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Clinical Characteristics of Niemann Pick Type C in New Mexican Patients

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Object. The authors review 11 known cases of Niemann Pick type C (NPC) in New Mexican patients to better characterize the natural history and disease progression in these patients.

Methods. The authors performed a retrospective review of data obtained from eleven patients with NPC seen in the Division of Pediatric Neurology at the University of New Mexico, Albuquerque, New Mexico. These patients attended routine follow up examinations conducted by a number of specialists to monitor disease progression.

Conclusions. The New Mexican cohort of NPC patients displayed an earlier age of onset, increased prevalence of vertical supranuclear gaze palsy as compared to previous study groups. Also of significance was the finding of two cases of psychosis occurring in adolescent patients. These findings demonstrate the importance of examination of extraocular movements in pediatric patients. NPC is more prevalent in New Mexico and should be kept on the differential during neurologic work-up.

Background and Rational

Historical Aspects

The German pediatrician Albert Niemann described the first case of Niemann-Pick Disease (NPD) in 1914, an Ashkenazi Jewish infant with massive hepatosplenomegaly and rapidly progressive neurodegeneration that subsequently led to her death at 18 months of age[3]. At autopsy, Niemann noted large, lipid-laden cells in her reticuloendothelial system similar to those found in Gaucher disease, but he was able to discount the diagnosis of Gaucher disease based on the age of onset, severe neurologic involvement, and the distinct histology of the foamy cells[3].

In 1927, Ludwig Pick reviewed reports of infants with rapidly progressive neurodegenerative disorders and delineated the disease described by Niemann as a unique clinical entity. The new syndrome was first described as "lipoid cell splenomegaly," in subsequent years it became known as NPD[7].

The first recognizable description of Niemann-Pick type C (NPC) appeared in Crocker and Farber's review of Niemann-Pick disease in 1958. Crocker later classified Niemann-Pick Disease into four groups based on biochemical and clinical criteria[7]. Niemann-Pick (NP) type A (Classic Infantile) has a common prevalence in the Ashkenazi Jewish population and is due to a deficiency of the enzyme acid sphingomeyelinase (ASM) which catalyzes the conversion of sphingomyelin to ceramide and phosphorylcholine[7]. Clinically these patients present with hepatosplenomegaly, central nervous system

symptoms, lung infiltration, and a cherry-red spot on the macula. Onset is infantile (around 6 months of age) and usually results in death by 2 to 4 years of age. NP type B (Visceral form) is also due to the deficiency of acid sphingomyelinase. The clinical presentation is similar to NPA with the exception of no CNS involvement. Onset is generally during early childhood, and progresses to death in early adulthood. This form of NPD is present in the Maghreb region of North Africa in addition to the Ashkenazi Jewish. NPA and NPB are diagnosed by identifying ASM activity in cultured fibroblasts and leukocytes. Genetic testing for the mutation, located on chromosome 11, is also done to confirm a clinical diagnosis. NP type C is due to a disruption in cholesterol trafficking. NPC presents as a slowly progressive neurologic disease with age of onset varying from infantile to adulthood. Crocker and Farber based their diagnosis of NPC on the presence of foam cells and increased tissue sphingomyelin. All of the classic neurologic features of NPC were present in their patients, and in addition they described several other presentations of NPC, including vertical supranuclear gaze palsy, ataxia, dystonia, dementia, cataplexy, dysarthria, plasticity, seizures, prolonged neonatal jaundice, hypotonia, and delayed motor milestones, isolated organomegaly and learning and behavioral problems[7]. NP type D has a similar presentation and progression as NPC, but its incidence has been limited to the French Acadians of Nova Scotia.

Clinical Manifestations

The "classic" clinical profile of the NPC patient occurs in 50 to 60 percent of cases and results from a normal pregnancy. Fifty-percent of these children have transient neonatal jaundice[7]. Development in early childhood is usually unremarkable, with the first signs of neurological impairment presenting as slight dementia and ataxia. Vertical supranuclear gaze palsy (VSGP) is the hallmark of this disease[7]. It first presents as an increase in saccadic latency, followed by subtle slowing of vertical saccades beginning in childhood. Voluntary vertical gaze is completely paralyzed in the late stages of the illness. The loss of postural tone usually occurs late in the illness and is evoked by a humorous stimulus (gelastic cataplexy); resulting falls may lead to repeated injury. Early childhood problems in school may be augmented by dysarthria, dysphagia and drooling. Dystonia, seizures and hepatosplenomegaly develop during early

childhood. Late childhood and adolescence is marked by increasing physical and intellectual disability. Psychiatric disturbances, including psychosis, may appear around the age of puberty. By this time, severe dysphagia may impede nutrition, and the upper airway is poorly protected. Death from pulmonary complications usually occurs in the teenage years or early adulthood[7].

Pathology

The pathologic features of NPC are that of a neurovisceral storage disease with foamy storage cells in the visceral organs and an accumulation of storage materials in neurons and glial cells of the nervous system. The most notable feature is splenomegaly, occasionally with associated hepatomegaly. Histologically, foamy cells (macrophages) and sea-blue histiocytes are seen in bone marrow preparations. In patients with a slowly progressive clinical course, the brain is often found to be atrophied. In severe cases of the disease, Purkinje and granular cells are lost and replaced with dense fibrillary gliosis. Those that survive demonstrate perikarya that are distended with storage materials. Cases with a prolonged course also show neurofibrillary tangles consisting of tau protein, similar to those seen in Alzheimer disease. Unlike Alzheimer disease, the tangles seen in NPC primarily affect the deeper layers of the cerebral cortex, thalamus, basal ganglia, hypothalamus, brain stem, and cingulate gyrus[7].

Pathophysiology

The cellular basis of NPC was unveiled while studying mutant BALB/c mice that have similar biochemical and pathologic findings to human NPC. In this murine model, a lesion in the intracellular processing of exogenous cholesterol was found[7]. This led to the finding that cultured NPC fibroblasts were deficient in their ability to synthesize cholesteryl esters during endocytic uptake of LDL and thus stored abnormal amounts of unesterified cholesterol[8]. Internalization of LDL, its transport to lysosomes, and lysosomal hydrolysis of cholesteryl ester are not impaired in NPC[8]. However, endocytosed cholesterol is sequestered in lysosomes and transport to the plasma membrane and the endoplasmic reticulum is impeded[8].

There are three homeostatic responses following cellular uptake of LDL cholesterol: (1) attenuation of de novo cholesterol synthesis; (2) depression of receptor mediated LDL uptake; and (3) activation of cellular cholesterol esterification[7]. The internalized and sequestered cholesterol of NPC fibroblasts fails to initiate the prompt homeostatic responses that serve to control and to balance intracellular cholesterol levels in normal cells[9]. Associated with the NPC mutation is a downregulation of the LDL receptor, a delayed suppression of 3-hydroxy-3-methylglutaryl-coenzymeA reductase (HMG-CoA reductase), and a defective stimulation of acyl-CoA:cholesterol acyltransferase expression[10]. These delayed metabolic responses lead to excessive intracellular accumulation of unesterified cholesterol which is primarily stored in lysosomes[9] [10].

Filipin staining has been used to assess the intracellular distribution of cholesterol. Filipin is a fluorescent probe that forms specific complexes with unesterified cholesterol[7]. In normal cells, filipin staining reveals cholesterol in the plasma membranes and some in intracellular structures. In contrast, staining of NPC cells reveals significant cholesterol in lysosomes[7]. This lysosomal sequestration is associated with impaired relocation to the plasma membrane, resulting in reduced amounts of cholesterol in the membrane.

Epidemiology and Clinical Genetics

NPC shows autosomal recessive inheritance with a prevalence in the general population of 1/150,000 live births[7]. Data concerning the epidemiology of the disease is limited, but the disease is panethnic. Two genetic isolates have been identified, French Acadians in Nova Scotia (formerly thought to be NPD) and Spanish-Americans in southern Colorado[3] [5].

Molecular Genetics

NPC has been demonstrated to result from mutations in either of two genes. The *NPC1* gene (mutated in 95% of patients) has been mapped to 18q11 and was isolated by positional cloning[2] [6] [1]. The *NPC2* gene (mutated in 5% of cases), mapped to 14q24[6], utilizes the mannose-6-phosphate receptor for

lysosomal targeting[4]. The NPC1 protein is an integral membrane protein that is primarily located in late endosomes and lysosomes, but is also found in smaller amounts within the Golgi apparatus. The protein contains 1278 amino acids and 13 transmembrane domains that are separated by luminal glycosylated loops[11]. Five of the transmembrane domains appear to be involved in cholesterol homeostasis. NPC1 also contains a cysteine-rich loop, a di-leucine lysosomal targeting motif, and a leucine zipper motif[11]. To date, 133 disease causing NPC1 mutations have been reported, with the majority of these being missense mutations. More than 1/3 of the mutations are concentrated within a cysteine-rich luminal loop[11].

Only three frequent mutations have been described. I1061T is found in patients of Western European descent, and accounts for 15% of the alleles in the United States[11]. This mutation is highly prevalent in patients from the Spanish-American isolate in southern Colorado and New Mexico[5].

Diagnosis

Diagnosis of NPC requires recognition of clinical signs and symptoms, with final confirmation coming from biochemical testing. The definitive diagnostic test is the analysis of dermal fibroblasts (a) morphologically by filipin staining to detect the intra-lysosomal accumulation of free cholesterol and (b) biochemically to monitor defective cholesterol esterification in LDL-challenged cells[4] [6]. If the suspected case comes from a line of NPC cases, diagnosis may be based on identification of the specific mutation. This is often difficult because the majority of cases are compound heterozygotes.

Treatment

While there is no specific treatment to stop the progression of NPC, supportive therapies are available. Cataplexy responds well to protriptyline or clomipramine[6]. The anticholinergic actions of these drugs may also be of benefit in treating drooling in patients with impaired swallowing. Standard anti-epileptic medications should be used to treat seizures, and anti-psychotics to treat psychoses. Dystonia may respond to anticholinergics and botox[6]. Physical therapy is essential to maintain fitness and mobility of

affected individuals. Swallowing must be regularly assessed and managed. Gastrostomy feeding may be needed once nutrition and prevention of aspiration become problematic[6]. An important aspect of NPC care is the multidisciplinary support for the affected individual and family. The diagnosis of this disease is devastating for families that now have to face the inexorable progress of the illness, and the lack of comprehension from family, friends, and many caregivers who are unfamiliar with the disease.

New Mexican Population

The New Mexico population has not been well studied since Wenger et al in 1977[12] in which nine cases of a lipid storage disease that they likened to Niemann Pick disease were described. They classified the clinical presenting picture into three types: (1) Infantile jaundice and hepatomegaly, made by diagnosis of neonatal hepatitis, in four cases; (2) Asymptomatic splenomegaly at age 1 to 5 years in four cases; and (3) Severe neurological deterioration between the ages of 6 and 14 in four cases[12]. Early neurological changes, manifested as delayed motor development, were demonstrated in seven of the nine, and school learning difficulties in eight of the nine patients. At the time of publishing, four of the nine had experienced severe neurologic deterioration. The most consistent neurologic finding was found to be vertical supranuclear gaze palsy in six of the nine participants. Histologically, seven of the nine were found to have large foamy histiocytes of the Niemann-Pick type, and variable numbers of sea blue histiocytes. The I1061T substitution, resulting from a T→C transition in exon 21 of the NPC1 gene, is highly prevalent in Hispanic patients from the Upper Rio Grande valley. Most of the families in the Upper Rio Grande valley can trace their ancestors to Spanish settlers who came up from Mexico in the late 17th and early 18th centuries[5]. It appears that one or more carriers of this mutation must have been present among this group of settlers. Due to founder effect, the carrier rate in this population may be as high as 1 in 30. The homozygous state of this mutation has been linked to the severe infantile phenotype of NPC[5].

In an attempt to understand the natural history of NPC in New Mexico, a historical review of eleven cases of Niemann Pick type C in patients of New Mexican descent was done. Clinical characteristics, and in particular, the neurological details of the disease are described in order to inform health care providers about Niemann-Pick type C in New Mexico. This will lead to earlier diagnosis and improved care of these patients and their families, and to inform other physicians about the natural history of this rare disease.

Clinical Material and Methods

Study organization. A standardized historical review of information collected from the medical records of the eleven known New Mexican patients with Niemann-Pick type C referred to the Pediatric Neurology Clinic at the University of New Mexico between 1970 and 2006. The database included demographics, birth and neonatal history, and documentation of the ages at which clinical signs (jaundice, splenomegaly, hepatomegaly, clumsiness), neurological signs (VSGP, dysarthria, a movement disorder [dystonia, dysmetria, or ataxia], cognitive difficulties [a decline in age-appropriate intelligence testing or a learning disability], seizures, spasticity, and loss of ambulation) first came to medical attention. Additional data from laboratory results include fibroblast cholesterol esterification studies and the results of neurophysiologic tests (EEGs and brain imaging where available.) The diagnosis of NPC was established by the presence of VSGP, bone marrow foam cells, defective cholesterol esterification and sphingomyelinase levels. Informed consent was waived due to this being a historical chart review. The study was approved by the University of New Mexico Human Research Review Committee prior to initiation.

Statistical methods. The age at which each neurological sign came to medical attention was determined, and the sequence of clinical events obtained for each patient. Descriptive statistics on patient demographics (age/sex), clinical signs, historic data, biochemical markers, neurophysiological tests, complications, treatment, and age at death were used to characterize the population of NPC patients.

In a retrospective review of the NPC clinical databases at The University of New Mexico Hospital, we identified eleven patients (six girls and five boys) in whom NPC had been diagnosed between 1970 and 2006. Information collected during the chart review ranged from the time of initial clinical contact to the most recent records available. We referred to clinic notes, operative reports, pathology results, and neuroimaging studies. Specific note was made to document general demographic data, clinical features consistent with the diagnosis of NPC, family history of NPC, presenting signs and symptoms, management of each patient and outcome.

Results

A diagnosis of NPC was established in all eleven patients; based on bone marrow biopsy, skin biopsy or sphingomyelinase levels. Table 1 provides a summary of the characteristics of cases. There were six female and five male patients. The majority of patients were of Hispanic descent, with 23% tracing relatives back to the Southern Colorado-Northern New Mexico area. A map of New Mexico indicating the area of residence of the patients is provided as Figure 1.

Figure 1. Location of Residence of 11 NPC patients in New Mexico.

The mean age of disease onset was 4.59 years (range newborn-11 years) with a mean age at diagnosis of 7.66 years (range newborn-16 years). Furthermore, the mean age of first clinical sign was 3.31 years (range newborn-11 years), and first neurologic sign at 6.55 years (range 18months-13 years). All patients exhibited features consistent with NPC to varying extents, ranging from jaundice, splenomegaly, VSGP, hypertonia and seizures. A family history for NPC was documented in two patients, with the later sibling receiving a diagnosis of NPC via prenatal amniocentesis.

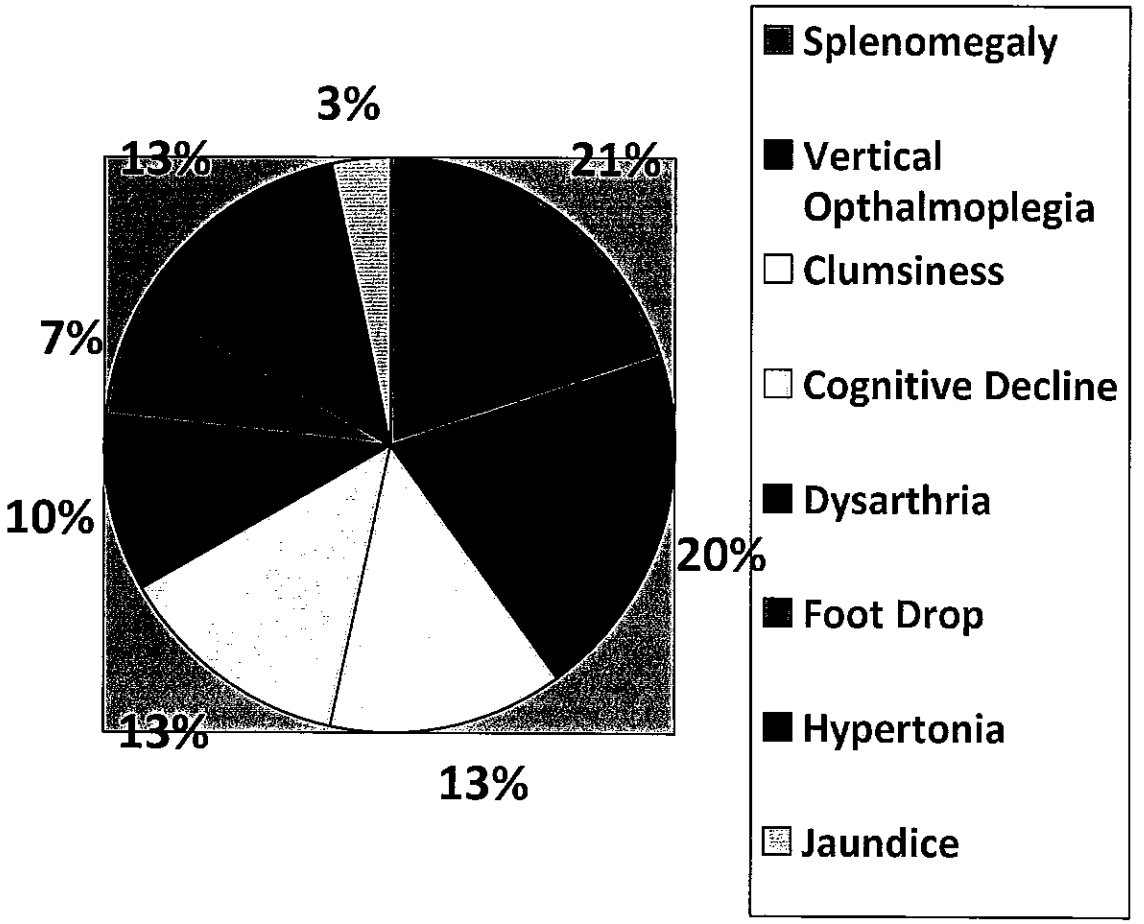
Table 1. Summary of Characteristics Obtained in 11 Patients with NPC.

Characteristic	Number of Patients
Sex	
Male	5
Female	6
Age at Diagnosis (years)	
Mean	7.66
Range	Newborn-16
Age at Presentation of first clinical sign(years)	
Mean	3.68
Range	Newborn-11
Age at Presentation of first neurologic sign(years)	
Mean	6.55*
Range	18months-13
Clinical Findings Consistent with NPC	
Hypertonia	9
Splenomegaly	8
VSGP	8
Seizures	5
Jaundice	4
Hepatomegaly	3
Psychosis	2
Epistaxis/Easy Bruising	2
Family History	
Present	2
Absent	9

* Medical Records did not indicate development of neurologic symptoms in two patients, data limited to one clinical note.

Nine of the eleven patients had documented occurrence of neurologic symptoms, with many displaying multiple symptoms. The most common presenting feature of NPC at disease onset was splenomegaly, exhibited by 54.5% of patients. This was also the most common sign present at time of diagnosis (Figure 2).

Figure 2. Symptoms present at time of diagnosis in eleven NPC patients.
More than one symptom may be present at time of diagnosis.



Despite the average age of onset of disease of 4.59 years old, the majority of patients did not display neurologic symptoms until after school age (Table 2). The most common neurologic symptom present was hypertonia, present in 81.8% of patients. VSGP was seen in 72.3% of patients, all with onset after 6 years of age. Psychosis was present in only two patients, developed between the ages of 14 and 16 years and required treatment of at least two weeks of inpatient psychiatry. The separation of NPC patients into birth-preschool onset and school-age onset based on the chronology of neurologic progression was used to identify those with a more aggressive course.

Table 2. Onset of Neurologic Signs in Type C Niemann Pick Disease.

Age at Onset	Cognitive difficulties (n)	Movement disorder (n)	VSGP (n)	Dysarthria (n)	Pyramidal Signs (n)	Nonambulant (n)
Birth-Preschool	3	2	0	2	1	1
School Age	6	7	8	6	7	6

Discussion

The eleven patients studied experienced disease onset at an average age of 4.6 years, with diagnosis not occurring until an average age of 7.66 years. Although NPC may present at any age, the classic presentation occurs in middle to late childhood, much later than was observed in our population. Classic NPC often presents with clumsiness and gait disturbance that quickly turns into frank ataxia. Observant parents may also notice impairment of vertical gaze as an early manifestation. The earliest clinical sign was splenomegaly in most cases, contrary to the report of neonatal jaundice in previous studies. The most common symptoms present at time of diagnosis were splenomegaly and vertical opthalmoplegia, each present in 19.4% of patients. Development of neurologic signs showed great variability; early detection of clumsiness and slurred speech occurred almost as frequently as those that did not exhibit neurologic symptoms until years after development of clinical signs.

For those patients in which information about age at time of death is known, the disease progression can be inferred from time of disease onset to time of death. Five patients met these criteria, with an average time for disease progression from onset to death of 10.2 years, with a range of 3 years to 15 years. Death statistics were also available for these five patients. The average age at time of death was 13.2 years, with a range of 3 years to 23 years. If one is infer that the patients lost to follow up died at the age of last clinical encounter, the average age of death would be 11.38 years, with a range of 18 months to 23 years. The most common cause of death was respiratory compromise leading to aspiration pneumonia in two

patients, an upper respiratory infection in one patient, sepsis in one patient and hematologic failure in one patient. Two patients are currently still alive; a male at 18 years old and a female at 29 years old.

The researchers were interested to find the variability of disease progression and severity in the two siblings afflicted with NPC. The first sibling displayed clumsiness and decreased clarity of speech at 3 years of age after having been diagnosed with splenomegaly at birth. By six years of age, his disease had progressed to VSGP, hypertonicity and dysarthria. Diagnosis was made at this time via bone marrow biopsy that demonstrated sea blue hisiocytes and decreased levels of sphingomyelinase. At the age of 7, the neurologic deterioration continued as he began to experience generalized motor seizures and decreased responsiveness. Autopsy performed following death at the age of 8 years revealed the cause of death to be aspiration pneumonia. Foamy histiocytes were present in the bone marrow, spleen and lymph nodes. When the mother of this patient became pregnant again, she sought out prenatal testing for her fetus. Through amniocentesis, NPC was diagnosed due to low sphingomyelinase levels. This child, also a son, displayed transient neonatal jaundice. It was not until 8 years of age that the family began to notice cognitive decline and absence of vertical eye movements. After hearing about experimental treatments for NPC in Mexico, the family decided to pursue calf RBC injections and magnet therapy in hopes of slowing the neurologic progression of disease. At 9 years of age, he began experiencing dysphagia and dysarthric speech. Between the ages of 11 and 12 years old he lost the ability to ambulate, began having seizures and developed nearly constant choreoathetoid movements. By 14 years of age he was unable to tolerate a normal diet secondary to increased episodes of choking. Prior to his death at 15 years of age from suspected respiratory compromise, he had lost the ability to speak, displayed gross hypotonia and appeared cachectic.

These two brothers, suspected to have the same disease causing NPC mutations displayed a noticeably different course of disease both in onset of symptoms, and progression of disease to time to death. This demonstrates that despite similar genetics, there is inherent variability in disease presentation.

Study Limitations and Future Questions

The primary limitation of this study originated in the study design. Due to this being a retrospective review of eleven clinical cases, many of the charts dated back to the 1970s. Over the years, there have been many advances in charting technique, vocabulary and laboratory and imaging reporting. Unfortunately, some clinical reports were illegible either due to poor paper quality or poor penmanship. For this reason, there are some data points that were not available for each patient, which made comparing progression and severity of disease in this instance difficult. Variations in individual reporting styles and exam maneuvers also led to differences among the medical records.

Although all eleven patients were seen at the University of New Mexico Division of Pediatric Neurology, many patients presented long after symptoms were initially noted by parents and primary care doctors. This may have resulted in recall bias as the history of disease was dependent on caregiver's memory. Another limitation was in frequency of clinical encounters. Two patients only had one clinical encounter, which limited the information available on these patients. Three other patients were lost to follow up at varying ages, leaving the authors to assume that death occurred shortly after last known clinical encounter.

Niemann Pick type C continues to be a rare neurologic disease with a higher than average incidence in populations from Southern Colorado-Northern New Mexico. Cases of mixed heritage do not rule out a founder effect in this disease. To further delineate the progression of disease in these patients, additional study is necessary. A prospective study of the longitudinal progression of Niemann Pick type C in New Mexican patients with special emphasis on the DNA mutations, treatment modalities implemented and effects would further help to shed light on this disease in our population. In our modern age, many diagnostic tests, and imaging techniques are available that were not when our original eleven patients were initially seen and diagnosed. Additionally, a collaborative regional registry among neighboring states (Colorado and Arizona) may identify additional patients.

Conclusions

Niemann Pick type C is a neurodegenerative lipidosis with significant phenotypic variability. The illness can present during the neonatal period with jaundice or remain latent until the second or third decade of life. The goal of this study was to characterize NPC in New Mexican patients, with special emphasis on the presenting signs and symptoms and disease progression. The separation of NPC patients into birth-preschool onset and school-age onset based on the chronology of neurologic progression identified patients with an aggressive course. In the New Mexican population, age at death ranged from 3-20+ years. In cases of complete dependence, painful dystonia and the need for surgical intervention, ranging from G-tube, to tracheostomy to orthopaedic intervention, was noted. Psychosis was present in two adolescent patients who exhibited later onset of disease, whereas previously psychosis was described in cases of adult onset. The New Mexican cohort of NPC patients displayed an earlier age of onset, and increased prevalence of vertical supranuclear gaze palsy as compared to previous study groups. These findings demonstrate the importance of examination of extraocular movements in the pediatric population. Niemann Pick type C is more prevalent in New Mexico and should be kept on the differential during neurologic work-up.

Appendix 1. Data Table of 11 New Mexican patients with NPC.

attached as separate document

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Appendix 1. Data Table of 11 New Mexican NPC patients.

Patient	Age of Onset	Age of Diagnosis	Method of Diagnosis	First Clinical Sign	First Neurologic Sign	SSx present at time of Dx	Rate of Progression to Disability	Complications	Treatment	Age at time of Death	Cause of Death	Ancestry	Family History
1	4 yo	6 yo	BM biopsy	Epistaxis (4yo)	Dystonia (13yo)	Splenomegaly	-	Splenectomy 8yo (1000gms) Pancytopenia (8yo)	Inpatient psych	Last known follow up 16yo		GPs-Southern CO-Northern NM Mom-South CO	None
2	Birth-prenatal U/S-HSM	1 yr 8mos	Skin Biopsy	Prenatal ascites on U/S, jaundice at birth	Arm twitching and failed speech development at 18mos	Arm twitching, HSM, clonus, DD	3 years	Splenectomy	Mannatech supplements, G-tube	Last known follow up at 3yo	Hematologic failure	Mom-German Dad-Mesilla NM	None
3	11 yo	15yo	BM biopsy	Difficulty writing legibly (11yo)	Gait changes, problems with vertical gaze and fine hand movements (11yo)	Clumsy, vertical opthalmoplegia, cognitive decline	-			Last known follow up at 15 yo		Santa Fe	None
4	8yo	11yo	BM Biopsy	Jaundice and splenomegaly at birth	Gait unsteady (18mos)	Slurred speech, clumsy, difficulty with vertical gaze, b/l foot drop, hypertonia, splenomegaly	15 years	Aspiration PNA, contractures	G-tube, bilateral LE tendon releases, Botox injections	23yo	Infection→ Sepsis	Mom-Espanola Dad-Espanola	None
5	3yo	6yo	BM biopsy with enzyme analysis	Splenomegaly at birth	Gait disturbance (3yo)	Dysarthria, vertical gaze prob, splenomegaly, hypertonia, ataxia	5 years			8yo	Aspiration PNA	Many generations in CO-NM area	yes
6-brother of 5	Birth-Prenatal amnio	birth	Prenatal amniocentesis displayed decreased sphingomyelinase	HSM and cognitive decline (8yo)	Loss of vertical eye movements (8yo)	Jaundice	15 years	RAD, contractures, scoliosis	Fetal cow RBC injections and magnet therapy in Mexico, G-tube, Seizure	15yo	Respiratory compromise	Many generations in CO-NM area	yes

Appendix 1. Data Table of 11 New Mexican NPC patients.

									medications				
7	4yo	8yo	BM biopsy with lysosomal enzyme confirmation	Splenomegaly, epistaxis, easy bruising (4yo)	Decreased motor function, disorientation (6yo)	Motor function decline, hand tremor, DD, absent vertical gaze, brisk DTRs, R foot drop	13 years	ADHD, Necrotizing fasciitis→anoxic injury→sepsis	G-tube, tracheostomy, calf RBC injection in Mexico, Seizure medications	17yo	URI	MGP-Penasco PGP-ABQ	None
8	11yo	15yo	Skin biopsy	Jaundice at birth, Falling when running, slowed speech(4yo)	Decreased up and down gaze (11yo)	Unusual hand movements, slowed speech, clumsy, dysarthria, problems with up and down gaze	7 years+ (alive)	Aspiration PNA, Bells Palsy	Inpatient Psych, G-tube, Psych meds	alive		M-Native American San Felipe D-Spanish heritage ABQ	None
9	2yrs 6mos	2yrs 6mos		HSM (2yrs 6mos)	-	HSM	-			Lost to follow up at 2yrs 6mos		MGP-Saudi Arabia	None
10	4 yo	16yo	Skin Biopsy	Cognitive decline, dysphagia, abnormal eye movments (4yo)	Dystonia, ataxia, head bobbing (4yo)	Cognitive decline, decreased coordination, decreased eye movement	26 years + (alive)	PNA x 3, AGE, Hypertriglyceridemia	Meds for agitation, insomnia, depression, spasticity. Zavesca trial to slow neurologic decline Tracheostomy	Alive		Espanola	None
11	3yo	3yo	Skin Biopsy	Splenomegaly (3yo)	-	splenomegaly	-	ADHD		Lost to follow up age 3yo		M-NNM Hispanic D-Caucasian	None