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Cystagon Treatment for Neuronal Ceroid Lipofuscinosis: An 8-Year Case Study

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Abstract

A case study conducted for 8 years from 2003 to 2010 with a one-year temporary interruption in 2008, revealed that Cystagon seemed to be a potential treatment agent for neuronal ceroid lipofuscinosis (NCL), also known as Batten disease. As the dosage of Cystagon increased, the numbers of lymphocytes containing granular osmiophilic dense deposits (GROD, one of the pathological hallmarks) decreased. When the dosage of Cystagon reached between 47 and 50 mg/kg body weight, the numbers of lymphocytes containing GRODs plateaued. Our 8-year follow-up suggests that Cysteamine (Cystagon) treatment may be a potentially promising agent for NCL treatment. It might be more accurate to say the Cystagon has improved some of the clinical manifestations, the quality of this patient's life, his behavior and functioning, but did not affect the overall disease progression. The parents also felt that Cystagon decreased the "psychotic manisfestation" – auditory and visual hallucination. Further studies with more patients using this medication are needed.

Keywords: Cystagon; Cysteamine; Neuronal Ceroid Lipofuscinosis; Treatments; GROD; Lymphocytes

Introduction

NCL represents a group of common progressive neurogenetic diseases that occur in infants, and children who have a global incidence of approximately 1 in 12,500 [1,2]. NCLs also can affect adults and are inherited in an autosomal recessive manner [3].

Neuronal ceroid lipofuscinoses (NCL, also known as Batten Disease) is an inherited fatal, neurodegenerative disease. A gene mutation causes a deficiency of enzymes that trigger lysosomal dysfunction, resulting in an abnormal accumulation of ceroid lipofuscin in the tissues of the brain, eyes, skin, and muscles [4].

The symptoms include an increased seizures, cognitive and mental impairment, and progressive loss of sight and motor skills. The symptoms continue to progress over several years. Due to the unusual presentation of symptoms and the complicated diagnostic process, it often takes many years from the first symptoms to correctly diagnose Batten disease [5].

Cysteamine and Cystagon (brand name) (Mylan Pharmaceuticals, Morgantown, WV) are used to treat cystinosis, a hereditary metabolic disorder that causes a build-up of the amino acid cystine in cells of the body. Cysteamine cleaves the disulfide bond with cystine to produce molecules that can escape the metabolic defect in cystinosis. Cystine build-up can cause kidney and eye problems, slow body growth, and weak bones. Cysteamine helps the body get rid of cystine and prevents these problems [5]. The consensus is that no treatment has been able to arrest NCL progression [6]. So far, there is no widely accepted treatment that can cure, slow down, or halt the symptoms of NCL. However, seizures may be controlled or reduced with the use of anti-epileptic drugs [7].

Materials, Methods, and Results from observations over 8 years

Whole blood samples of patients with possible NCL conditions were sent from various medical centers and clinics to the Speciality Clinic Laboratories (SCL) of our Institute for diagnostic evaluation using electron microcopy (EM). A diagnosis of NCL is based on finding 5% or more of lymphocytes containing any one of these four pathological hallmarks: GROD (granular osmiophilic dense deposit), Finger print profile, Curvilinear body, and Rectilinear body [8-10]. The patient in this case was born in 1987. His first blood sample was taken as his treatment began in 2003 (Table 1). The EM examination showed the diagnostic presence of GRODs in 36 of 250 (14.4%) peripheral blood lymphocytes in June of 2003 (Figures 1A & 1B; Table 1 and Figure 2).

Patient description and history

The patient is a French-Canadian male, who at age 16 was diagnosed with atypical juvenile neuronal Ceroid lipofuscinosis (AJNCL)/ Batten Disease with a ceroid lipofuscinoses-neuronal associated gene mutation (CLN1).

He developed vision problems at around 7 years of age. He had progressive vision loss secondary to retinitis pigmentosa. He had his first seizure at age 13. The EEG results were abnormal. He began to have difficulties concentrating in school. At 15 years old, he had a 36-hour long episode of confusion with both auditory and visual hallucinations.

At 16 years of age, an MRI and PET Scan of the brain showed generalized atrophy and findings consistent with encephalopathy. The diagnosis of Batten disease with a CLN1 mutation and deficient PPT (palmitoyl protein thioesterase) activity was made at age 16.

Once diagnosed with Battens disease, our patient was enrolled in a treatment trial with Cystagon beginning on 6/24/2003. He has remained on Cystagon for the past 8 years, and he is still continuing to receive Cystagon medication.

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Accession #	Lab #	Collection Date	Specimen	Diagnosis	GRODs	RB	CB	NSP	Mitochondria
221765	2010-	7-Jul-2010	Buffy Coat		16	4		27	
220947	2010-05	14-Jan-2010	Buffy Coat	Borderline NCL	9	6		54	Numerous
219974	2009-28	8-Jul-2009	Buffy Coat	NCL	27				
218921	2009-04	28-Jan-2009	Buffy Coat	NCL	23				
217873	2008-44	16-Jul-2008	Buffy Coat	Juvenile onset INCL	17				
214736	2007-44	18-Jul-2007	Buffy Coat	Juvenile onset INCL	17				
213470	2007-05	16-Jan-2007	Buffy Coat	Juvenile onset INCL	17				
212250	2006-67	5-Jul-2006	Buffy Coat	Juvenile onset INCL	17				
211261	2006-09	24-Jan-2006	Buffy Coat	Juvenile onset INCL	17	Some			Some degenerated
209905	2005-63	12-Jul-2005	Buffy Coat	Juvenile onset INCL	19				Some degenerated
208608	2005-02	12-Jan-2005	Buffy Coat	Juvenile onset INCL	19				Some degenerated
207868	2004-62	7-Jul-2004	Buffy Coat	Juvenile onset INCL	23				
207337	2004-07	27-Jan-2004	Buffy Coat	Juvenile onset INCL	25				
206965	2003-65	7-Oct-2003	Buffy Coat	Juvenile onset INCL	29				
206604	2003-43	17-Jun-2003	Buffy Coat	Juvenile onset INCL	36				

GROD=Granular Osmiophilic Dense Deposit; RB=Rectilinear Body;
CB=Curvilinear Body; NSP=Non-Specific; NCL=Neuronal Ceroid Lipofuscinosis; INCL=Infantile Neuronal Ceroid Lipofuscinosis.

Table 1: Profiles of a male patient born on Oct. 4th, 1987 with Neuronal Ceroid Lipofuscinosis.

EEG results

He had an EEG performed every six months. The EEG's were all abnormal, but remained relatively unchanged.

Further studies showed an absence of activity of the enzyme Palmitoyl-Protein Thioesterase in fibroblasts, consistent with the CLN1 gene-associated with NCL (0.00 nmol/hr/mg protein with control of 22.1 nmol/hr/mg protein). Molecular studies for mutations in the gene CLN1 identified a homozygous mutation c223A>C(T75P) in this gene.

Clinical conditions and issues

The following information was obtained from the clinical notes:

6/03 – 15 yrs 8 mo. Responds verbally to father. Walk, runs & kicks ball.

10/ 03 - 16 yrs –Walks- uses step machine. Toilets self.

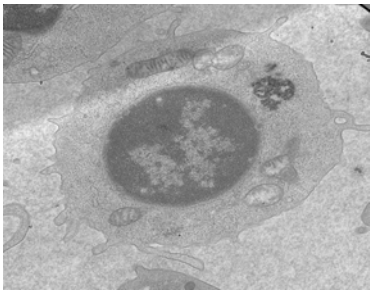

Figure 1A: Electron micrograph showing the presence of a GROD in an NCL lymphocyte (bar=500 nm).

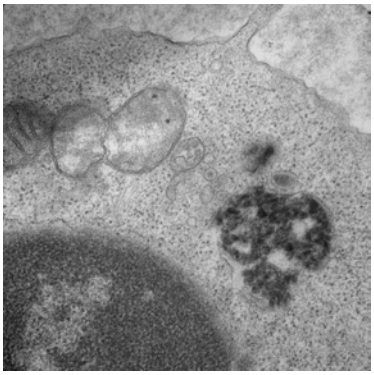

Figure 1B: Higher magnification of Figure1A showing more details of the GROD (Bar=250 nm).

1/04 - 16 yrs 3 mo- Walks. Enjoys singing. Cataract surgery on left eye.

7/04 – 16 yrs 9 mo- Walking with some assistance. He had cold/flu in March.

Cystagon stopped for a brief period- hallucinations, poor walking and poor concentration reappeared. After Cystagon restarted- hallucinations stopped, walking improved and concentration improved.

1/06 – 18 years / 3 months old Walks with walker / cane. Navigates house well.

Last seizure 6 months ago.

7/06 - 18yr 8 months- Walks well

Date mm-y	Dose	body weight in kg	mg/kg	Comments
Jul-03	2400	81	29.6	
Oct-03	3600	90	40	
Jan-04	3600	86	42	
Jul-04	3600	87	41.4	
Jan-05	3600	90	40	
Jul-05	3600	94	38.3	
Jan-06	4500	90	50	
Jul-06	4200	89	47	
Jan-07	3900	81.5	47.8	
Jul-07	3900	82	47.5	
Jan-08	3900	82	47.5	
Jul-08	3900	78	50	
Jan-09	3900	79.4	49.1	
Jul-09	3600	76	47.4	
Jan-10	3300	69	47.8	gradual decrease
Jul-10	2250	60.3	37.3	
May-11	3150	64	50	

Table 2: Application of different dosages of Cystagon (mg/kg body weight) and time points for the treatment of neuronal ceroid lipofuscinosis.

Cystagon Protocol Worksheet

Cystagon Protocol: Dosage: 50mg /kg/day (maximum dose) Start with ¼ to ½ dose and slowly increase over 4-6 weeks. Capsules are available in 50 mg capsule and 150 mg capsule.

For example, if a patient has a body weight 81 Kg and is taking the maximum dose of 50mg/kg/day, then, 50x81=4,050 mg/day. He will need to take the large capsule, 150 mg capsule for this situation. Then, he needs to take 4,050/150/4 times a day=6 to 7 capsules every 6 hours for 4 times per day.

1/07 - 19yr 3 months - Walks slow, is able to hop and jump with assistance.

7/07 - 19 yr 9 months- Uses treadmill walks a few miles with assistance

1/08 - 20 years 3 months – Walks 2-3 km per day. Tremors present

7/08 - 20 yr 6 months - No seizures. Uses walker. Gait shuffling.

1/ 09 - 21 yr 3 months old - continues to go on long walks with Dad. But falls on daily basis.

Needs to be fed

Seizures began again – had five seizures.

7/09 – 21 year old 9 months - Daily seizures occur. Uses wheelchair.

1/10 - 22 years 3 months old Uses wheelchair - ambulates short distances only. Limited 1-2 word speech. Has difficulty swallowing hard foods. Seizures well controlled with meds. Incontinent wears depends.

7/11- 22 yrs 9 months - No longer speaking. No longer able to ambulate – one or two steps only. Small seizures. Wears depends but defecates in toilet.

5/11 – 23 yrs old 7 months – Can no longer stand – Non ambulatory. Non verbal. Had two grand mal seizures in November. Wears depends but defecates in toilet.

11/11 - 24 yrs old – One seizure per day. Eats and drinks thickened pureed foods.

Wears depends but defecates in toilet. Non verbal – but makes noises and tries to speak.

He is currently living at home with his parents. He is receiving Occupational therapy, physical therapy and supportative nursing services. He is being handfed a pureed diet.

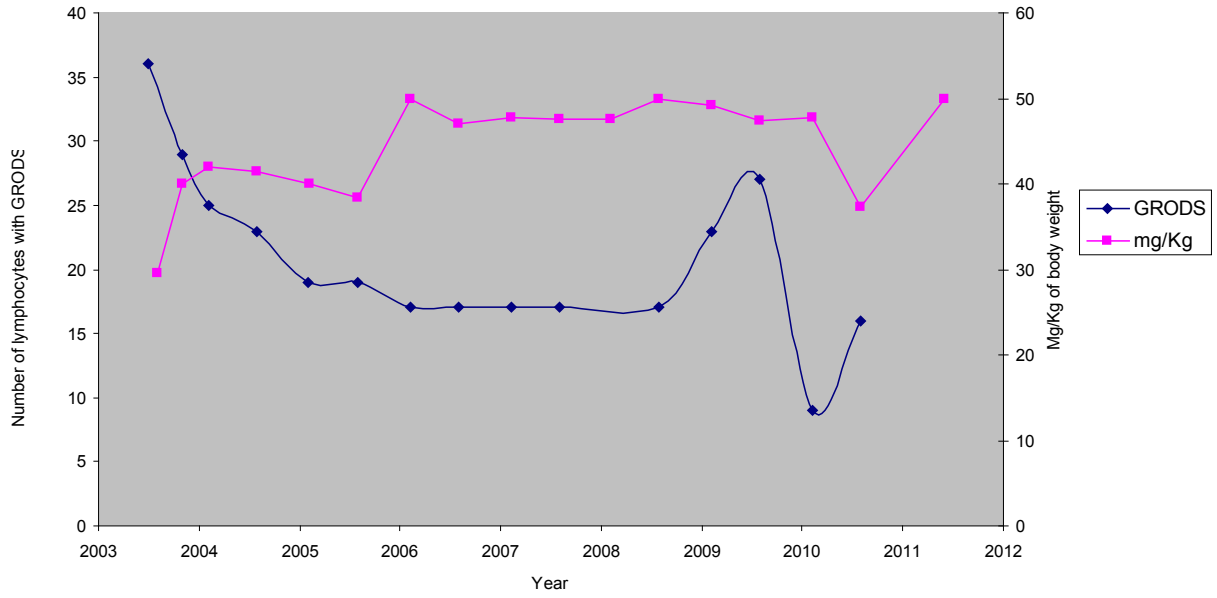

Figure 2: Cystagon dosages and numbers of lymphocytes containing granular dense deposits (GRODs) in 250 lymphocytes.

Note: Table 1 revealed that the examination of blood samples was interrupted in January of 2008 due to the illness of the co-author, Krystyna Wisniewski, but was continued in July. Table 2 showed that Cystagon was still administratered both in January and July of 2008.

As the trial progressed, his vision progressively got worse and he continued to have seizures, generalized tremors increased, and gait became increasingly unsteady until he was unable to ambulate.

Specifically, he first received Cysteamine treatment with 29.6 mg/Kg body weight in 2003 (Table 2). The overall quantitation by counting the numbers of cells (lymphocytes) containing GRODs in 250 cells revealed a gradual reduction of lymphocytes containing GRODs as the treatment with Cysteamine proceeded each year (Table 1 and Figure 2) . The dosage of Cysteamine given to this patient varied at each treatment time at our Institute as listed below (Figure 2 and Table 2). The numbers of lymphocytes containing GRODs in this patient decreased gradually from 36 (in June, 2003) to 16 in July, 2010 with a brief spike of GRODs likely due to a brief disruption of treatment in 2008 (Figure 2 and Table 1 and 2).

Conclusions/Discussion

The aim of this case study was to document that Cystagon may be a potential treatment agent for NCL, because as the dosage of Cystagon increased, the numbers of lymphocytes containing granular osmiophilic dense deposits (GRODS) decreased.

We think the life expectancy for patients with Battens disease maybe increasing due to better medical care, medical advances and the option of inserting a feeding tube. However, we are not sure of the life expectancy of patients with this type of mutation. It might be more accurate to say the Cystagon has improved some of the clinical manifestations, but did not affect the overall disease progression.

Parents statements

The parents have chosen to continue the Cystagon treatment. They felt that Cystagon has improved some of the clinical manifestations and has improved the quality of their son's life. They also felt that Cystagon decreased the "psychotic manifestations"- auditory and visual hallucinations. They stated when the medication was stopped for a brief period, the hallucinations reappeared, when the medication was restarted, the hallucinations stopped. They also felt it improved his behavior and functioning.

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