



Concurrent Baylisascaris Procyonis and Varicella Zoster Virus Infection in a Child with Purine Nucleoside Phosphorylase Deficiency

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Abstract

Purine Nucleoside Phosphorylase (PNP) is a ubiquitous enzyme that plays a role in purine metabolism, with the highest expression levels found in lymphocytes. Deficiency of this enzyme caused by autosomal recessive mutations, leads to impairment of DNA replication and cellular proliferation. PNP deficiency constitutes a rare form of Severe Combined Immunodeficiency (SCID) resulting in impaired T-cell function and recurrent life threatening infections. More than half of patients also suffer from neurological dysfunction thought to result from toxic metabolite buildup. The only known cure for this disease is Hematopoietic Stem Cell Transplantation (HSCT). This is a case report of a three-year-old boy with PNP deficiency who developed concurrent systemic Baylisascaris Procyonis and Varicella Zoster Virus (VZV) infection with ocular manifestations necessitating systemic therapy and pars plana vitrectomy.

Keywords: Purine nucleoside phosphorylase; Varicella zoster virus; Baylisascaris procyonis

Introduction

Purine Nucleoside Phosphorylase (PNP) is a ubiquitous enzyme that plays a role in purine metabolism via the purine salvage pathway [1,2]. This enzyme is found in most cell types and has differential expression, with the highest expression found in lymphoid tissues [2]. PNP cleaves the purine-sugar bond of Guanosine, Inosine as well as their deoxygenated forms (Deoxyguanosine and Deoxyinosine), forming Guanine and Hypoxanthine, which are salvaged to Guanosine Tri Phosphate (GTP) [3]. PNP deficiency leads to accumulation of intracellular deoxyguanosine and its abnormal phosphorylation to deoxyGuanosine Tri Phosphate (dGTP), which impairs DNA replication and consequently hinders cellular proliferation, while at the same time leading to depleted GTP levels [2]. PNP deficiency is a rare autosomal recessive immune disease first described by Giblett et al. [4] in 1975. Fewer than 80 cases have been reported in the literature since that time [2]. It represents 4% of patients with Severe Combined Immuno Deficiency (SCID); a disease characterized by absence or dysfunction of T (and sometimes) B-Lymphocytes leading to impaired cellular and humoral immunity [2,5,6]. The PNP gene is composed of 6 Exons and resides on the long arm of chromosome 14 [5,7]. To date there have been 24 separate mutations identified in PNP deficiency, with a wide variety of phenotypic presentation, therefore no associations between the patient's genotype and phenotype can be made [2,8]. Roughly two-third of patients also suffers from neurological dysfunction including motor spasticity, and developmental delay. The molecular mechanisms of neurological impairment in PNP deficiency have not been fully elucidated, but are thought to result from either depletion of GTP or toxic levels of dGTP [2,3,9]. Recent studies on PNP-Knockout mice revealed smaller than average cerebellum, while MRI imaging on some patients with PNP revealed diffuse cortical atrophy [3,9]. Diagnosis can be established by measuring PNP enzyme activity in red blood cells, and confirmed through genetic analysis. The prognosis of PNP deficiency remains poor, and no patient has survived beyond the second decade of life without Hematopoietic Stem Cell Transplantation (HSCT), which is the only curative treatment to date [2]. We present a case of concurrent systemic Baylisascaris Procyonis and Varicella Zoster virus (VZV) infection with ocular manifestations in a child with PNP deficiency.

Case Presentation

We were consulted on a three-year-old boy transferred to our facility from a local community hospital for treatment of Herpes Zoster Ophthalmicus with superimposed MRSA infection, and altered

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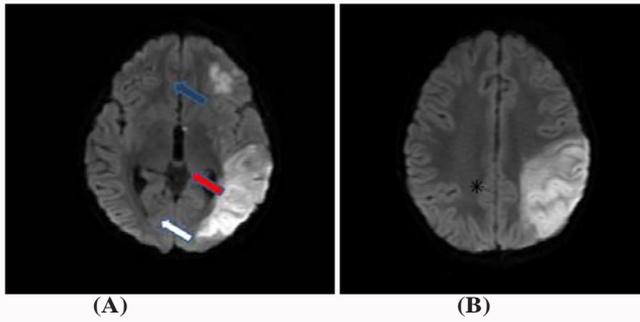


Figure 1: MRI Brain Diffusion Weighted Imaging. (A) Axial diffusion weighted imaging (DWI) notable for large region of diffusion restriction involving parts of the left occipital lobe (white arrow), left temporal lobe (red arrow), as well as the inferior left frontal lobe (blue arrow) consistent with infarction. (B) Axial DWI notable for large region of diffusion restriction involving the left parietal lobe (asterisk).

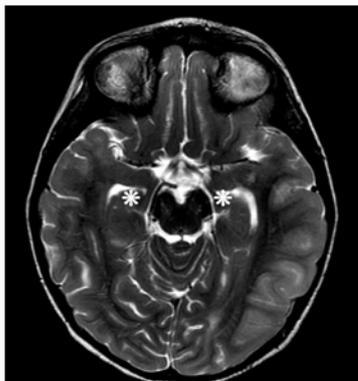


Figure 2: MRI Brain-T2 Axial. Hyperintense T2 signal involving the cortical gray matter of the bilateral medial temporal lobes (uncus) representing meningitis vs. cerebritis (asterisk).

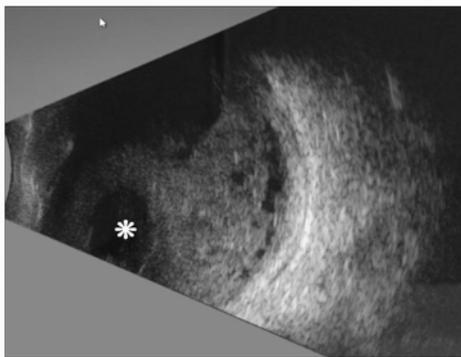


Figure 3: B-Scan Left Eye. B-Scan was consistent with multiple cystic hyperechoic signals in the vitreous cavity (asterisk).

mental status in the setting of underlying neutropenia. The patient had a history of previous Herpes Zoster infection in the left flank 6 months prior to presentation. His past medical history was significant for cerebral palsy, developmental delay, and what was thought to be viral induced neutropenia, which was treated with Neupogen in the past. The patient's family history was otherwise non-significant. On presentation, his initial ocular examination was notable for vesicular lesions in the V1 distribution on the left with Hutchinson's sign, without corneal involvement. Posterior examination was notable for a splinter hemorrhage in the left eye, however no evidence of vitritis was noted, and the remainder of the posterior exam were otherwise

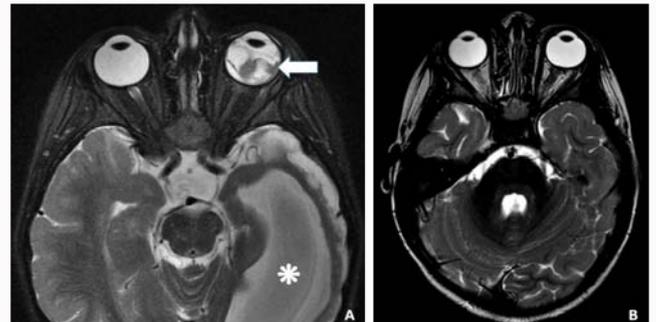


Figure 4: MRI Brain-T2 Axial. (A) Axial T2 fat saturated image notable for several thick curvilinear septations within the left globe, which demonstrate nodular enhancement with subretinal fluid collection (white arrow). Cystic encephalomalacia involving the entire left hemisphere with some sparing of the orbital frontal gyrus, as well as ex vacuo dilatation of the left lateral ventricle in area of previous stroke (asterisk). (B) Axial T2 Image taken five months prior to image A, demonstrating absence of septations.

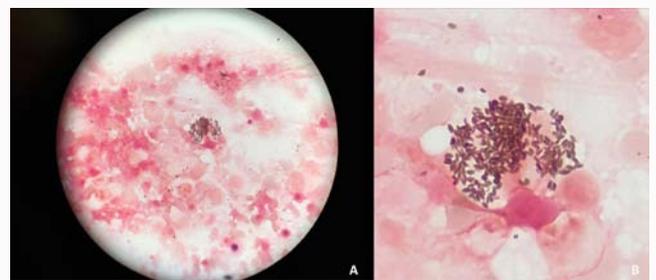


Figure 5: Gram Stain of Vitreous Fluid. (A) Gram stain notable for gram positive rod like structures. (B) Higher Magnification was consistent with melanosomes, likely liberated during pars plana vitrectomy.

unremarkable. The patient started treatment with systemic antibiotics and Acyclovir and a thorough systemic workup was initiated. His hospital course was complicated by a large infarct involving the left temporal, parietal, frontal, and occipital lobes with diffuse cerebritis (Figure 1 and 2). He also developed elevated Intra Cranial Pressure (ICP), as well as seizures necessitating seizure treatment and the placement of a Camino bolt for ICP monitoring. A lumbar puncture revealed eosinophilia, presence of Varicella Zoster virus (VZV) by Polymerase Chain Reaction (PCR), and Baylisascaris antibodies in his Cerebro Spinal Fluid (CSF). He was treated with a 28-day course of systemic Albendazole and was discharged three months after his initial presentation with prophylactic dosing of Valacyclovir, Bactrim and anti-seizure medication. During his hospital course the patient did develop HZV keratitis in the left eye, with a resultant paracentral area of sub epithelial haze. However, prior to discharge the patient had no evidence of active ocular inflammation or infection. Eight weeks after discharge the patient was seen in our clinic for a routine evaluation and was started on Prednisolone Acetate 1% in the left eye in order to decrease his corneal scarring. The patient was stable until three months post hospital discharge when he was seen in our clinic for periorbital swelling in the left eye associated with 3+ conjunctival injections without active keratitis. An Exam under Anesthesia (EUA) was notable for 2+ conjunctival injection and a superficial corneal epithelial defect in the left eye without obvious infiltrates, a hazy anterior chamber with 360 degree posterior synechiae and rubeosis. There was evidence of dense vitritis without a clear view to the posterior pole. A B-scan was notable for multiple cystic appearing hyperechoic signals in the vitreous cavity (Figure 3). A follow up

MRI was notable for new nodular enhancing septations with a proteinaceous component within the vitreous cavity concerning for endophthalmitis (Figure 4). The patient was taken for emergent pars plana vitrectomy, lensectomy, membrane peel and endolaser for multiple retinal breaks, silicone oil, as well as scleral buckle for repair of retinal detachment. Vitreous sample was sent for microbiologic evaluation and was negative for bacteria and parasites. Gram Stain of the vitreous sample was also performed and initial findings were concerning for *Baylisascaris* eggs, however further evaluation by our ocular pathologist revealed them to be consistent with melanosomes (Figure 5). The patient was then discharged with a suppressive dose of Albendazole added to his medication regimen given concerns for recurrent *Baylisascaris* infection. Subsequent testing revealed the patient to have PNP deficiency and he is undergoing workup for bone marrow transplantation.

Discussion

Baylisascaris Procyonis is a large roundworm of the family ascarididae that is a common parasite in raccoons. Human infection occurs through ingestion of eggs, which can present as three main clinical syndromes including Visceral Larva Migrans (VLM), Neural Larva Migrans (NLM) and Ocular Larva Migrans (OLM) [10]. OLM is caused by access of the nematode to the eye through the retinal arteries and can manifest as Diffuse Unilateral Subacute Neuroretinitis (DUSN), characterized by vision loss, papillitis, and vitritis [10]. *Baylisascaris Procyonis* is considered the primary etiologic agent in the large nematode variant of DUSN [11,12]. Systemic infections resulting in devastating eosinophilic meningoencephalitis, as well as co-infection with herpes simplex virus with ocular manifestations have been reported in the past in both adults and children [11,12]. However, to our knowledge this case represents the only known case of concurrent systemic *Baylisascaris Procyonis* and VZV infection with ocular involvement in a patient PNP deficiency. Although vitreous cultures for bacteria and parasites were negative in our patient, there was not enough sample to perform a Western blot assay employing the rBPAG1 antigen, which remains the gold standard for serodiagnosis of *Baylisascaris Procyonis* [10]. Nonetheless, our patient had significant unilateral vitritis and retinal detachments in the setting of positive CSF testing for *Baylisascaris Procyonis*, which significantly raises the suspicion for DUSN. Interestingly, our patient was previously diagnosed with cerebral palsy and developmental delay of unknown etiology. However, given our patient's underlying diagnosis, his neurological and cognitive dysfunction is likely related to PNP deficiency rather than cerebral palsy. Studies in mice have shown that early PNP replacement prevented cerebellar damage and motor abnormalities [9]. Furthermore, it has been shown that

while HSCT can reconstitute immune function; it does not reverse neurological damage [9]. These findings underscore the importance of early diagnosis in these children to prevent progressive neurological dysfunction, and devastating sequelae from CNS infections.

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