**Case Report: Voltage Gated P/Q Type Calcium Channel Antibodies
Associated with Cerebellar Degeneration**

Running Title: VGCC Ab in Pediatric PCD

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Abstract

Paraneoplastic cerebellar degeneration (PCD) is a rare neurologic condition characterized by diffuse cerebellar dysfunction and magnetic resonance imaging (MRI) evidence of cerebellar atrophy over time. It has been associated with several auto-antibodies and malignancies in adult patients. To date, only six cases have been described in male children. We report a case of an 8 year old girl with prodrome of abdominal pain and vomiting followed by acute onset of diplopia, dysarthria, dysmetria and ataxia, who was found to have cerebellar degeneration in association with P/Q type calcium channel antibodies. This is the first described pediatric case of PCD in association with P/Q type calcium channel antibodies.

Keywords: paraneoplastic; cerebellar degeneration; voltage gated calcium channel antibodies; child; female

Introduction

Paraneoplastic cerebellar degeneration (PCD) is a rare neurologic syndrome associated with numerous cancers, most commonly small-cell lung cancer, gynecological and breast cancers and Hodgkin's lymphoma. It is thought that paraneoplastic antibodies are produced as the body's immune reaction to an underlying and usually yet undetected malignant process. The resultant syndrome is a byproduct of the antibodies' effect on normal structures.¹ PCD is clinically characterized by a prodromal phase of dizziness, nausea and vomiting which can last weeks or months. This is followed by relatively acute onset of ataxia, diplopia, dysarthria and at times dysphagia.^{1,2}

This syndrome is predominantly seen in adults, though six pediatric cases have been reported in boys with Hodgkin's lymphoma.³⁻⁸ In three of these cases auto-antibodies were isolated, one with anti-PCAb⁶ and two with anti-Tr.⁷⁻⁸ Although up to 41% of adult patients with small cell lung cancer (SCLC) and PCD are found to have voltage gated calcium channel antibodies (VGCC Ab),⁹ there have been no pediatric cases of PCD reported in association with this antibody.

Case History

An 8 year old girl with a two month history of intermittent abdominal pain and occasional diarrhea experienced several episodes of vomiting after eating 5 days prior to admission. Two days prior to presentation, she had increasing difficulty with walking and had fallen several times with no loss of consciousness. The day after admission, she complained of double vision and kept her left eye preferentially closed. Over the course of the next 3 days, vomiting and double vision persisted. She complained that she was dizzy, describing intermittent "room spinning." Her speech became slurred. She denied headache, weakness or numbness, fevers, chills, trauma, cough or recent travel.

On examination, her vital signs were normal. She was irritable but cooperative. She had nystagmus in all directions of gaze, and though extraocular movements appeared full she had horizontal diplopia in all directions. She had dysarthria with a scanning speech pattern as well as truncal ataxia and severe bilateral, symmetric dysmetria. She was unable to stand or walk unsupported. Strength and sensation were normal; reflexes were diminished with

flexor plantar responses. Routine serum studies and urine toxicology were negative. An MRI of the brain with and without contrast (Figure 1) was normal. CSF examination revealed 14 WBC/ μ L with lymphocytic predominance, 34 RBC/ μ L, protein of 15mg/dL and glucose of 56mg/dL. EEG was normal. An extensive serologic workup performed in search of inflammatory markers, infection, rheumatologic markers, endocrine function, vitamin levels, heavy metals, genetic and metabolic etiologies was negative (Table 1). The only significant positive value was an elevated ANA at 1:80. Screening for occult malignancy with extensive serum and urine testing and imaging was negative (Table 1). A course of IV methylprednisolone 250mg Q6 hours x 3 days did not improve the symptoms. After a 5-day (2g/kg total) course of IVIG, she had marked improvement in vision, speech, coordination and gait. At discharge, she had no visual complaints, was able to feed herself with only very mild dysmetria and was able to walk with assistance. After discharge, serum paraneoplastic examination showed elevated voltage gated calcium channel antibodies (VGCC) (433 pmol/L, normal range <71 pmol/L).

She was readmitted approximately 3 months later with symptoms similar to time of presentation, although milder. She reported “dizziness” and was found to have nystagmus. Her gait became more ataxic and she required full assistance to ambulate. She received another 5-day course of IVIG at 2g/kg total, with modest improvement. Her dizziness resolved and nystagmus and ataxia were significantly improved. She was able to walk with only minor assistance at the time of discharge.

As of 17 months after presentation, her speech retained a scanning quality and though she walked unsupported with a narrow based gait, she was unsteady. She had mild bilateral finger to nose dysmetria, which did not affect her ability to perform most tasks, with improvement in handwriting. Despite the continuing clinical improvement repeat serum antibodies were elevated (0.59 nmol/L, normal <0.02 nmol/L) Repeat brain MRI revealed diffuse cerebellar atrophy (Figure 2). Due to the stable nature of her deficits and overall clinical improvement, further immunomodulatory therapies have not been prescribed. Repeat screening for malignancies with MRI abdomen and CT chest was negative.

Discussion

PCD is a rare neurologic syndrome which occurs mainly in adults with malignancies. Clinically, patients present with a subacute course of pancerebellar dysfunction including ataxia and nystagmus. They may also experience nausea, vomiting and at times vertigo, dysarthria and diplopia.¹ Initial neuroimaging is typically normal; however, MRI evidence of cerebellar atrophy becomes evident over time. Pathologically, there is a subacute loss of Purkinje cells in the cerebellum.¹⁰

PCD is typically associated with SCLC, gynecological and breast cancers and Hodgkin's lymphoma.¹ Multiple antibodies have been implicated (Table 2) with varying degrees of frequency. The most common antibody detected is anti-Yo, occurring in 37-53% of patients with PCD, regardless of malignancy, while VGCC antibodies are found in only 2-12% of PCD patients.¹¹⁻¹² VGCC antibodies have been most often identified in PCD patients with SCLC, occurring in 24-41% of this subset of PCD patients.^{2,9}

Adults with PCD and VGCC antibodies often have minimal recovery of their cerebellar symptoms in response to immunotherapy (corticosteroids, plasma exchange, IVIG, tacrolimus and cyclophosphamide) and/or treatment of their malignancy.^{1,2,9} This may be due to the loss of Purkinje cells in the cerebellum.^{2,10}

PCD is extremely rare in children with only six reported cases.³⁻⁸ All were boys ranging in age from 8 years to 19 years old, diagnosed with Hodgkin's lymphoma either concomitantly with neurologic symptom onset, or thereafter with the longest interval being 3 years to cancer diagnosis. Three of the cases reported isolated antibodies thought to be associated with the syndrome (one with anti-PCAb,⁶ two with anti-Tr^{7,8}), and only one reported MRI evidence of cerebellar atrophy diagnosed 3 weeks after the onset of the neurologic symptoms concurrently with the diagnosis of Hodgkin's lymphoma.⁶ None of these patients received immunotherapy at the time of their neurologic symptoms, but all had chemotherapy at the time of cancer diagnosis. One patient succumbed to the cancer 10 months after diagnosis and remained neurologically disabled until the time of his death.³ The other five had varying degrees of improvement of the neurologic symptoms after going into remission with chemotherapy for cancer.⁴⁻⁸ The two patients who were identified as anti-Tr positive^{7,8} had dramatic improvement in neurologic symptoms though some residual deficits remained. The patient with anti-PC antibodies improved somewhat but remained quite disabled and unable to walk.⁶ Significant neurologic improvement was also reported in the two remaining patients in whom specific antibodies were not identified.^{3,4}

To our knowledge, this is the first report to date of a girl with PCD associated with VGCC antibodies without any evidence of a malignancy in whom immunotherapy with IVIG produced significant improvement. Although the syndrome recurred, a second round of IVIG was also helpful in controlling the symptoms. This case highlights the importance of pursuing a thorough search for etiology of ataxia.¹³

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Figure 1. Normal MRI Brain at presentation (A. Axial T2 flair; B. Sagittal T1)

A.

B.

Figure 2. Repeat MRI Brain, 1-year interval shows cerebellar atrophy (A. Axial T2 flair; B. Sagittal T1)

A.

B.

Table 1. Negative/Normal Diagnostic Evaluations

Category	Test
Inflammatory	ESR, CRP, CSF oligoclonal bands and myelin basic protein
Autoimmune	anti-SM, anti-Ro, anti-La, RF, anti DNA, celiac panel, comprehensive immunoglobulins, Gq1b, serum autoantibodies (Hu, Ma2, Yo, Ri, CAR, CV2, Zic4, VGKC, Ampiphysin, AChR, NMDA)
Infectious	EBV (IgG/IgM), HCV (IgG/IgM), HIV, lyme, parvo, VZV IgM, mycoplasma IgM, ASLO, HepA IgM, RPR, CSF culture and viral panel
Endocrine	TFTs, urine HVA, AFP
Nutritional	B12, ferritin, lipid panel
Metabolic/Genetic	Lactate, pyruvate, CPK, ceruloplasmin, urine electrolytes, fritaxin
Neoplastic	Abdominal and pelvic ultrasound, abdominal and pelvic MRI, CT chest, urine metanephrines, serum AFP, HCG, LDH

Table 2. Autoantibodies in PCD

Autoantibody	Associated Malignancy
Anti-Yo	Breast, Uterine, Ovarian
Anti-Hu	SCLC
Anti-Tr	Hodgkin's lymphoma
Anti-CRMP5/CV2	SCLC, thymoma, gynecological
Anti-Ri	Breast, gynecological, SCLC
Anti-mGluR1	Hodgkin's lymphoma
Anti-Ta/Ma2	Testicular, lung
Anti-VGCC (P/Q Type)	SCLC
Anti-SOX1	SCLC
Anti-ZIC4	SCLC
PCA-2	SCLC