20 mg/day and RIS 0.75 mg/day.

Discussion

The case presented above exhibited five typical symptoms of KBS, except for visual agnosia, and may be considered as an incomplete form of the syndrome. In a clinical situation, incomplete KBS is likely to occur more often than the complete syndrome and the presence of at least three of the above-mentioned symptoms is usually sufficient to establish the diagnosis of KBS (3). However, besides these typical symptoms of KBS, our case showed some other symptoms [such as hyperactivity, impulsivity, aggressive behaviors, excessive talking, indifference to relationships, and motor/verbal perseverations (manifested as asking the same questions or using the same sentences too many times, and asking for hand shaking frequently while shaking his own hand)] which could be difficult to explain by the diagnosis of KBS. The question here is whether latter symptoms could be a part of KBS or they are mainly the results of frontal lobe involvement. We think that diffuse infarcts over the right hemisphere, including the frontal lobe, may account for the presence of latter symptoms as it is mentioned above that frontal lobe syndrome may include this kind of symptoms. As a matter of fact, the main underlying psychopathological mechanism in both symptom clusters seems quite similar. Clinically, a pervasive lack of behavioral inhibition is an important factor in the formation of symptoms in KBS. Lack of inhibition is also one of the main clinical pictures of frontal lobe, orbitofrontal syndrome. This may account for most of the symptoms other than KBS. The concurrence of KBS and frontal lobe syndrome following cerebrovascular disease has been reported in adult patients previously (10). Compared with adults, focal neurological deficits are more commonly reported in children with KBS (3,5). Unilateral involvement of the right temporal lobe may raise some concerns about the diagnosis of KBS. Because the original description of KBS involves bilateral temporal lobes (amygdala) damage, it has been usually accepted that unilateral damage would not cause the syndrome (3). However, there are some reports describing similar symptoms with left temporal lobectomy (11) and right amygdala damage (12). Therefore, it is not clear whether the unilateral or bilateral involvement of the temporal lobes is responsible for the formation of KBS in this case. Besides the main pathology in the right temporal lobe following cerebrovascular accident, the coincidental presence of an arachnoid cyst in the left temporal lobe may actually suggest bilateral involvement of the temporal lobes.

Despite the potential explanations above, the exact etiology of the clinical picture remains unclear in our case due to the presence of several probable causative factors (such as meningoencephalitis, cerebrovascular accident, arachnoid cyst and epilepsy), all of which have been reported to be associated with KBS. Additionally, the role of valproate in the formation of his clinical picture also remains unclear at this point. Although he developed cerebrovascular accident at the first week of hospitalization, our patient did not display the symptoms during hospitalization (20 days) or during the one-month period after discharge. The emergence of symptoms just after adding valproate to the treatment regimen may prompt us to consider the role of valproate in the formation of the clinical picture. There are some case reports of treatment-related KBS in children who were treated with intrathecal methotrexate (7,13). However, it is not possible to make a certain conclusion on whether this clinical picture was induced or triggered by...
valproate or it was just a chance. The continuation of the clinical picture after discontinuation of valproate may suggest possible triggering rather than inducing role of the medication.

To date, there is no specific treatment of either syndrome. However, several case studies reported the efficacy of CBZ (14), serotonin reuptake inhibitors (15,16) and RIS (7) in the treatment of behavioral symptoms in KBS. Behavioral symptoms responded to the combination of RIS and MPH quite well rather than either medication alone in this case. He required relatively higher doses, particularly for MPH, and tolerated medications well. Our rationale for adding MPH was based on previous reports suggesting efficacy of MPH in attention-deficit hyperactivity disorder (ADHD) secondary to traumatic brain injury (17).

In terms of differential diagnosis, one may consider the possibility of a bipolar mood disorder. However, we did not consider bipolar disorder for several reasons. Despite the presence of several nonspecific symptoms, our patient did not have core manic symptoms like elevated /expanded mood and grandiosity. In addition, past neurological history, neuroimaging findings and clinical characteristics favoured the diagnosis of KBS rather than bipolar disorder and, there was no family history of bipolar disorder.

In conclusion, we believe that this case may contribute to the understanding of pathophysiological mechanisms and management of behavioral symptoms of KBS and orbitofrontal syndrome in children. However, more systematic research studies are warranted on these topics.

References