Adult Onset Alexander Disease Presenting as Psychogenic Polydipsia Induced Recurrent Hyponatremia as the Initial Symptom: A Case Report.

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Case report

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Abstract

Background

Alexander disease (AxD, OMIM 203450) is a rare and generally fatal disorder of the central nervous system associated with heterozygous mutations in glial fibrillary acidic protein (*GFAP)* gene. Neuroradiological and clinical features of adult onset AxD is characterized by involvement of hindbrain structures. Psychiatric manifestations and extensive white matter lesions are very sparse in adult onset AxD.

Case presentation

We diagnosed a female with AxD presenting with recurrent hyponatremia caused by psychogenic polydipsia as initial symptom at the onset age of 52-year-old. Neurological examination revealed slightly cognitive decline and brisk deep tendon reflex (DTR) in bilateral lower limbs. The symptoms commonly seen in adult onset AxD such as pseudobulbar signs, ataxia and spasticity were not found in the clinical course of disease. Her mother and elder brother had a history of schizophrenia. The patient has had a history of compulsive water drinking as well as personality change in recent years. Her brain magnetic resonance imaging (MRI) showed extensive involvement of white matter without atrophy of medulla oblongata and cervical spinal cord. The next generation DNA sequencing (NGS) showed a likely pathogenic nonsense mutation C1237C>T(pR413*) in GFAP-ε isoform.

Conclusions

Our report enriches the understanding of familial adult onset AxD. Our case also contributes to evidence of pathogenicity of the variants in GFAP-ε as the cause of adult onset AxD.

Background

Alexander disease (AxD) is a rare, sporadic or autosomal dominant clinically heterogeneous disorder of the central nervous system associated with mutations in the coding region of glial fibrillary acid protein (*GFAP*). According to the age of onset, three subtypes have been distinguished: infantile, juvenile and adult [1]. The clinical and neuroradiological presentation of adult onset AxD is very different from that of early onset AxD. Adult onset AxD is clinically characterized by spasticity, ataxia bulbar, pseudobulbar and pyramidal signs. Atrophy or signal changes of medulla and upper cervical cord on MRI were found in most cases of adult onset AxD, while cerebral white matter abnormalities were rare and limited to the periventricular rim. Psychiatric manifestations and extensive white matter lesions are very sparse in adult onset AxD. We investigated a patient with leukodystrophy who was finally diagnosed as adult onset AxD presented with psychogenic polydipsia induced recurrent hyponatremia as initial symptom.

Case Presentation

The 52-year-old female was the second of two children of non-consanguineous Chinese parents. Her medical history was unremarkable except for an approximately 5L daily water intake and a personality change in the past 2-3 years. The onset of psychosis is so insidious that the patient fails to notice the symptoms and visit the doctor. Psychiatric consultation when she was first referred to us suggested a diagnosis of schizophrenia. Family history revealed a history of schizophrenia in both her mother and brother. The patient was nearly functioning well until she had an episode of fever following intermittent headache, nausea, vomiting and delirium. Although her fever was cured after antibiotic therapy, symptoms of dizziness, nausea and vomiting were not improved, and a sudden disturbance of consciousness occurred after ten days. Cranial computed tomography (CT) showed diffuse low signal in symmetrical bilateral subcortical white matter. Blood tests were unremarkable except for low serum sodium concentration (121 mmol/L). Her symptoms and consciousness were improved after combined treatment with methylprednisolone, intravenous immunoglobulin (IVIG), antibiotics, mannitol and sodium supplementation. The same symptoms as well as hyponatremia (119 mmol/L) reoccurred two weeks later and were improved rapidly again after sodium supplementation. She complained of anxiety and a burning sensation in the gastrointestinal tract without water. Neurological examination revealed mild cognitive decline and brisk deep tendon reflex (DTR) in the bilateral lower limbs. Blood tests including complete blood count, routine chemistry test, thyroid functions, aldosterone, cortisol, TORCH and antinuclear antibody spectrum were unremarkable. The fluid deprivation test excluded the diagnosis of diabetes insipidus. Her brain magnetic resonance imaging (MRI) showed extensive bilaterally symmetrical white matter hyperintensities involving the periventricular, thalamus and centrum semiovale as well as the brainstem region, without gadolinium enhancement. Diffusion weighted imaging (DWI) revealed slight hyperintensity in brainstem areas (Fig1a-h). Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV), electroencephalogram and polysomnography showed unremarkable results. A total of three serial lumbar puncture tests were normal except for slightly increased cerebrospinal fluid pressures ranging from 200 to 280 mmH2O. Autoantibodies of paraneoplastic neurological syndrome and autoimmune encephalitis were negative. An NGS-based gene panel including 189 gene which are involved in leukodystrophy and leukoencephalopathy was used for testing. A heterozygous nonsense mutation c.1237C>T(pR413*) was detected in the alternative exon 7A of GFAP-ε (Fig1i). The other family members (her brother and daughter) declined genetic testing and MRI examination.

The patient was followed up with phone interview six months and one year later after discharge. No new disturbance of consciousness occurred in this patient after approximately three months of water restriction and antipsychotic treatment. She discontinued agent therapy for her basically relieved condition. There has been no gait and balance disorder, dysphonia so far in this patient. A mildly disorganized speech and impaired communication can still be observed in this patient.

Discussion And Conclusions

AxD were divided into three forms traditionally based on the age of onset: infantile, juvenile and adult. Early onset AxD was prominently frontal-lobe involved and characterized by bilateral white-matter lesions. The clinical and neuroradiological

presentation of adult onset AxD is very different from that of early onset AxD. The

abnormalities of adult onset AxD are mainly concentrated in the brainstem-spinal cord junction and typically experience pseudobulbar symptoms such as dysarthria and

dysphonia, ataxia and palatal myoclonus. While the neurological characteristics of

adult onset AxD are well documented as above mentioned, there is sparse information

about neuropsychiatric symptoms. The MRI features of our patient is more consistent

with leukodystrophy. The clinical presentation and neurological findings of leukodystrophy are often nonspecific. Psychiatric manifestations especially psychoses

have been commonly described in leukodystrophies; however, association of

psychoses with AxD has been rarely reported. Occasionally a case of adult onset AxD

that was concurrent with cerebral contusion presenting with demented symptoms was

reported [2]. Occasional case reports of mild cognitive, visual, and auditory abnormalities in adult onset AxD are on record. Psychogenic polydipsia is

characterized by excessive fluid intake and accompanied by compensatory polyuria.

Psychogenic polydipsia is caused by psychiatric disorders, often schizophrenia

spectrum disorder, with an incidence of 11 to 20%. The onset of polydipsia and psychiatric symptoms was very insidious in our patient. Thus, faced with a patient

with progressive mental disorder and leukodystrophy on MRI, a genetic investigation

of *GFAP* gene is recommended.

In adult onset AxD, an extensive white matter involvement on MRI in our patient is as rare as her psychiatric manifestations. MRI plays an important role in diagnosis of adult onset AxD because of a wide range of clinical presentation in this group. Detailed neuroradiologic findings included medulla oblongata and cervical spinal cord atrophy, hilum of dentate nucleus hyperintense and periventricular white matter abnormalities. Although the characterizations of MRI in the adult-onset group displayed diversified signs, many do show a unique tadpole-like feature of brain stem and upper cervical cord, which is characterized by marked atrophy of the medulla oblongata and cervical spinal cord, although the

pontine base remains intact [3, 4]. The leukodystrophy in MRI is not prominent in adult variants. Approximately 90% cases showed marked medulla oblongata atrophy and 50% had deep or periventricular white matter lesions [1]. Supratentorial periventricular abnormalities and cerebral involvement are less likely to appear in patients with age over 40 years at onset of the disease [5]. In our case, MRI findings showed severe hyperintensity of extensive periventricular white matter without atrophy in medulla oblongata and cervical spinal cord which is rare in adult onset AxD.

Our report enriches the understanding of familial adult onset AxD. To the best of our knowledge, this is perhaps the first case report of adult onset AxD presenting as psychogenic polydipsia in the world literature. This study expands the mutation spectrum of leukodystrophy presenting with psychiatric manifestations.

Abbreviations

AxD: Alexander disease; DNA: deoxyribonucleic acid; NGS: next generation DNA

sequencing; MRI: magnetic resonance imaging; DWI: diffusion weighted imaging;

FLAIR: fluid attenuated inversion recovery; *GFAP*: glial fibrillary acidic protein;

MRA: magnetic resonance angiography; MRV: magnetic resonance venography;

CSF: cerebral spinal fluid;

Declarations

Ethics approval and consent to participate This case report has been approved by the Committee of Clinical Investigation at Shandong Provincial Hospital affiliated to Shandong University of Science and Technology and conformed to the principles of the Declaration of Helsinki.

Consent for publication Written informed consent was obtained from the patient for genetic analysis and publication of this case report. A copy of the written consent is available for review by the Editors-in-Chief of this journal

Availability of data and materials All data generated or analyzed during this study are included in this published article.

Competing interests. The authors declare that they have no conflict of interest.

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Authors' contributions HL and SG analyzed and interpreted the patient data regarding the disease and genetic analysis. JY analyzed and interpreted the MRI imaging and was a major contributor in writing the manuscript. All authors have read and approved the final manuscript.

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References

[1] Balbi P, Salvini S, Fundaro C, Frazzitta G, Maestri R, Mosah D, et al. The clinical spectrum of late-onset Alexander disease: a systematic literature review. J Neurol 2010;257(12):1955-62.

[2] Namekawa M, Takiyama Y, Honda J, Shimazaki H, Sakoe K, Nakano I. Adult-onset Alexander disease with typical "tadpole" brainstem atrophy and unusual bilateral basal ganglia involvement: a case report and review of the literature. BMC Neurol 2010;10:21.

[3] Farina L, Pareyson D, Minati L, Cecherini I, Chiapparini L, Romano S, et al. Can MR imaging diagnose adult-onset Alexander disease? AJNR Am J Neuroradiol 2008;29(6):1190-6.

[4] Van der Knaap MS, Ramesh V, Schiffmann R, Blaser S, Kyllerman M, Gholkar A, et al. Alexander disease: ventricular garlands and abnormalities of the medulla and spinal cord. Neurology 2006;66(4):494-8.

[5] Pareyson D, Fancellu R, Mariotti C, Romano S, Salmaggi A, Carella F, et al. Adult-onset Alexander disease: a series of eleven unrelated cases with review of the literature. Brain 2008;131(Pt 9):2321-31.

Figures

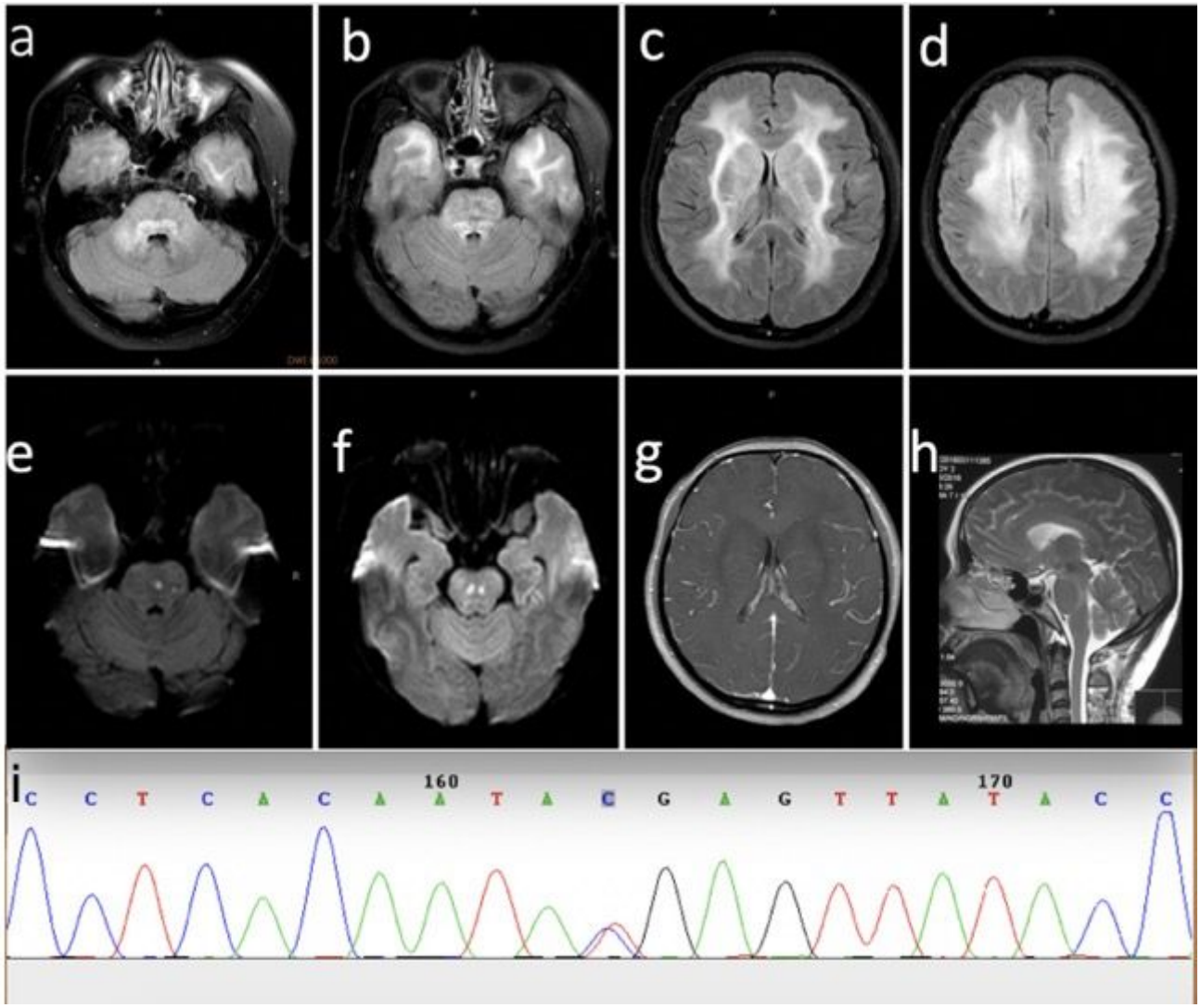

Figure 1

Brain MRI of a patient with adult onset AxD presenting with psychiatric symptoms. T2 FLAIR image showing symmetrical hyperintense signal in the brainstem, temporal pole, basal ganglia and centrum semiovale region (a, b, c and d). DWI image showing diffuse limitation lesion in brainstem (e and f). Contrast MRI brain showing no enhancement (g). T2 image showing no atrophy of the medulla oblongata and the cervical spinal cord (h). Electropherograms of the GFAP exon 7A region containing a heterozygous nonsense mutation point: c.1237C>T, leading to an amino acid change in p.R413* (i).