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Type 2 Gaucher disease among in Ashkenazi Jews

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Abstract

Patients with Gaucher disease (GD) are typicslly divided into 3 types based on the presence and rate of progression of the neurologic manifestations. While type 1 GD has a strong predilection in the Jewish Ashkenazi population, both other types lack such a propensity. We report the occuranve of type 2 GD in six pregnancies in three Jewish families in Israel, and also review seven additional cases of type 2 GD in Ashkenazi Jewish families patients reported in the literature. Geneotypic analysis of probands from the three Israeli families demonstrate that all carried two heterozygous glucocerebrosidase mutations. We conclude that type 2 GD in Ashkenazi Jews is extremely rare, but that phenotypically it does not differ significantly from this form of thee disease in other ethnic groups. The recurrence of multiple cases in families emphasizes the need for proper diagnosis and genetic counseling regarding type 2 GD among Ashkenazi Jews

Keywords

type 2 Gaucher; Ashkenazi Jews; Glucocerebrosidase; lysosomal storage disorder

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Introduction

Gaucher disease(GD), the most common lysosomal storage disease, results from the deficiency of the lysosomal enzyme glucocerebrosidase. Patients with GD have been divided into three types, based on the presence and rate of progression of the neurologic manifestations [1]. In type 1, the non-neuropathic form, clinical manifestations are restricted to the hematopoetic system and visceral organs. Type 2 and 3 both affect the central nervous system (CNS, but exhibit differing rates of neurological deterioration. Patients with type 2 GD (GD2), the acute neuropathic form, present with symptoms either prenatally or during infancy, and all die before the age of 3 years [1; 2], while type 3 GD, the sub acute neuropathic form, has a more protracted course. Both type 1 and 3 are genotypically and clinically heterogeneous [3]. Traditionally, type 2 was considered the most uniform type, but case studies demonstrate that this type is also clinically heterogeneous [4].

The 3 clinical forms are pan-ethnic in occurance, but type 1 has a strong predilection among Ashkenazi Jews, with an incidence of 1 in 350 to 450 live births, compared to an incidence of 1 in 40,000 to 50,000 in the general population. The incidence of type 2 and 3 in the general population are 1 to 500,000 and 1 to 50,000 respectively. An extensive search of the literature for patients with GD2 in Ashkenazi Jewish families revealed a surprising dearth of cases. We report six new cases of GD2 among three Israeli Jewish families, and summarize the descriptions of 7 additional cases reported in four families. Recognizing this fatal form of GD in Ashkenazi Jews is especially critical when counseling parents regarding prenatal diagnosis and recurrence risks..

Cases rReports

Family 1

A female baby, the first child born to non-related Ashkenazi Jewish parents and the product of an uneventful pregnancy, was healthy until the age 3 months when she developed recurrent vomiting, persisting over the next 3 months. On evaluation at 6 months, she was found to have followed the third percentiles for weight and height up to 3 months and then demonstrated a decline. On physical examination she appeared developmentally delayed and hypotonic, and had a spleen palpable at 6 cm. below the costal margin Laboratory studies revealed elevated liver enzymes (SGOT-83 U/L GIVE Normal limits (NL), alkaline phosphatase-184 U/L NL=) and pancytopenia (WBC-1.4 $\times 10^9$/L, hemoglobin-8 g/dL and platelates-90 $\times 10^9$/Luse conventiona units). The acid phosphatase level was 65.7 U/L NL A bone marrow examination revealed the presence of many Gaucher cells.

The child deteriorated with increased hypotonia, the development strabismus, swallowing difficulties and massive vomiting. At 8 months she underwent a Nissen fun duplication for massive gastro-esophageal reflux and a feeding gastrostomy was inserted. A brain CT did not show any abnormalities. Deterioration continued and she died at the age of 1 year. DNA analysis of child and parents revealed a compound heterozygosity formutations L444P and IVS2(+1) in the infant and both parents carried a mutant allele.

The family subsequently had two healthy children and then a pregnancy terminated because of a prenatal diagnosis of GD2. They then had a spontaneous miscarriage post amniocentesis. During their sixth pregnancy, prenatal diagnosis was not performed.

The sixth pregnancy resulted in a term male baby was born after an uneventful pregnancy and delivery. He had an Apgar score of 10 at 5 minuntes and a birth weight of 2750 grams. Jaundice was noticed 1 day post delivery. Physical examination at birth revealed a normal appearing baby with mild jaundice, hepatosplenomegaly with a liver palpated at 5.5 cm and

spleen at 6 cm below the costal margins. The neurologic examination was normal. The diagnosis of GD2 was confirmed after birth by enzyme and molecular studies. No Gaucher cells were seen on bone marrow aspiration.

His laboratory studies at presentation included a WBC-5.73 $\times 10^9$/L, Hemablobin level -15.6 mg/dL, and a platelet count of -89 $\times 10^9$/L. His total bilirubin level was 11.8 mg/dL with a direct bilirubin of 5.7 mg/dL. Liver function studies included a SGOT of 508 U/L, SGPT of 259 U/L, GGT of 240 U/L, LDH of 928 U/L, and an alkaline phosphatase of 436 U/L.

At the age of 4 days the patient was started on Imiglucerase (Cerezyme©) at a dose of 120 U/Kg/week. Deterioration was noticed by the age of 4 months, with a decreased response to sounds, and by 5 months there was decreased visual acuity and developmental delay, with progressive deterioration. Ophthalmoparesis was noticed at 8 months, together with a progressive difficulty in swallowing, which worsened gradually until his death at the age of 9 months.

EEG were preformed and interpreted as normal for age at 1 and 7 months, and MRI studies were normal for age at 3 and 9 months. He also underwent brain stem, auditory and somatosensory evoked potential (BERA) studies at 1.5 months revealing norrmal hearing but brain stem????. These changes were suggestive of a degenerative and demyelinative process. At 9 months, these functions deteriorated further, with severe bilateral dysfunction of the brain stem, but without involvement of the auditory nerves.

The child's bilirubin level remained stable for 2 months and ranged between 7–10 mg/dl and he underwent a complete evaluation for prolonged jaundice. Although ultrasound of the liver showed normal biliary vessels and a normal gall bladder, a liver scan with TC-DIPA showed an enlarged liver with no demonstration of bile vessels, compatible with biliary atresia. Liver biopsy also demonstrated biliary atresia, showing marked cholestasis with proliferation of bile ducts and fibrosis, and a few Gaucher cells. There was no evidence of hemolysis, intrauterine infection, cystic fibrosis, α1 antitrypsin deficiency or any other metabolic disease including galactosemia. A Casey operation was scheduled for the biliary atresia, but spontaneous resolution ?????occurred while waiting for the operation.

Lumbar puncture (LP) was performed on fouroccasions??: at the age of 2 and 5.5 months, with no evidence for enzyme activity at 1, 3 and 24 hours post transfusion of 600U (120U/Kg/w) imiglucerase. Lack of enzyme in CSF was confirmed in the LP sample 24 hours after treatment by Western blot analysis.

Family 2

A male baby was born after an uneventful 39 weeks pregnancy and delivery to a non-related Ashkenazi Jewish father and a Syrian Jewish mother. Apgar score was 10 at 5 min. Birth weight was 3440 gram. Strabismus was noticed soon after birth. At 10 weeks he had viral meningitis. At the age of 4 months, breast feeding was replaced by a vegetarian?? Soy based? Remedia® formula because of frequent coughing and failure to thrive. At the age of 5 months hypertonicity was noted and physiotherapy was initiated. Two months later a batch of thiamine deficient Remedia® formula was found to cause severe thiamine deficiency in a few exclusively Remedia® formula fed infants in Israel and so he was treated with thiamin supplement with some improvement in hypertonicity IS this really relevant?. An MRI of the brain was normal. at age 7 months he was admitted for respiratory distress and worsening bronchiolitis. Physical examination revealed generalized mild tachypnea of 32/min, oxygen saturation of 86 % on ambient air, hypertonicity and an unexplained hepatosplenomegaly with both liver and spleen palpable 3 cm below the costal margin. Ocular apraxia was noted on ophthalmologic examination. Lab studies on admission: normal CBC, SGOT 104 U/L,

GGT 94 U/L. and anacid phosphatase of 56.5 U/L (normal up to 6.6 U/L). Abone marrow aspiration showed storage cells suspected to be Gaucher cells. The beta-glucocerebrosidase level was 2 nmole/h/mg protein (healthy control 15.5 nmole/h/mg protein) confirming the diagnosis of GD Molecular workup disclosed a genotype of L444P/L444P+A456P.

The child recuperated from bronchioliti, but continue to have recurrent episodes of aspiration over the next 2 months, when he was readmitted for severe aspiration pneumonia with respiratory distress. He died at the age of 10 months due to respiratory failure.

Family 3

A third family of Ahkenaxzi Jewish background had a pregnancy terminated for hydrops fetalis. The fetes was found to be affected with GD2 based upon?????? The same family had a second fetus similarly affected that was also terminated.[5]. Both fetuses had geneotype ??????

Discussion

Table 1 summarizes our cases along with other previously reported cases in the literature. Another seven Jewish GD2 infants have been previously reported. A male diagnosed age 1 month and died aged 7 months he was reported in 1948 [7]. In 1962 two siblings were described, one symptomatic at 3 months of age who died aged 7 months and the second who died at 10 months of age [8]. In 1967 a 6 month old baby boy was diagnosed and died at age 10 months, and he had a brother who died at age 10 months [9]. Severe biliary atresia is not commonly reported, in GD2. However 7 of 10 infants with GD2 had increased liver enzymes [10].

Genotypes and phenotype of GD2 vary substantially with significant heterogeneity of both. Mutations reported in GD2 include deletions, fusion alleles and recombinant alleles. Phenotypically, patients may present as prenatal hydrops fetalis, infants with the collodion baby phenotype and as infants diagnosed after several months of life [11].

Among the three families which we describe, all were compound heterozygous. While there are more than 300 mutations known to cause Gaucher disease [12], five account for more than 96 percent of type 1 alleles in Ashkenazi Jews. Interestingly, only 2 of these mutations, L444P and IVS2+1, were found in our Jewish GD2 patients. L444P was seen singly and as part of a complex allele as L444P+A456P.

It could be asked s why GD2 is so rarely reported in Ashkenazi Jewish children. One reason is that the common N370S allele is not associated with neuronopathic disease and has a gene frequency of about 75% among Ashkenazim of all alleles. Other rarer alleles may have a similar effect but 10–20% of genes can contribute to type 2 or 3 disease phenotype??. If the chance of two Ashkenazi Jews not having a protective gene is 10–20%, 1–4% of all cases of Gaucher disease in Ashkenazi Jews would be expected to have GD2. Since at least 500 patients have been diagnosed in Israel we would expect to se additional GD2 patients..

The techniques used to genotype infants with GD@ is crucial. Because of the relative frequency of rare alleled, total gene sequencing is recommended. Care most be take to accureately characterize any allele carrying mutation L444P. Stone et al has found that among GD2 cases thought to be homozygous for L444P, all had at least one allele resulting from a recombinaion with the glucocerebrosidase pseudogene [5].. To our knowledge, no Ashkenazi Jewish L444P homozygote patients have been described.. Although the true homozygosity was thought to be incompatible with life???? Not in our papers![5], 31 patients homozygosoty for L444P have been described but these cases would seem to have a

modifying gene that protects them from early intrauterine death and gives very variable phenotypes [13], but as stated before, this has not been described in Jewish patients. Thus it would seem reasonable to presume that the reason for the rareness of this condition in Jews is due to the fact that the genotype L444P/L444P is lethal. None of this makes sense delete

Phenotypically, two of our patients were diagnosed at 6 and 7 months and the third was diagnosed in the first week of life because of GD2 diagnosed in a sibling. [5]. This distribution is similar to the time of diagnosis reported in the largest group of 31 patients with GD2 which included 7 cased with intrauterine death, 7 cases that were diagnosed at birth, and 17 patients that presented at the age of several months [5]. Clinical manifestations in our small series included hypotonia, strabismus and swallowing difficulties in one child, decreased response to sounds and decreased visual acuity followed by ophthalmoparesis??? and difficulty in swallowing in one child and ocular apraxia in the third child. The phenotype and the onset of symptoms does not differ from that described by Mignot et al [10]

The published life span for GD2 ranges from intrauterine death at 22 weeks of gestation to survival to the age of 30 months [5]. Patients have been grouped into two different goups, one a perinatal- lethal form and the other a more classic acute neuronopathic form.

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References

1. Knudson, AG.; Kaplan, WD. Genetics of the sphingolipidoses. In: Aronson, SM.; Volk, BW., editors. Cerebral Sphingolipidoses. New York: Academic Press; 1962. p. 396
2. Frederickson, DS.; Sloan, HR. Glucosyl ceramid lipidoses: Gaucher's disease. In: Stanbury, LB.; Wingarten, JB.; Frederickson, DS., editors. The Metabolic Basis of Inherited Disease. New York: McGraw-Hill; 1972. p. 730-759.
3. Bloom S, Erikson A. Gaucher disease-Norrbottnian type: Neurodevelopmental, neurological and neuropsychological aspects. Eur J Pediatr. 1983; 140:316–322. [PubMed: 6628452]
4. Sidransky E, Sherer DM, Ginns EI. Gaucher disease in the neonate: a distinct Gaucher phenotype is analogous to a mouse model created by targeted disruption of the glucocerebrosidase gene. Pediatric Research. 1992; 32:494–498. [PubMed: 1437405]
5. Stone DL, Tayebi N, Orvisky E, Stubblefield B, Madike V, Sidransky E. Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease. Hum Mutat. 2000; 15:181–188. [PubMed: 10649495]
6. Reissner K, Tayebi N, Stubblefield BK, Koprivica V, Blitzer M, Holleran W, Cowan T, Almashanu S, Maddalena A, Karson EM, Sidransky E. Type 2 Gaucher disease with hydrops fetalis in an Ashkenazi Jewish family resulting from a novel recombinant allele and a rare splice junction mutation in the glucocerebrosidase locus. Mol Genet Metab. 1998; 63:281–288. [PubMed: 9635296]
7. Schairer E. Die Gehirnveranderungen beim Morbus Gaucher des Sauglings. Virchows Arch. 1948; 315:395–406. [PubMed: 18882045]
8. Banker, BQ.; Miller, JQ.; Crocker, AC., editors. The cerebral pathology of infantile Gauchers disease. New York: Academic Press; 1962.
9. Adachi M, Wallace BJ, Schneck L, Volk BW. Fine structure of central nervous system in early infantile Gaucher's disease. Arch Pathol. 1967; 83:513–526. [PubMed: 6024729]
10. Mignot C, Doummar D, Maire I, De Villemeur TB. Type 2 Gaucher disease: 15 new cases and review of the literature. Brain Dev. 2006; 28:39–48. [PubMed: 16485335]
11. Tayebi N, Stone DL, Sidransky E. Type 2 gaucher disease: an expanding phenotype. Mol Genet Metab. 1999; 68:209–219. [PubMed: 10527671]

12. Koprivica V, Stone DL, Park JK, Callahan M, Frisch A, Cohen IJ, Tayebi N, Sidransky E. Analysis and classification of 304 mutant alleles in patients with type 1 and type 3 Gaucher disease. Am J Hum Genet. 2000; 66:1777–1786. [PubMed: 10796875]

13. Goker-Alpan O, Hruska KS, Orvisky E, Kishnani PS, Stubblefield BK, Schiffmann R, Sidransky E. Divergent phenotypes in Gaucher disease implicate the role of modifiers. J Med Genet. 2005; 42:e37. [PubMed: 15937077]

14. Orvisky E, Sidransky E, McKinney CE, Lamarca ME, Samimi R, Krasnewich D, Martin BM, Ginns EI. Glucosylsphingosine accumulation in mice and patients with type 2 Gaucher disease begins early in gestation. Pediatr Res. 2000; 48:233–237. [PubMed: 10926300]

Table 1

clinical feature of GD2 ashkenzi Jews patients

Case No.	Source	Sex	Age at Diagnosis [m]	Mutation	Disease in family	Carriers in family	Age at Death [m]
1	This study	F	6.5	L444P / IVS2(+1)	subsequent 1 prenatal Dg 1 brother	1 subsequent sister	12
2	This study	F	1st week	L444P / IVS2(+1)	1 sister 1 prenatal Dg	1 sister	9
3	This study	F	Prenatal	ND	2 sisters		Pregnancy terminated
4	This study	M	7	L444P/L444P+A456P	none	not known	10
5	Schairer at al [7]	M	1	ND	none (?)	not known (?)	4
6	Banker et al [8]	M	3	ND	1 brother	NA	7
7	Banker et al [8]	M	Post mortem	ND	1 brother	NA	10
8	Adachi et al [9]	M	6	ND	1 brother	NA	10
9	Adachi et al [9]	M	NA	ND	1 brother	NA	10
10	Reissner et al [6] Orvisky at al [14]	NA	Prenatal	Rec A/IVS 10 + 2T>G	1 sibling	Both parents	Teminated pregnancy week 22
11	Reissner et al [6] Orvisky at al [14]	NA	Prenatal	?	1 sibling	Both parents	Teminated pregnancy week 11