JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Clinical Case Reports

Case Report

Complex Dysexecutive Syndrome and Agonistic Dyspraxia in a Patient with Bullous Pemphigoid

Marko G. Klissurski[1*], Mery L. Gantcheva[2], Nikolay L.Topalov[3], Ivo Sp. Petrov[2]

City Clinic Cardiology Center University Multiprofile Hospital, Ltd., Sofia,

[1]Unit of Neurology and

[2]Clinic of Cardiology

[3]St. Naum" Multiprofile Hospital for Active Treatment in Neurology and Psychiatry; Medical University of Sofia; Bulgaria

**Corresponding author: Dr. Marko G. Klissurski, 127 Okolovrasten pat Street, 1407 Sofia, Bulgaria, Tel: +359 2 90 38 109/552; Fax: + 359 2 90 38 036; Email: mklissurski@yahoo.com*

Received: 02-05-2016

Accepted: 03-25-2016

Published: 04-04-2016

Abstract

We are presenting a difficult diagnostic clinical case of a patient who developed a complex dysexecutive and disconnection syndrome with a rare form of hand apraxia, and bullous pemphigoid (BP). The differential diagnosis included a subacute toxic leukoencephalopathy and autoimmune encephalitis. The patient had a moderate exposure to propane-butane/CO, caused by a gas leak from a faulty household appliance. Reversible diffuse leukoencephalopathy with delayed evolution and toxic-hypoxemic etiology was our final diagnosis. It was made after a detailed study of our patient's medical history, and the extensive examinations conducted simultaneously. The possibility of autoimmune antibody-mediated non-vasculitic encephalitis, during severe BP, was excluded with serum, CSF, and antinuclear antibodies examination. The treatment assigned was non-specific, leading the patient to a very good recovery after a six-month period. Some of the key elements that helped us to identify the correct diagnosis and consequently the appropriate therapy were: 1) Time-led graphic model of all the changes occurring throughout the development of his condition, providing us with a specific visual time-frame; 2) Analysis of the nonspecific brain MRI white matter changes; 3) The unique pattern of hand dyspraxia. This is a case of a rare primary neurological pathology and secondary skin involvement with BP. It also illustrates a favorable recovery after a broad white matter injury with a corpus callosum disconnection which caused a neuropsychiatric disorder and agonistic dyspraxia (AD).

Keywords: Agonistic Dyspraxia; Bullous Pemphigoid; Toxic-Hypoxemic Leukoencephalopathy

Abbreviations:

BP: Bullous Pemphigoid;

WMLEP: White Matter Leukoencephalopathy;

AD: Agonistic Dyspraxia;

MMSE: Mini Mental State Examination;

NIHSS: National Institute of Health Stroke Scale;

GLCS: Glasgow-Liege Coma Scale;

CSF: Cerebrospinal Fluid;

BBB: Blood-Brain Barrier

Introduction

The development of delayed and reversible white matter leukoencephalopathy (WMLEP) with a wide spectrum of personal, cognitive, and motor disturbances is a common observation following toxic-hypoxemic incidents [1-4]. It could be caused by a variety of toxins, therapeutic or illicit drugs [5]. The occurrence of BP followed by an immune-mediated encephalitis due to a CO exposure, however, were very unusual observations [6, 7].

BP is one of the most common autoimmune subepidermal blistering diseases [6, 8, 9]. It can be associated with different neurological conditions, stroke, multiple sclerosis, dementia, parkinsonism, and epilepsy [8-11]. It was rarely reported in association with antineuronal antibody-mediated encephalitis [7,10,11].

Agonistic dyspraxia (AD) as a specific type of "alien hand" syndrome is also rare but well-described disorder observed in patients having corpus callosum disconnection, parietal and frontal lesions with variable etiology [12,13]. Evolution and therapy of different cases of AD and complex cognitive deficit after toxic-hypoxemic encephalopathy have not been well studied.

Case Presentation

A 60-year old Caucasian right-handed male presented with weakness in the right limbs, disorientation, and severe psychiatric and neurocognitive syndrome for three months. The patient's past medical history states type 2 diabetes mellitus and unremarkable family history.

The disorder started on January 4th, 2013 when he was found collapsed at home in a helpless condition, disoriented, and confused. He had lapses of consciousness, and complained of vomiting, and muscle weakness. The patient was found and taken to the hospital by a friend who came to see him in the afternoon of the next day. The patient acted slightly disoriented and complained of weakness in the right-side extremities. Due to his state of confusion, he did not mention the smell of gas to his physician. Five days later, edema and weakness in the right arm occurred. He was treated with non-steroid anti-inflammatory drugs and vitamins on an outpatient basis. He was subsequently hospitalized due to suspicion for subclavian artery thrombosis. Anticoagulation therapy with acenocumarol was initiated. Transitory elevated transaminases values of ASAT and ALAT were observed up to 280 U (<40 U). After discharge, the patient started to behave inadequately, complaining of pain in the right arm. Two weeks later (on January 23rd, 2013) he presented with "features of sensory-motor aphasia". He was admitted to a neurology clinic with a suspicion of stroke. Brain CT and MRI was unremarkable. After discharging him, the patient gradually became very inert. He stopped talking and walking. Parallel to the cognitive worsening, a vesicular bullous exanthema appeared on the left thoracic area, progressively involving the whole body. On 20.02.2013, he was admitted to a dermatological clinic. The patient presented with dyschromatic maculae on the lower abdomen, legs and arms without scars. The majority of initial lesions were large tense bullae with clear fluid. The mucous membranes were not affected. The diagnosis of BP was confirmed by histopathology and immunofluorescence. The biopsy specimen showed subepidermal blister with polymorphous infiltrate. Direct immunofluorescence demonstrated a linear band of IgG deposit along the dermoepidermal junction. Indirect immunofluorescence detected IgG circulating autoantibodies on the skin basement membrane. On repeat MRI scan of the brain and neck, no specific pathology was found. An opinion about cerebral vasculitis was expressed. A high-dose corticosteroid therapy with 6-methylprednisolone was started successfully for three days, with two weeks tapering, and maintenance of 20 mg daily after that.

Three months after the initial incident (in March 2013), we observed the following physical, neurological, and psychiatric constellation. General examination revealed an asthenic habitus and normal vital signs. There were no active skin BP lesions but only hypo and hyperpigmented maculae over the chest, arms and legs. Breath sounds were clear with no wheezes or riles. Heart auscultation revealed no murmurs, rubs, or gallops. His abdomen was soft, non-tender with no hepatosplenomegaly. The extremities had no clubbing, cyanosis, or edema. Neurological examination showed a mild central lesion of the right facial nerve and positive oral automatisms. A right-sided central arm paresis had also signs of peripheral involvement with a hypotrophy of the interossei muscles. Deep tendon reflexes were bilaterally exaggerated, more at the right side, and a positive Babinski response was found in the right leg. Grasping reflex was observed with the left hand. Gait was difficult and shaking with eyes opened. Apraxia of the right hand was moderate to severe, with motor perseverance. When the patient was asked to grasp or touch something, he withdrew his dominant hand backward. Unusual motor behavior was consistent with AD [12,13] because the patient performed agonistic movements with a contralateral left hand upon instruction to the right hand. In rare instances when he activated his right hand, he did so very clumsy and slowly. An impressive global cognitive dysfunction was evident with apathy, abulia, emotional retardation, hypophoria, and executive dysfunctions. The patient was apsychotic, roughly orientated to place, but disoriented to time. His speech was poor, extremely non-fluent, with no dysarthria or aphasia. Thinking process was viscous with a long latency of response. The patient answered

questions with only one word, seldom with simple sentences. A partial agnosia mainly for geometric figures was noted. He could recognize colors and letters, slowly nominating objects. The sensory system was not examined precisely due to the cognitive dysfunction. Mini-Mental State Examination (MMSE) score was difficult to evaluate but roughly about 11/30. The patient had an indwelling urinary catheter and dependent for care. His National Institute of Health Stroke Scale (NIHSS) score was 12, and Glasgow-Liege Coma Scale (GLCS) 16 points. An electrocardiogram demonstrated normal sinus rhythm, and a chest X-ray was unremarkable. Carotid duplex findings were consistent with nonstenostic plaques of the bilateral common and internal carotid arteries. The transcranial color coded duplex study detected reduced velocities in both MCA. An electroencephalogram was nonspecific with no paroxysmal activity. A new MRI of the brain demonstrated mild diffuse confluent subcortical T2 lesions within white matter and corpus callosum (Figure 1a, b).

The laboratory investigations showed unremarkable complete normal blood count (except WBC 11.2), ESR, CRP, electrolytes, coagulation profile, and urinalysis panels. The biochemistry panel was also within normal limits except for glucose (8.1 - 11 mmol/l). Cerebrospinal fluid (CSF) was clear with no elevated pressure. The cell examination revealed mild inflammatory reaction with leukocytes 15.10^6/l (Ly 70%, Sg 30%). No intrathecal synthesis was found but mild hyperproteinorachia (total protein 0.53 g/l, and normal glucose, chlorides and lactate values). The serum and liquor electrophoresis revealed normal protein fraction distribution. The antibodies towards CMV, EBV, VZV, VHS was negative. Syphilis TPHA, HIV 1/2, complement C3, C4, and Borrelia burgdorferi ELYSA IgG, IgM were negative. IL-6 was normal. Specific anti-neuronal voltage-gated potassium-channel and N-Methyl-D-Aspartate receptor antibodies were not found, as well as Yo, Ri, Hu, and Ma2 antinuclear antibodies. Total prostate specific antigen was not elevated. The serum and CSF work-up for vasculitis and autoimmmune process was negative.

Figure 1a, b. Brain axial MRI at 2 month showed initial diffuse confluent subcortical T2 hyperintense lesions within white matter and corpus callosum.

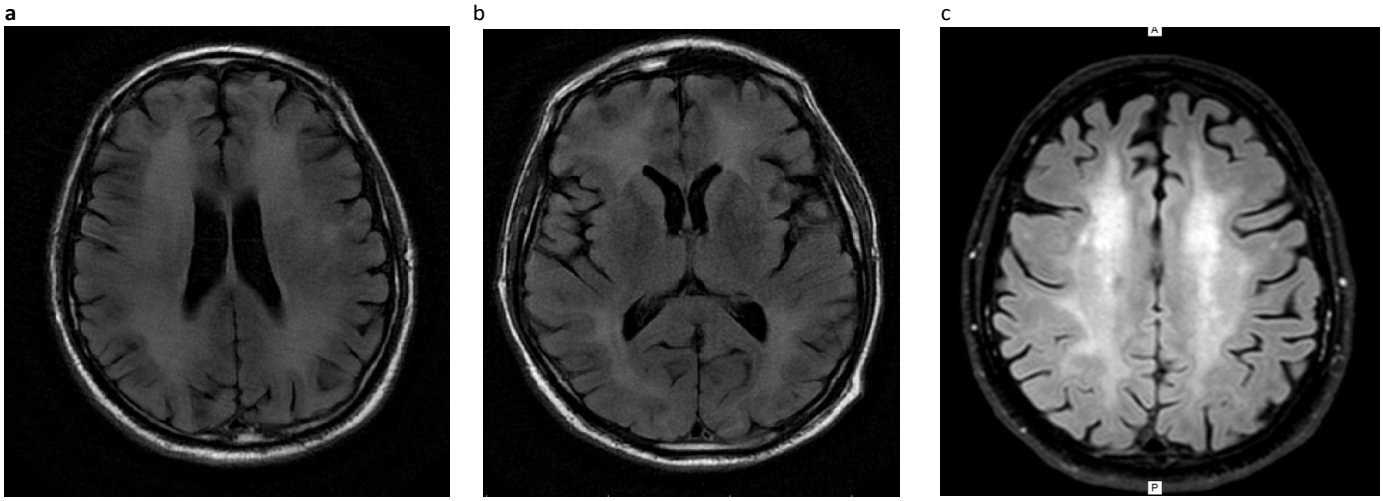
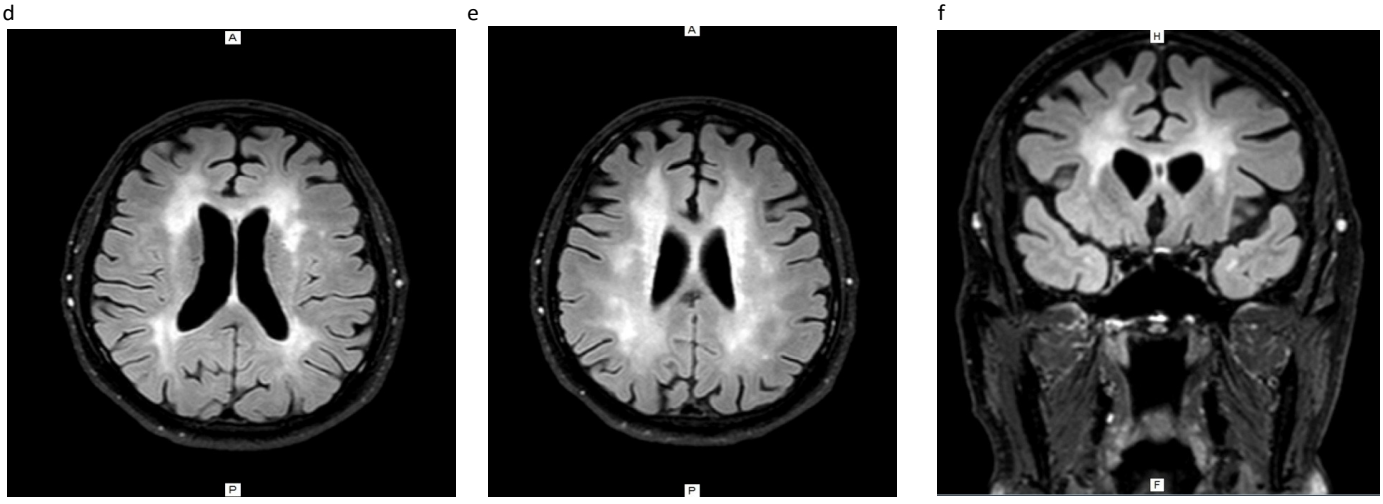


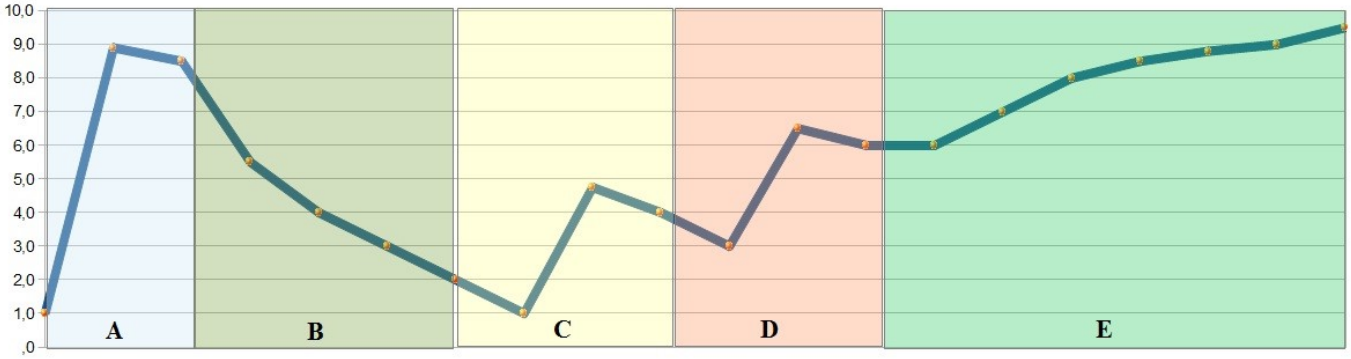
Figure 1c, d, e. Follow-up MRI at 9th month demonstrated multiple relatively symmetric diffuse bilateral subcortical periventricular, however more intense than in previous MRI T2 and FLAIR lesions, within white matter in the frontal, parietal and temporal regions.
Figure 1f. Coronary plane with partial involvement of the truncus of corpus callosum.



A comprehensive history was impossible to be taken from the patient himself. With the help of the patient's daughters and available documentation, we created a detailed history time-chart (Figure 2). Based on the information that was obtained and compiled, a diagnosis of delayed toxic-hypoxemic WMLEP was made. The treatment with acenocoumarol was stopped. Galantamine hydrochloride (Nivalin 10-30 mg PO), L-dopa (Madopar 150 mg PO), venlafaxine 37,5 mg PO, pyracetam (Nootropil 3,0 IV), citicoline (Somazina 1000 mg IV), 6-methylprednisolone (Urbazon 20 mg PO), nicergoline (Sermion 30 mg PO), pentoxifylline (Agapurin 400 mg PO), plus active rehabilitation were recommended.

home, a classical biphasic course of quick initial recovery with gradual neurobehavioral, motor worsening thereafter (Figure 2, Period A and B), MRI neuroradiologic diffuse non-specific white matter abnormalities, and a favorable clinical recovery despite imaging findings [2,5,14,15]. Previous studies indicated that MRI changes would not be visible at the beginning of disorder [16], as such were detected in our patient at the third and ninth month. Despite that it was not medically noted, the history chart we created convinced us that the condition started after an exposure to CO or CO_2, due to an overnight gas leak from a faulty gas heater. First CT and MRI were normal, and

Figure 2. Graphic chart of the patient's history and relative clinical and neurocognitive status:
(Abscissa axis represents relative disease evolution periods: A - an initial impact and improvement at home in January 2013, B- first hospitalization concerning stroke and clinical worsening, C- treatment for BP at the Clinic of Dermatology; D- diagnostic evaluation and treatment at City Clinic; E – follow –up period, September - October 2013)
(Along Ordinate axis, 0 – represents relative maximal clinical deficit, and 10 maximal clinical improvements).



On a follow-up examination during the third and the sixth month, the patient demonstrated significant clinical improvement. MMSE was 27/30, NIHSS 2, and GLCS 20 points. He was able to care for himself at home, had non-restricted gait, adequate behavior, and speech. The dominant right hand executed all common clinical praxis tests. He was even interested in when he could start driving a car again. Follow-up MRI at 9th month (Figure 2, Period E) revealed multiple relatively symmetric bilateral subcortical mainly periventricular T2, and FLAIR lesions, within white matter in the frontal, parietal, temporal regions, and in the truncus of corpus callosum (Figure 1c, d, e, f). The lesions were with higher signal intensity than in previous MRI findings. Mild to moderate diffuse brain atrophy was also present.

Discussion

Before presentation to our clinic, the etiology of the progressive psycho-organic and focal neurologic syndrome of our patient was not established. We concluded that his diagnosis was delayed toxic-hypoxic leukoencephalopathy, because of the following reasons: a suspicious episode of gas exposure at due to the presence of hand edema, hemiparesis and aphasia-like syndrome, dominant in the initial clinical picture, the patient was treated for a vascular disorder. During the time of his first hospitalization, nine days after the incident, there was brief ASAT and ALAT elevation, also raising our index of suspicion about possible intoxication.

Several studies demonstrated moderate to high prevalence of neurological disorders (including autoimmune encephalitis) in patients with BP, however, the pathophysiologic mechanisms of association between neurological diseases and BP are not completely known [8-11]. The probable link between BP and encephalitis could be explained by the presence of an immunologic cross-reactivity. According to Chen et al BP antigens, such as BPA1 and BPA2, act as autoreactive antigens in the brain and skin [17]. That is why after reviewing the literature about BP and neurological complications, as alternative differential options we considered: autoimmune encephalitis associated with BP, and BP after neurological disorder [6-8,10]. Neurological symptoms in patients with toxic WMLEP as well as with BP may be subtle, with insidious disease onset, leading to diagnostic delay [11]. Along with

preceding neurocognitive deficit, a month after a low dose of toxic exposure, a severe diffuse dermatologic BP attack occurred in our patient. Theoretically, pathogenic antibodies could migrate through compromised blood-brain barrier (BBB) and cause encephalitis with the appropriate neurologic syndrome. We did not detect anti-neuronal antibodies and BBB dysfunction and no evidence to support such a hypothesis. Limitation of our work-up was that we were not able to study circulating reactive antibodies against brain antigens in the sera of our patient, as a link to the development of his cutaneous disease [8, 17]. Nor it was performed a transfer of his serum IgG on to a rat brain, as did Soni et al in their case [7]. Our examinations did not show evidence of CNS infection, vasculitis, malignancy or paraneoplastic syndrome which could be associated also with BP [10,11,18]. From the data obtained, we could only speculate that a BP was provoked by toxic exposure or/and by medications used in the initial phase of his illness.

The first-mentioned cognitive improvement of the patient occurred after high-dose corticosteroid therapy, at a dermatological clinic, as reported by the patient's daughters (see Figure 2, Period C). It could be an *ex juvantibus* explanation for an autoimmune process involving brain antigens. However, other authors reported that the systemic corticosteroids and antioxidants also improve neurocognitive dysfunction in patients with delayed postanoxic WMLEP [1-3,5]. The treatment of our patient was non-specific stimulation of some important brain neuro-mediators involved with white matter disconnection, such as acetylcholine, dopamine, serotonin, and norepinephrine. Small maintenance corticosteroid dose was suggested for three months as a prophylaxis to BP relapse.

As a conclusion, this case illustrates a favorable recovery after a broad white matter injury with a corpus callosum disconnection which caused a neuropsychiatric disorder and AD. The use of visual aids, such as the proposed infographics in particular, could be clinically beneficial for a correct understanding of how the different events correlate to each other over time. The differentiation of several types of brain disconnection with AD, and the neuropsychiatric syndrome is extremely rare, and still pose a great challenge to practical and MRI correlation [14]. The common causes of diffuse and especially reversible WMLEP classification should include the most frequent home and environmental intoxications, such as CO, CO_2, as well as chemotherapy and drug abuse [4, 18]. We confirmed previous studies stating that a toxic etiology should be investigated in every case of the subacute neuropsychiatric syndrome [3,5,14,18] and that MRI information is essential for providing us with a more accurate differential diagnosis [15,16]. The mild to moderate MRI changes found at the second month in our patient were associated with significant neurocognitive decline, however at the 9^{th} month, we observed a significant neurocognitive improvement despite multiple WMLEP abnormalities.

Finally, we have not proved whether our neuropsychiatric disease was a coincidence or a complication with BP, however in the future cases, it is important to look for such evidence. It should be also underlined that primary brain pathology was followed by a secondary skin involvement with BP that is in accordance with previous reports.

Acknowledgements

We would like to thank the daughters of the patient for their support and contribution to the process of diagnosis and treatment, and to Jennifer Walker for precise manuscript editing.

References

1. Blackburn DJ, Alix JJ, Sarrigianis P, Hoggard N, Bandmann O. Delayed toxic-hypoxic encephalopathy. Pract Neurol. 2013, 13(2): 114-119.

2. Molloy S, Soh C, Williams TL. Reversible Delayed Post-hypoxic Leukoencephalopathy. AJNR Am J Neuroradiol. 2006, 27(8): 1763-1765.

3. Tormoehlen LM. Toxic Leukoencephalopathy. Neurol Clin. 2011, 29(3): 591-605.

4. Kwon OY, Chung SP, Ha RY, Yoo IS, Kim SW. Delayed post-tanoxic encephalopathy after carbon monoxide poisoning. Emerg Med J. 2004, 21(2): 250–251.

5. Filley CM, Kleinschmidt-DeMasters BK. Toxic Leukoencephalopathies. N Engl J Med. 2001, 345: 425-432.

6. Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. Br J of Dermatol. 2012, 167(6): 1200-1214.

7. Soni A, Irani SR, Lang B, Taghipour K, Mann R et al. Immunotherapy responsive autoimmune encephalopathy associated with bullous pemphigoid. J Neurol Neurosurg Psychiatry. 2009, 80(12): 1412-1413.

8. Cordel N, Chosidow O, Hellot MF, Delaporte E, Lok C et al. Neurological disorders in patients with bullous pemphigoid. Dermatology. 2007, 215(3): 187-191.

9. Tarazona MJ, Mota AN, Gripp AC, Unterstell N, Bressan AL. Bullous pemphigoid and neurological disease: statistics from a dermatology service. An Bras Dermatol. 2015, 90(2): 280-282.

10. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: a population-based case–control study. J Invest Dermatol. 2011, 131(3): 631–636.

11. Taghipour K, Chi CC, Vincent A, Groves RW, Venning V et

al. The association of bullous pemphigoid with cerebrovascular disease and dementia: a case–control study. Arch Dermatol. 2010, 146(11): 1251–1254.

12. Aboitiz F, Carrasco X, Schrőter C, Zaidel D, Zaidel E et al. The alien hand syndrome: classification of forms reported and discussion of a new condition. Neurol Sci. 2003, 24(4): 252-257.

13. Lavados M, Carrasco X, Pena M, Zaidel E, Zaidel D et al. A new sign of callosal disconnection syndrome: agonistic dyspraxia. A case study. Neurocase. 2002, 8(6): 480-483.

14. Renaud DL. Clinical approach to leukoencephalopaties. Semin Neurol. 2012, 32(1): 29-33.

15. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. Neurology. 2009, 72(8): 750–759.

16. MacKinney AM, Kieffer SA, Paylor RT, SantaCruz KS, Kendi A et al. Acute toxic leukoencephalopathy: Potential for reversibility clinically and on MRI with Diffusion Weighted and FLAIR imaging. AJR Am J Roentgenol. 2009, 193(1): 192-206.

17. Chen J, Li L, Chen J, Zeng Y, Xu H et al. Sera of elderly bullous pemphigoid patients with associated neurological diseases recognize bullous pemphigoid antigens in the human brain. Gerontology. 2011, 57(3): 211-216.

18. Filley CM. The behavioral neurology of cerebral white matter. Neurology. 1998, 50(6): 1535-1540.