**Case Report - Sample work**

# Anti-Glutamic Acid Decarboxylase Auto Antibody associated neurological disorder in patient with ALL treated with standard protocol

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Objective: To report two cases with anti-GAD antibodies associated neurological disorder in patients with ALL who received standard chemotherapeutic protocols.
Clinical presentation and intervention: Case 1, acute leukemia of T-cell/myeloid mixed phenotype developed motor neurological symptoms while on induction protocol. Anti-GAD antibodies were demonstrable in the CSF and serum, and the patient responded to Intravenous Immunoglobulin (IVIG) therapy. He was found to have a copy of ERCC variant gene.
Case 2, a relapse of B-ALL with allogeneic HBMT had progressive neurological symptoms. Anti-GAD65 antibodies were demonstrable in the serum, but not the CSF. The patient did not respond to IVIG and had to be given plasmapheresis and steroids. 2-year follow-up status of both patients is provided.
Conclusion: Immunological etiology with Anti-GAD antibodies needs to be considered in the differential diagnosis of central and peripheral neurological illness in ALL patients on standard chemotherapeutic protocol. IVIG is an effective treatment for this condition. However, in case of inadequate or no response, plasmapheresis with steroid or rituximab should be considered. Long-term management is required to prevent and manage relapse of autoimmune neurological illness.

## INTRODUCTION

Neurological complications in patients on leukemia chemotherapy can be related to drug neurotoxicity, infections, or abnormal immunological response [1], [2]. Though Guillain-Barre syndrome in ALL patients on chemotherapy have been reported in literature [1]–[3], reports of anti-GAD antibodies are few [4]. Here, we present two cases with central and peripheral neurological affection associated with demonstrable autoantibodies in the CSF and/or serum. One patient was heterozygous for DNA repair gene variant while the other was a case of relapse with allogeneic HBMT on immunosuppressants. The possible etiologies, mechanisms, diagnosis, treatment, and long-term management is discussed for both cases.

## CASE REPORTS

*Case 1:* A 17 year old male with no significant past medical history was diagnosed with T-cell/myeloid mixed-phenotype acute leukemia in September 2015. Induction protocol included Dexamethasone, Vincristine, Daunorubicin, PEG-asparaginase, Cyclophosphamide, Thioguanine,Cytarabine and intrathecal Methotrexate, Hydrocortisone and Cytarabine. His initial clinical course was complicated by hyperleukocytosis, tumor lysis syndrome after initiation of PEG-asparaginase and respiratory failure. After resolution of these complications, he developed difficulty speaking and decreased strength in all his extremities and neck muscles. His bladder and bowel function, as well as swallowing and mentation were intact. There was no subjective feeling of numbness or tingling. His neurological examination was significant for partial deficits of left VI (abducens) and Left VII (Facial) nerves, diminished gaze upward, proximal, and distal weakness in both upper and lower extremities, absent ankle reflex bilaterally. Sensation was intact. Eventually, his speech slowly improved but motor deficits persisted.

Magnetic Resonance imaging (MRI) of the brain revealed non-occlusive left sigmoid sinus thrombosis and scattered punctate hemorrhage. MRI of cervical, thoracic, and lumbar spine was negative for any abnormal findings. Cerebrospinal fluid (CSF) analysis showed elevated protein of 233 milligrams per deciliter (mg/dL). Nerve conduction studies were consistent with moderately severe predominantly axonal peripheral motor neuropathy. Vincristine was withheld due to these findings. Patient's symptoms of proximal muscle weakness were suggestive of steroid myopathy. However, high protein level in CSF raised concern of Guillain-Barre syndrome. Treatment with Intravenous immunoglobulin (IVIG) was initiated. Further testing of CSF revealed presence of anti-glutamic acid decarboxylase (GAD), autoantibodies (ABs), Ganglioside GM1 ABs, myelin-associated glycoprotein Abs and ganglioside complex (GD1a and GD1b) Abs were absent.

Neurological status started to improve gradually after completion of 5 day of IVIG therapy and eventually completely resolved. 2 years later while being on maintenance therapy, patient experienced new onset seizure approximately 15 minutes after administration of methotrexate. MRI brain was repeated and showed resolution of

non-occlusive left sigmoid sinus thrombosis. Levetiracetam was initiated for seizure prophylaxis. It was completed weaned off at the time of completion of maintenance therapy.

Patient participated in non-therapeutic prospective observational trial involving Next Generation Sequencing of Normal Tissue in Pediatric Oncology Patients. He was found to have one copy of pathogenic ERCC2 variant in germline sample.

*Case 2:* A____ year girl who was a known case of B cell ALL in remission since ----- , had a relapse in March 2015 for which treatment was initiated. Within a couple of months in May 2015, the patient developed gradually progressive weakness with increased difficulty in walking and lumbar pain. There was difficulty in swallowing which required flexing her neck to complete the process. There was no paresthesia or numbness. There was dysarthria and emotional lability. No viral-like symptoms or diarrhea was reported prior to the event. Neurological exam revealed right-sided weakness with intact sensation with pseudotumor palsy.

Laboratory analysis showed normal CRP, normal ammonia level, normal serum pyruvate, normal urine organic acids. Autoimmune panel showed normal levels of NMDA receptors Abs, voltage gated potassium channel-complex (VGKC-complex) Abs, Anti-Sjögren's-syndrome-related antigen A and B (SSA and SSB) Abs. Oligoclonal bands were absent in CSF. However, GAD-65 antibodies were elevated in the serum but negative in CSF. Thyroid peroxidase (TPO) Abs were noted to be elevated in the serum.

MRI brain showed increasing large areas of white matter toxicity involving the bilateral centrum semiovale and corona radiata, left greater than right. Matched unrelated donor Allograft Hemopoietic Stem-Cell Transplantation (HSCT) was done in September 2015.

In view of neurological symptoms, Tacrolimus was withheld, and patient was started on Sirolimus. Patient was treated with 2 gm/kg of IVIg over 2 days. Despite this intervention her neurological status further deteriorated. Giving this deterioration Sirolimus was discontinued. High dose of methylprednisolone (250 mg daily) and plasmapheresis were added to daily IVIg. Followed by the intervention, the neurological status gradually was improved. Repeat levels of GAD Abs showed a reducing trend.

Patient was noted to have increasing EBV titers. Rituximab was initiated and IVIg was discontinued. Repeat MRI showed resolution of T2 hyperintense signals. Frequency of plasmapheresis was reduced to once in a fortnight. As symptoms were improving, steroid was tapered off, prednisone 40 mg then methylprednisolone 5 mg daily were administered. Within 6 months, in November 2015 GAD65 was undetectable. As plasmapheresis frequency was decreased, GAD Abs increased in early 2016 and symptoms got worse. Plasmapheresis was slowly tapered off in the next 2 years.

## DISCUSSION

The presentation of neurological disorders in children on cancer chemotherapy specially leukemia chemotherapy has been reported in literature. Such neurological syndromes are related directly to the toxicity of chemotherapeutic agents, infections, or a dysfunctional immune system with production of autoantibodies [4]. The

raised levels of anti-GAD antibodies in the CSF and serum has been reported in in a section of patients presenting with symptoms of motor neuropathy and some encephalopathy [5]. Classically, there is no sensory involvement in these cases [6]. Literature has revealed the positive response of patients with such neurological symptoms to IVIG therapy [4].

In the first case, a single copy of pathogenic ERCC gene variant was found in the germline. ERCC gene mutation has been classically reported with xeroderma pigmentosum. The ERCC gene is a DNA repair gene and mutations in this allow DNA damage to accumulate in cells predisposing them to turn cancerous [7]. In addition, ERCC variants with defective DNA repair are also known to cause neurological symptoms mostly motor and cognitive with some sensory manifestations like hearing loss, possibly by the same mechanism i.e. build-up of non-fatal DNA damage [8].

We are unaware of any reported case of ERCC heterozygosity in patients of leukemic chemotherapy developing neurological symptoms and studies in this respect are limited. However, the possibility of defective DNA repair function though partially or in selected cells cannot be ruled out as a predisposing factor in case 1. Oxidative stress induced by chemotherapeutic agents with release of free radicals with suboptimal DNA repair function could have manifested with autoimmune neurological illness8.

Neurotoxicity due to chemotherapeutic agents especially Vincristine and infectious etiology that may not present with classical symptoms are important differential diagnosis to be borne in mind. Demonstration of autoantibodies in the CSF and to a lesser extent in the serum, helps in clinching the autoimmune etiology.

Tacrolimus neurotoxicity is noted in almost 25 to 30% patients [9] and needs to be considered in case 2. However, Tacrolimus levels were always within therapeutic range, her renal functions were normal, and she continued to have progressive neurological symptoms even after discontinuing the drug, which makes it an unlikely etiology.

Though several chemotherapeutic agents used in leukemia chemotherapy cause neurotoxicity, notable in this case is the role of Fludarabine induced neurotoxicity. Fludarabine is a purine analogue with chemotherapeutic actions and immunosuppressive activity, which makes it a good choice in allogeneic transplantation patients [10]. Fludarabine related neurotoxicity in high doses is progressive, irreversible, and sometimes lethal [3]. However, this is unlikely in case 2.

Anti-GAD65 antibodies were demonstrated in the serum and not in the CSF, that prevents making a conclusive diagnosis. The possibility of autoimmune encephalitis with GAD antibodies is also likely in her case. Dramatic response to IVIG is seen in most cases and confirms the autoimmune nature of the neurological symptoms. In the absence of response to IVIG or worsening of symptoms to IVIG like in case 2, in the presence of strong suspicion or demonstrable autoantibodies, plasmapheresis with steroid therapy should be instituted.

Finally, GAD associated encephalitis has variable prognosis. It may include a spectrum of near complete recovery to relentless progression. IVIG is a safe, effective, noninvasive method of treatment in these patients with good response [11]. Patients who do not respond to IVIg, can be treated with plasmapheresis, high dose prednisone or rituximab [12], [13].

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