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Anti-Dipeptidyl-Peptidase-Like Protein-6 Antibody Encephalitis: A Clinical form of Autoimmune Encephalitis. The First Malian Case Report

Keïta Kaly[1*], Traoré Kankou[2], Togo Maïmouna[2], Sangaré Ama[1], Sinayoko Adama[1], Stéphane Loique Djeugoué[1], Mallé Mamadou[1], Cissoko Mamadou[1], Dembélé Ibrahima Amadou[1], Sy Djibril[1, 6], Traoré Djénèbou[1, 6], Pamanta Sory Ibrahim[3], Maïga Alassane Baneye[4], Yalcouyé Abdoulaye[4], Sangaré Modibo[5, 6], Diallo Seybou Hassane[2, 6], Coulibaly Thomas[4, 6], Landouré Guida[4, 6], Soukho Assétou Kaya[1, 6], Dembélé Mamadou[6], Traoré Hamar Alassane[6]

[1]Department of Internal Medicine, University Hospital Center of the Point G, Bamako, Mali
[2]Department of Neurology, Gabriel TOURE University Hospital Center, Bamako, Mali
[3]Dpartment of Rheumatology, University Hospital Center of the Point G, Bamako, Mali
[4]Department of Neurology, University Hospital center of the Point G, Bamako, Mali
[5]Malaria Research and Training Center (MRTC), University of Sciences, Techniques and Technologies of Bamako (USTTB), Bamako, Mali
[6]Faculty of Medicine and Odontostomatology, University of Sciences, Techniques and Technologies of Bamako (USTTB), Bamako, Mali

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***Corresponding author:** Keïta Kaly
Department of Internal Medicine, University Hospital Center of the Point G, Bamako, Mali

Abstract **Case Report**

***Introduction*:** Among the different types of autoimmune encephalitis, anti-Dipeptidyl peptidase-like protein 6 (anti-DPPX) antibody encephalitis is characterized by its clinical polymorphism associating neuropsychiatric manifestations including cerebellar ataxia, agitation, confusion, abnormal movements (myoclonus, tremor), convulsion, dysautonomic syndrome and sleep disorder; urinary symptoms; dermatological symptoms and digestive symptoms; and the presence of a specific antibody called anti-Dipeptidyl peptidase-like protein 6 (anti-DPPX) antibody. We report, to our knowledge, the first Malian case report of probable anti-Dipeptidyl peptidase-like protein 6 (anti-DPPX) antibody encephalitis diagnosed in a young woman in Internal Medicine. ***Case Presentation*:** A 38-year-old Malian female, multiparous with no history of abortion, was hospitalized in internal medicine department at the University Hospital Center of the Point G in august 2024 with 2-years history of chronic intermittent diarrhea and abdominal pain of which the current episode accompanied with early postprandial vomiting started 2 weeks ago. Her medical and surgical histories included the gestational arterial hypertension and the caesarean section complicated by a postoperative wound infection and a lower limb thrombophlebitis in 2017. In 2021, the patient complained of chronic headache, dizziness, urgenturia and hypersudation evolving in the context of significant progressive weight loss, asthenia, anorexia and intermittent prolonged fever. In 2022, the neurological symptoms worsened with adjunction of plantar burning, tingling, prickling, sometime itching, walking and balance disorder leading intermittently the astasia-abasia, tremor of the extremities, and hypersomnia. Six months prior to admission, she presented with an achromic patch on the areola of the right breast, multiple scarring bullous lesions in the form of hypochromic patches, priritus, and hair loss. Then, three weeks before admission, she complained of a chronic productive cough no accompanied of chest pain or dyspnea. In addition, anamnesis revealed the progressive onset of amenorrhea and her family reported that she presented sometime difficulty to decide, to understand and execute certain tasks. The physical examination revealed an astasia-abasia, a tremor of the extremities; a generalized amyotrophy and the inability to stand and to walk; an achromic macules on the areola of the right breast, multiple scarring bullous lesions in the form of hypochromic macules, scratching lesions, and alopecia. On admission, the erythrocyte sedimentation rate was 55 mm at the first hour and the blood C-reactive protein level was 28.85 mg per liter. Blood test for antinuclear antibody was two times positive with speckled pattern and anti-SSA antibody was positive. Anti-DPPX6 antibody was not tested. Magnetic resonance imaging of the brain displayed cerebellar hypoplasia with moderate tetraventricular dilatation. Anti-dipeptidyl-peptidase-like protein-6 antibody encephalitis was raised. Cerebellar ataxia associated with tremor of the extremities, hypersomnia, paresthesia, dysautonomic syndrome (labile blood pressure, urgenturia, tachycardia and hypersudation), digestive manifestations, dermatological manifestations, the significant weight loss, the positivity of certain autoantibodies and the cerebellar hypoplasia associated with tetra-ventricular dilation detected on brain tomodensitometry and magnetic resonance

imaging enabled to rule in the diagnosis of probable anti-dipeptidyl-peptidase-like protein-6 antibody encephalitis. The postoperative wound infection was suspected to be a triggered factor. The retained comorbidities were the denutrition, gastritis of undetermined origin and malaria. The treatment with prednisone at a dose of 1 mg per kilogram of body weight a day with tapering course until the minimum effective dose associated with adjuvant therapy was initiated. This was preceded by a bolus of methylprednisone at a dose of 1000 mg a day for 5 days. After ophthalmological examination, cortisone-sparing treatment with hydroxychlororquine at a dose of 400 mg a twice day was started. Comorbidities were appropriately treated. ***Conclusion*****:** It appears from our observation that such clinical polymorphism include the cerebellar ataxia associated with tremor of the extremities, hypersomnia, paresthesia, dysautonomic syndrome, digestive manifestation, dermatological manifestation and significant weight loss and the presence of non specific antibodies as antinuclear antibody should raise the question of anti-DPPX antibody encephalitis and impose the anti-DPPX6 antibody testing and morphological examinations.
Keywords: Autoimmune encephalitis, anti-DPPX encephalitis, autoimmune diseases, internal medicine, Mali.

INTRODUCTION

Autoimmune encephalitis is one of the most common causes of noninfectious encephalitis, which can be triggered by tumors and infections or can be cryptogenic [1]. Among the different types of autoimmune encephalitis, anti-DPPX antibody encephalitis is characterized by its clinical polymorphism associating neuropsychiatric manifestations including cerebellar ataxia, agitation, confusion, abnormal movements (myoclonus, tremor), convulsion, dysautonomic syndrome and sleep disorder; urinary symptoms; dermatological symptoms and digestive symptoms; and the presence of a specific antibody called anti-DPPX antibody [2-4]. In addition, non-organ-specific autoantibodies (e.g., antinuclear antibodies) are frequently found in this affection, thus raising a wide range of differential diagnoses such as systemic lupus erythematosus and Whipple's disease [1]. Etiopathogenically, unlike autoimmune cerebellar ataxia, it is characterized by involvement of the hippocampus, cerebellum, striatum and myenteric plexus on which are expressed the autoantigen dipeptidyl peptidase-like protein 6 (DPPX) [5] and explaining its various clinical manifestations in addition to its corollary of chronic inflammation.

We report, to our knowledge, the first Malian case report of probable anti-Dipeptidyl peptidase-like protein 6 (anti-DPPX) antibody encephalitis diagnosed in a young woman in Internal Medicine.

CASE PRESENTATION

A 38-year-old Malian female, multiparous with no history of abortion, was hospitalized in internal medicine department at the University Hospital Center of the Point G in august 2024 with 2-years history of chronic intermittent diarrhea and abdominal pain of which the current episode accompanied with early postprandial vomiting started 2 weeks ago. Her medical and surgical histories included the gestational arterial hypertension and the caesarean section complicated by a postoperative wound infection and a lower limb thrombophlebitis in 2017. In 2021, the patient complained of chronic headache, dizziness, urgenturia and hypersudation evolving in the context of significant progressive weight loss, asthenia, anorexia and intermittent prolonged fever. Initial investigations were not contributive. Non-specific treatment enabled a slight improvement. In 2022, the neurological symptoms worsened with adjunction of plantar burning, tingling, prickling, sometime itching, walking and balance disorder leading intermittently the astasia-abasia, tremor of the extremities, and hypersomnia. The unconventional treatment privileged by the family had not led to any improvement. An outpatient neurological consultation in February 2023 revealed cerebellar hypoplasia with tetraventricular dilatation (cerebral tomodensitometry) (Figure 1). Examination of the cerebrospinal fluid revealed pleocytosis. The patient was lost to follow-up. Six months prior to admission, she presented with an achromic patch on the areola of the right breast, multiple scarring bullous lesions in the form of hypochromic patches, priritus, and hair loss. Then, three weeks before admission, she complained of a chronic productive cough no accompanied of chest pain or dyspnea. In addition, anamnesis revealed the progressive onset of amenorrhea and her family reported that she presented sometime difficulty to decide, to understand and execute certain tasks.

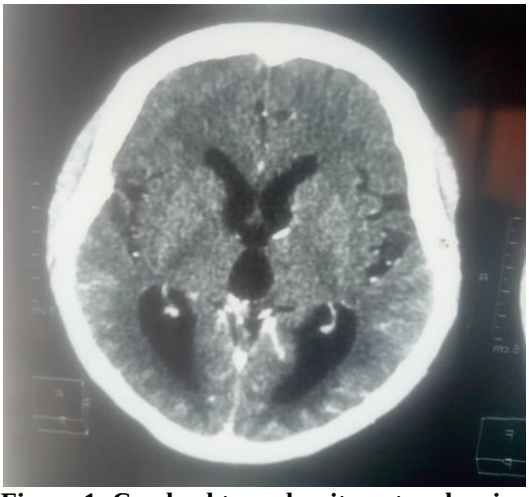

Figure 1: Cerebral tomodensitometry showing tetraventricular dilatation

On physical examination, the Karnofsky performance status score was 40%, the supine blood pressure was 111/83 mmHg, the sitting blood pressure was 99/30 mmHg, the standing blood pressure was not assessed, the heart rate was 140 beats per minute, the respiratory rate 28 cycles per minute, the temperature was 37.6°Celsius and the Body Mass Index (BMI) was 16.73 kilogram per square meter. The neurological examination revealed an astasia-abasia (rendering so difficult to perform movement coordination tests in order to highlight cerebellar ataxia, mainly during the finger-nose-finger test, the heel-knee-shin test and Romberg's sign), and a tremor of the extremities. The muscle strength testing was unremarkable. The sensory system and the cranial pairs examinations were difficult. The digestive examination did not reveal any abnormalities except the carious teeth. The generalized amyotrophy and the inability to stand and walk were the abnormalities observed on the rheumatological examination. The dermatological examination noted an achromic macules on the areola of the right breast, multiple scarring bullous lesions in the form of hypochromic macules, scratching lesions, , and alopecia. The crackling rales were not found on pulmonary auscultation.

On admission, the complete blood count showed a hemoglobin level of 10.8 g per deciliter, a mean corpuscular volume of 90.6 femtoliter, and a mean corpuscular hemoglobin concentration of 33.3 picograms. The inflammatory workup showed that the erythrocyte sedimentation rate (ESR) was 55 mm at the first hour (normal range, 0 to 29 millimeter) and the blood C-reactive protein level was 28.85 mg per liter (normal value, < to 6 mg per liter). Blood test for antinuclear antibody was two time positive with speckled pattern but anti-smith antibody, anti-native DNA antibody, anti-Sm RNP antibody, anti-SSB antibody, anti-Scl70 antibody, anti-Jo1 antibody, anti-CCP antibody and rheumatoid factor were negative. In addition, serologic testing for anti-SSA antibody was positive. Anti-DPPX6 antibody was not tested. The hormonal workup showed a slightly elevated prolactin level of 53.94 ng/ml. TSHus, FT4, cortisol, FSH and LH levels were unremarkable. The infectious disease workup, which included tuberculosis, HIV infection, B hepatitis, C hepatitis, SARS-COV2 infection and infectious colitis, was unremarkable. Thick blood smear was positive. Renal and hepatic functions were normal. Blood ionogram showed a slight decrease in kalaemia. Magnetic resonance imaging of the brain displayed cerebellar hypoplasia with moderate tetraventricular dilatation (figure 2). Electroencephalogram and electroneuromyogram were not performed. Brain biopsy was not performed. Oeso-gastro-duodenal fibroscopy revealed an erythematous pangastritis.

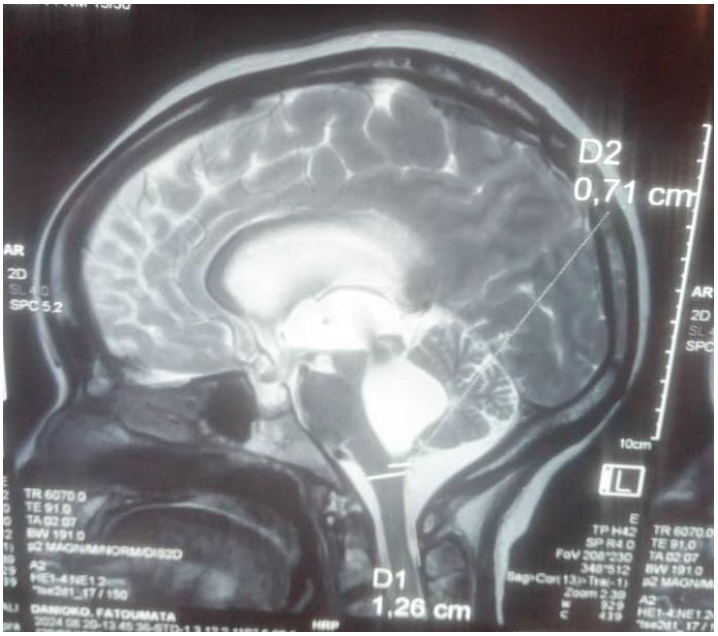

Figure 2: Magnetic resonance imaging of the brain showing the cerebellar hypoplasia with moderate tetraventricular dilatation

Anti- dipeptidyl-peptidase-like protein-6 antibody encephalitis was raised.

Cerebellar ataxia associated with tremor of the extremities, hypersomnia, paresthesia, dysautonomic syndrome (labile blood pressure, urgenturia, tachycardia and hypersudation), dermatological manifestations, digestive manifestations, the significant weight loss, the positivity of certain autoantibodies and the cerebellar hypoplasia associated with tetra-ventricular dilation detected on brain tomodensitometry and magnetic resonance imaging (Figure 1 et 2) enabled to rule in the diagnosis of probable anti-dipeptidyl-peptidase-like protein-6 antibody encephalitis. The postoperative

wound infection was suspected to be a triggered factor. The retained comorbidities were the denutrition, gastritis of undetermined origin and malaria.

The treatment with prednisone at a dose of 1 mg per kilogram of body weight a day with tapering course until the minimum effective dose associated with adjuvant therapy was initiated. This was preceded by a bolus of methylprednisone at a dose of 1000 mg a day for 5 days. After ophthalmological examination, cortisone-sparing treatment with hydroxychlororquine at a dose of 400 mg a twice day was started. Comorbidities were appropriately treated.

On the five day of her hospitalization, general symptoms, dysautonomic syndrome, digestive signs and paresthesias were improved; tremors was slightly ameliorated ; and there was the persistence of gait disorder. On the ten day of her hospitalization, the patient was discharged against medical advice. The long and perilous itinerary and the financial difficulty were the reasons given.

DISCUSSION

The autoimmune encephalitis are a group of immune-mediated brain diseases that frequently associate with pathogenic antibodies against neuronal or glial proteins. There are now more than 20 autoimmune encephalitis described that individually or collectively fulfill criteria of rare diseases (defined in the US as fewer than 200 000 affected people), in other words a immunological rare diseases [6]. In United State of America (Minnesota), the prevalence of autoimmune encephalitis on January 1, 2014 of 13.7/100,000 was not significantly different from that of all infectious encephalitis with 11.6/100,000 [7]. The relative prevalence of different autoimmune encephalitis remains an opened research question in the literature [8]. Autoimmune encephalitis especially anti-DPPX antibody encephalitis is rarely reported in African medical literature and no case have been reported in Mali [9]. We report the first Malian case of probable anti-Dipeptidyl peptidase-like protein 6 (anti-DPPX) antibody encephalitis diagnosed in a young woman.

The clinical phenotype of anti-DPPX antibody encephalitis is extremely various including cerebellar ataxia, agitation, confusion, abnormal movements (myoclonus, tremor), convulsion, dysautonomic syndrome and sleep disorder; urinary symptoms; and digestive symptoms [2, 3]. The Table 1 shows the comparison of the characteristics of 2 reported cases in the literature.

Authors	**Bjerknes *et al*., [4]**	**Our case presentation**
Country	Norway	Mali
year	2022	2024
Weight loss	weight loss of 18 kg.	significant progressive weight loss
Cerebral ataxia	unsteady gait with some truncal ataxia	walking and balance disorder leading intermittently the astasia-abasia
Cognitive disorders	she also had memory deficits with problems recalling details of her medical history. She repeated the same sentences, had difficulties changing topics during conversation, and had difficulties concentrating	difficulty to decide, to understand and execute certain tasks.
Speech disorders	Not found	Not found
Sleep disorders	insomnia.	hypersonnia
Seizure	Not found	Not found
Movement disorders	Not found	tremor of extremities
Dysautonomic syndrome	Not found	tachycardia, urgenturia, instability blood pressure, hypersudation
Paresthesia	painful, burning sensations and paresthesia, primarily in the extremities	plantar burning, tingling, prickling, sometime itching
Psychiatric manifestations	reduced facial expressions, a low mood, and significant apathy	Not found
Digestive manifestations	nauseous, little appetite, and diarrhea	chronic prodromal diarrhea, abdominal pain, vomiting
Dermatological manifestations	red erythema on her chest and had slight general pruritus.	achromic macules on the areola scarring bullous lesions in the form of hypochromic macules, scratching lesions, and alopecia

Authors	**Bjerknes *et al*., [4]**	**Our case presentation**
Biological inflammatory syndrome	routine screening of blood was normal	Found
Cerebrospinal fluid analysis	normal cell count and moderately increased level of protein	pleocytosis
Anti-DPPX antibody	high titres of anti-DPPX antibodies were found in serum (10^6) and cerebrospinal fluid (10^3)	Not perform
Other non-specific antibodies	anti-nuclear antibody were negative	anti-nuclear antibody and anti-SSa antibody were positve
Brain Tomodensitometry	normal	cerebellar hypoplasia, ventricular dilatation
Brain Magnetic Resonance Imaging	normal	cerebellar hypoplasia, ventricular dilatation
Electroencephalogram	frequent focal low-frequency activity on the left frontotemporal area, both arrhythmic and single waves.	Not performed
Electroneuromyogram	active denervation and nerve conduction study showed slight axonal and demyelinating motor and sensory changes in the lower extremity	Not performed
Treatment	high- dose intravenous corticosteroids (methylprednisolone 1 g) for 5 days with subsequent slow dose tapering of prednisolone over several months. Initial treatment with methylprednisolone improved the patient's condition. She was subsequently treated with an infusion of rituximab (1,000mg) beginning 1 month after discharge and with two additional rituximab treatments (500mg each) at 6-month intervals.	IV methylprednisolone, oral steroids: moderate improvement but lost for follow up.

Our clinical findings are similar to those found in Bjerknes et al. case report [4]. In addition, it is comparable to the Reported symptoms in 65 patients with DPPX antibody-associated encephalitis [2, 3, 5, 10]. In patients clinically suspected to have autoimmune encephalitis, but with no detectable autoantibody in serum or CSF, recollection and repeat testing of both serum and CSF is recommended [11]. In our case, the anti-DPPX antibody was not tested because of the low socio-economic status of the patient and the impossibility to perform these texts in Mali.

The main differential diagnosis was the autoimmune cerebellar ataxia to which the digestive manifestation as prodromal diarrhea may be a negative symptom. Our patient presented a (chronic intermittent diarrhea, abdominal pain and vomiting) related to the myenteric plexus involvement. In addition there is the involvement of skin with unclear mechanism. The patient presented a dermatological manifestation (achromic macules on the areola of the right breast, multiple scarring bullous lesions in the form of hypochromic macules, scratching lesions, and alopecia), as was reported in these studies [4, 12]. Taken togother, the patient's clinical profile is typical for anti-DPPX antibody encephalitis but not for anti-N-methyl-D-aspartate receptor (anti-NMPR) antibody encephalitis, anti-A-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPAR) antibody encephalitis, anti-gamma-aminobutyric acid receptor (anti-GABA-AR) antibody encephalitis, anti-gamma-aminobutyric acid receptor (anti-GABA-BR) antibody encephalitis, anti-voltage-gated potassium channel-complex (anti-VGKC) antibody encephalitis, anti-Glutamic acid decarboxylase (anti-GAD) antibody encephalitis, anti-Glycine receptor (anti-GLyR) antibody encephalitis, anti- Metabotropic glutamate receptor 1 (anti-mGluR1) antibody encephalitis, anti- Metabotropic glutamate receptor 5 (anti-mGluR5) antibody encephalitis and limbic encephalitis [2, 3, 4]. The classification criteria evaluated were insufficient to retain systemic lupus erythematosus (EULAR/ACR 2019) [13], scleroderma (EULAR/ACR 2013) [14], dermatopolymyositis (Bohan and Peter 1975) [15], rheumatoid arthritis (EULAR/ACR 2010) [16], mixed connective tissue diseases Kasukawa's criteria 1988 [17]. Neurological manifestations are extremely rare in autoimmune dermatological diseases, as compared to autoimmune encephalitis [18].

CONCLUSION

It appears from our observation that such clinical polymorphism include the cerebellar ataxia associated with tremor of the extremities, hypersomnia, paresthesia, dysautonomic syndrome, digestive manifestation, dermatological manifestation and significant weight loss and the presence of non specific antibodies as antinuclear antibody should raise the question of anti-Dipeptidyl peptidase-like protein 6 (anti-DPPX) antibody encephalitis and impose the anti-DPPX6 antibodies testing and morphological examinations. Multidisciplinary management including

the neurologist and the internist is necessary to improve the quality of life of these patients.

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