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Metachromatic Leukodystrophy: a Case of Triplets with the Late Infantile Variant and a Systematic Review of the Literature

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Abstract

Metachromatic Leukodystrophy is a rare disorder with great clinical variability. We report the first case of triplets with the late infantile form of the disease and their systematic progression of symptoms. We reviewed the literature and identified all human studies that reported new cases since 1921. We analyzed survival by decade to assess the impact of historical changes in management of care. Mean age at death and 5-year survival from onset of symptoms for late infantile, juvenile and adult phenotype were 4.2 years and 24.9%, 17.4 years and 70.3%, and 43.1 years and 88.6% respectively. 5-year survival of cases reported after 1990 was significantly better than cases reported before 1970 in all subtypes of metachromatic leukodystrophy (late infantile: 52% vs. 14%, juvenile: 100% vs. 46%, adult: 95% vs. 67%). Survival in the late infantile subtype was worse than in other subtypes. Survival significantly improved over time in all subtypes.

Keywords

metachromatic leukodystrophy; demyelination

Introduction

Metachromatic Leukodystrophy is an autosomal recessive inherited disease with a deficiency of the lysosomal enzyme arylsulfatase A1. This results in accumulation of sulfated glycolipids in the myelin sheaths of the nervous system and to a lesser extent in visceral organs like liver, gallbladder and kidney1. In the central nervous system this accumulation results in progressive demyelination. metachromatic leukodystrophy is

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subdivided into three clinical subtypes according to age of onset: late-infantile, juvenile and adult 1,2. The impact of genetic and environmental factors is not well understood.

Clinical, radiological and laboratory findings in these subtypes have previously been reported, however the composite overall survival of these patients remains unknown. To explore this further we reviewed the literature since description of the first metachromatic leukodystrophy patient in 19213. We describe triplets with late infantile onset metachromatic leukodystrophy, two identical and one fraternal, who share a common environment, have the same genetic mutations and demonstrate a remarkable synchronicity in neurological decline.

Case Report

The triplets were born via cesarean section at 29 weeks gestation. Two boys were identical twins and one was fraternal. The mother had suffered from fetal alcohol syndrome and had a history of developmental delay and depression. Aside from bed rest, the pregnancy was unremarkable. Their Apgar scores were 8 and 8 at 1 and 5 minutes respectively. They had a typical neonatal intensive care unit course, which included evaluation for sepsis and possible necrotizing enterocolitis, apnea and bradycardia. Cranial ultrasounds revealed no intracranial hemorrhage. The triplets were in the neonatal intensive care unit for approximately two months and then discharged home on routine oral feedings without a requirement for supplemental oxygen or medications.

Initially, developmental progress was achieved in all domains. The triplets rolled over at 10 months, sat up at 11 months, began crawling at 12 months and walking at 15 months. By 16 months they were speaking in 2 to 3 word sentences, feeding themselves with utensils and adequately navigating through fine motor tasks.

Around 16 months of age, there was a rapid and striking change in development in the three boys. Regression in motor skills was recognized first. The gross motor skills were more affected than the fine motor skills. They lost their ability to walk, crawl, sit up, and roll over. Loss of head control followed. During that time, the family noted left-sided ptosis in all three. Over the next few weeks their speech and language skills declined to the expression of one-syllable words. They also lost fine motor skills and pincer grasp. Deep tendon reflexes were preserved.

A battery of metabolic and genetic testing was performed, including plasma amino acids, urine organic acids, cerebrospinal fluid neurotransmitters and amino acids. All were within normal range. A brain MRI showed T2 hyperintense periventricular lesions that were difficult to distinguish from normal terminal myelination zones (Figure 1A). Measurement of arylsulfatase A activity in leukocytes showed levels of 4.5, 7.8 and 8.1 nmol/h/mg protein in the triplets versus a normal mean of about 80 nmol/h/mg protein. Urine analysis showed an increase in sulfatides, confirming the diagnosis of metachromatic leukodystrophy. DNA analysis revealed one copy of the common LI mutation (G459+1A) in each child. The other mutation in these children is a deletion starting between intron 6 and exon 8 and extending

beyond the end of the gene. These are both severe mutations likely to lead to a late infantile presentation.

By 24 months of age, they developed progressive truncal hypotonia with peripheral spasticity. All three displayed persistent fisting of the hands, facial weakness, and diffuse hyperreflexia. A nerve conduction study revealed normal conduction velocities in the median, ulnar, tibial and peroneal nerves.

At 36 months of age they began to complain of pain with minimal passive movement of the limbs, particularly the legs. This was aggravated during activities such as dressing and physical activity but did not occur at rest or when unprovoked. Pain episodes led to increased dystonia and worsened spasticity. Progressive lower extremity spasticity, especially in the gastrocnemius, led to plantar flexion of the feet at rest. Baclofen was initiated to alleviate the worsening spasticity. Hip radiographs did not reveal uncovering of subluxation of the femoral heads. Regarding development, they continued to use single words, identify body parts through pointing, smile and have meaningful interactions with their parents and caregivers.

In the subsequent months they developed oromotor dysfunction and difficulty with weight gain. A swallow study documented aspiration of thin liquids. All three children underwent surgery for gastric tube placement. For the next several months, no aspiration problems or airway obstruction occurred. None of the triplets had seizures, either clinically or electrographically. Gastric motility slowed and continuous feeds with frequent breaks and venting were required to maintain comfort. Gabapentin was initiated to help with neuropathic-enteral pain. Over time, the boys' nutritional status declined secondary to the feeding intolerance. They developed iron deficiency. A follow-up MRI was performed at 4 years of age and confirmed radiographic progression of white matter disease in all three (see Figure 1B). The boys became less interactive and required increased levels of voice and tactile stimulation to respond.

Literature Review Methods

We undertook a systematic review to identify human studies of metachromatic leukodystrophy that reported new cases. We searched PubMed from 1920 through June 30th, 2006 using the terms: "Metachromatic", "Leukodystrophy", "MLD" (metachromatic leukodystrophy), and combinations of these terms. Additionally, we manually reviewed the reference lists of all the other publications for other potential data sources. This search was repeated four times by two reviewers (AM and HWM) independently. Data abstraction was done by one reviewer (AM or HWM or FE) and verified independently by one of the other two reviewers. We only included studies that reported new cases with definite diagnosis of metachromatic leukodystrophy. We used the subtypes as assigned by the original publication. In the absence of definitive subtype, we assigned the subtype considering manifestations, its rate of progression and age at the onset of symptoms (late infantile: 0.5–4 years, juvenile 4 – 16 years, adult > 16 years). Studies were excluded if they did not provide either: a) age at the onset of symptoms, or b) age at death or last follow-up. We also

excluded studies limited exclusively to patients receiving transplants. Sufficient information on ethnicity of the patients was not available and thus it was not included in the analysis.

Survival analyses, as function of years since onset of symptoms, were performed using the Kaplan-Meier and Cox proportional hazard method and log-rank test using the statistical software package STATA 8 (College station, Texas). When the date of death was not known, the record was censored in the analysis as of the date of last follow-up. To assess the impact of historical changes in management of care we analyzed survival by decade in the three phenotypes.

Results

We identified 142 eligible studies and information about 303 cases was extracted. The first included case occurred in 1921,reported by Witte et al3. Ninety-eight patients of the late infantile subtype from 50 studies4–53, 78 patients of the juvenile subtype from 42 studies22, 24, 26, 27, 30, 49, 50, 54–88, and 127 patients of the adult onset subtype from 69 studies3, 7, 14, 22, 27, 30, 81–144 were identified and are summarized in Table 1.

Symptoms in the late infantile group were poorly reported in general but well illustrated in our case report. Out of 38 late infantile cases for which detailed clinical features were provided, 61% patients presented with motor or gait abnormalities and 39% patients presented with seizures. In the juvenile group, 66% presented with inattention and difficulties at school, 26% with gait difficulties, 18% with tremor or ataxia, 13% with neuropathy and 5% with seizures. In the adult group, 72% presented with dementia and behavioral difficulties, 16% with psychosis and schizophrenia, 28% with neuropathy, and 12% with seizures.

Survival

In all three subtypes, both sexes were equally affected, and there was no gender difference in survival (late infantile p=0.115, juvenile p=0.955, adult p=0.688). In the late infantile subgroup, 62/98 (63.3%) of patients were reported to have died at a mean age of 4.2 years. In the juvenile subgroup, 30/75 (38.5%) patients died at a mean age of 17.4 years. In the adult subtype, 35/127 (28%) died at a mean age of 43.1 years. 5-year and 10-year survival in these types are depicted in table 1 and figure 2.

When comparing survival in patients whose manifestation started before two years of age (n=79) with patients who manifested at and after two years (n=19), we did not find any significant difference (p=0.765). Similarly in the juvenile subtype, a cut-off of six years of age at initial manifestation did not affect the survival [4–6 group (n=13) versus 6–16 group (n=61), p=0.365]. However, the 19 patients whose age at onset of disease was between two and four years (classified as late infantile) performed significantly worse than those 13 patients whose disease started between four and six years (classified as juvenile) ($p<0.001$). Overall survival was better in patients with the adult subtype than the late infantile or juvenile subtype ($p<0.001$ and p=0.005 respectively).

The analysis by decades (1921–2006) showed that survival significantly improved over time in all subtypes as depicted in figure 3. 5-year survival of cases reported after 1990 was significantly better than the cases reported before 1970 in all subtypes of metachromatic leukodystrophy.

Discussion

In this study we described the first case of triplets with the late infantile form of the disease and their systematic and synchronous progression of symptoms. We performed a pooled survival analysis of 303 metachromatic leukodystrophy cases published as single case reports and small series over a nearly 80-year period in order to shed more light on the natural history of metachromatic leukodystrophy than was previously available. Survival in the late infantile subtype was worse than the other two subtypes. Adult patients had the most favorable disease course, with a median survival from the time of diagnosis of 25 years. Interestingly, we found an increase in survival in all age groups over time, and in absence of disease modifying or curative therapies this likely reflects improvement in supportive care alone. Survival was similar in patients within the same subtype and did not change with age at symptom onset within subtype.

As our case report of triplets with progressive spastic body paresis demonstrates, disease progression in the late infantile form of metachromatic leukodystrophy is remarkably systematic. As in 61% of reported cases, the triplets' first symptom was motor regression. They lost their ability to walk within a few days of each other due to rapid progression in lower extremity muscle tone. Left-sided ptosis was noted in all three at 32 months of age. Significant gastric dysmotility led to major feeding discomfort and malnutrition. The late infantile form of this disease is a devastating diagnosis of limited life expectancy.

Our review of historical data found that only 50% of infants with metachromatic leukodystrophy survive beyond 2.7 years after their 1st symptoms. The 5-year survival was 25%. Of note, however, milder cases may have been under-reported. Caution must be exercised in extrapolating the rate of progression from the age of death. In our experience, a rapid clinical decline does not necessitate short survival. With measures of gastric tube placement, hygiene precautions and adequate antibiotic coverage, patients can survive in a vegetative state for months and years. We note that 5-year survival has improved since 1970. Despite the fact that no changes in treatment occurred, survival improved, probably due to improved supportive care.

The initial symptoms in the juvenile and adult metachromatic leukodystrophy patients are predominated by behavioral difficulties. The insidious nature of cognitive symptoms poses problems in early recognition and challenge clinicians across disciplines. Some metachromatic leukodystrophy patients with juvenile disease can benefit from hematopoietic stem cell transplantation if performed early in the course 66, 145. Recently, adult patients with metachromatic leukodystrophy have also been transplanted. Better techniques for early diagnose are urgently needed.

While the present therapeutic options for metachromatic leukodystrophy are very limited, recent progress in the technology of enzyme replacement and gene therapy has been made146. Animal models of metachromatic leukodystrophy have been partially cured by both interventions146, 147. It remains to be seen whether enzyme replacement therapy will have long-term benefit for the central nervous system; one may envisage that it could be used in combination with other approaches. The impact of novel therapies will have to be measured against the defined clinical variability presented in our study. The survival patterns we derive from a review of the literature cannot replace a carefully conducted natural history study in order to establish the rate of progression of metachromatic leukodystrophy.

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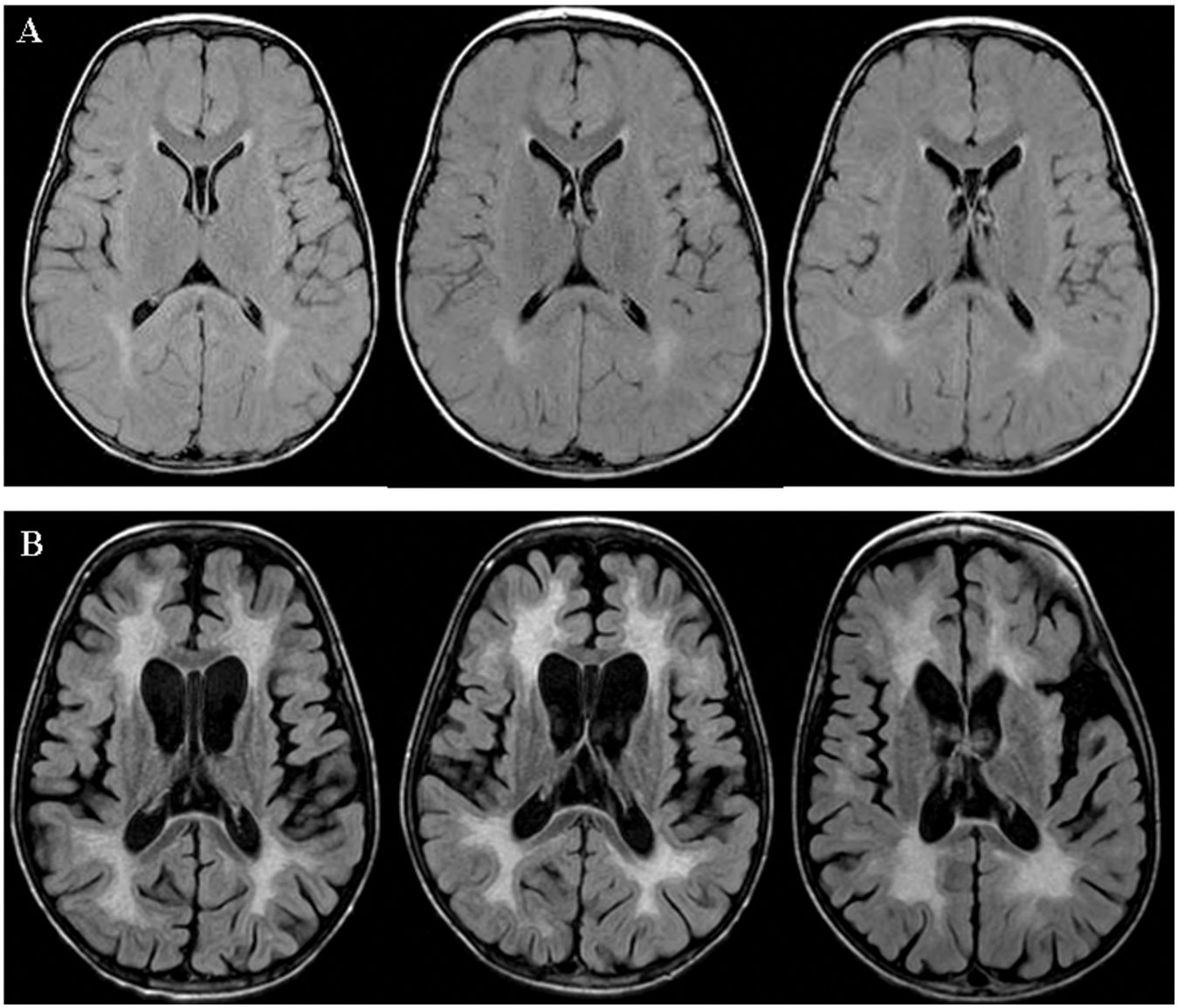

Figure 1.

Brain MRI of triplets at 15 months (**A**) and 4 years (**B**) of age. Axial fast fluid-attenuated inversion recovery (repetition time = 10,000 milliseconds, echo time = 140 milliseconds, inversion time: 2200 milliseconds) images are shown.

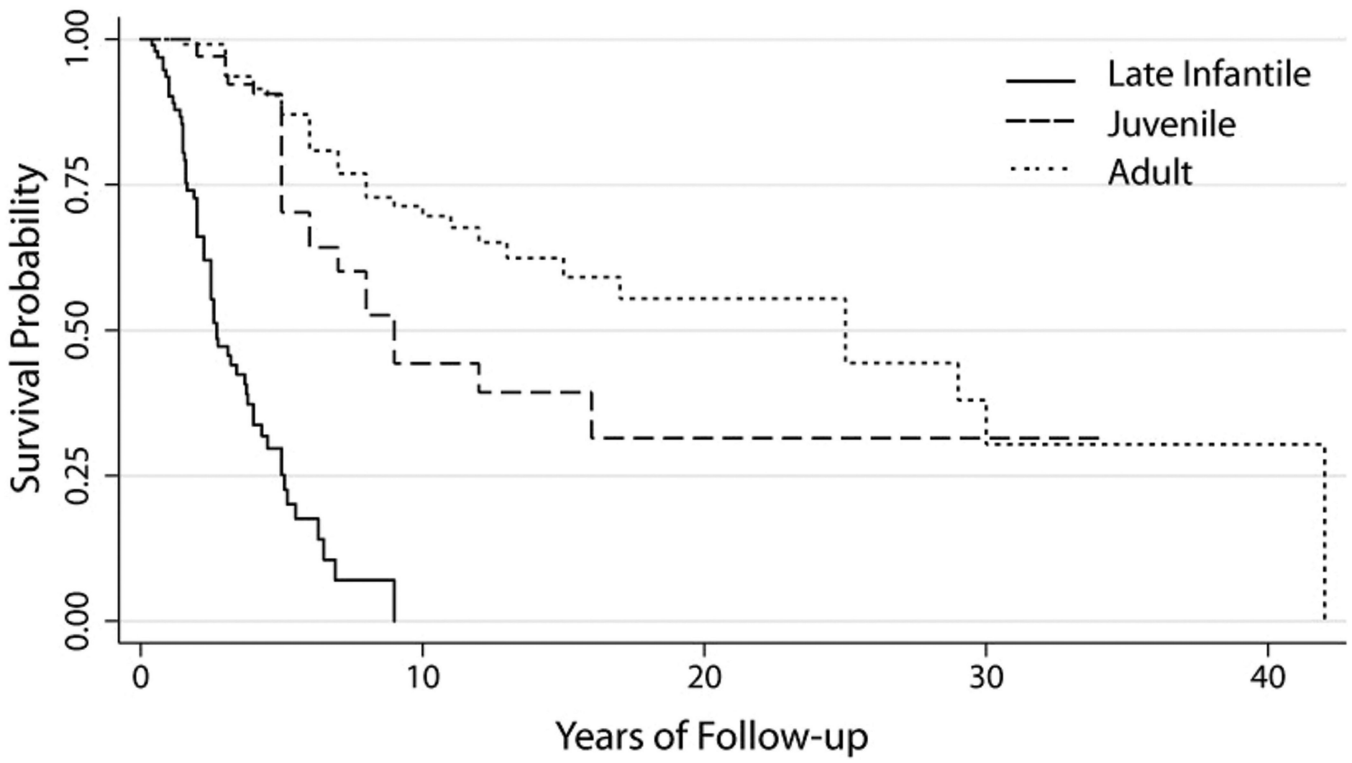

Figure 2.
Comparison of survival probability from onset of symptoms in the three subtypes of metachromatic leukodystrophy.

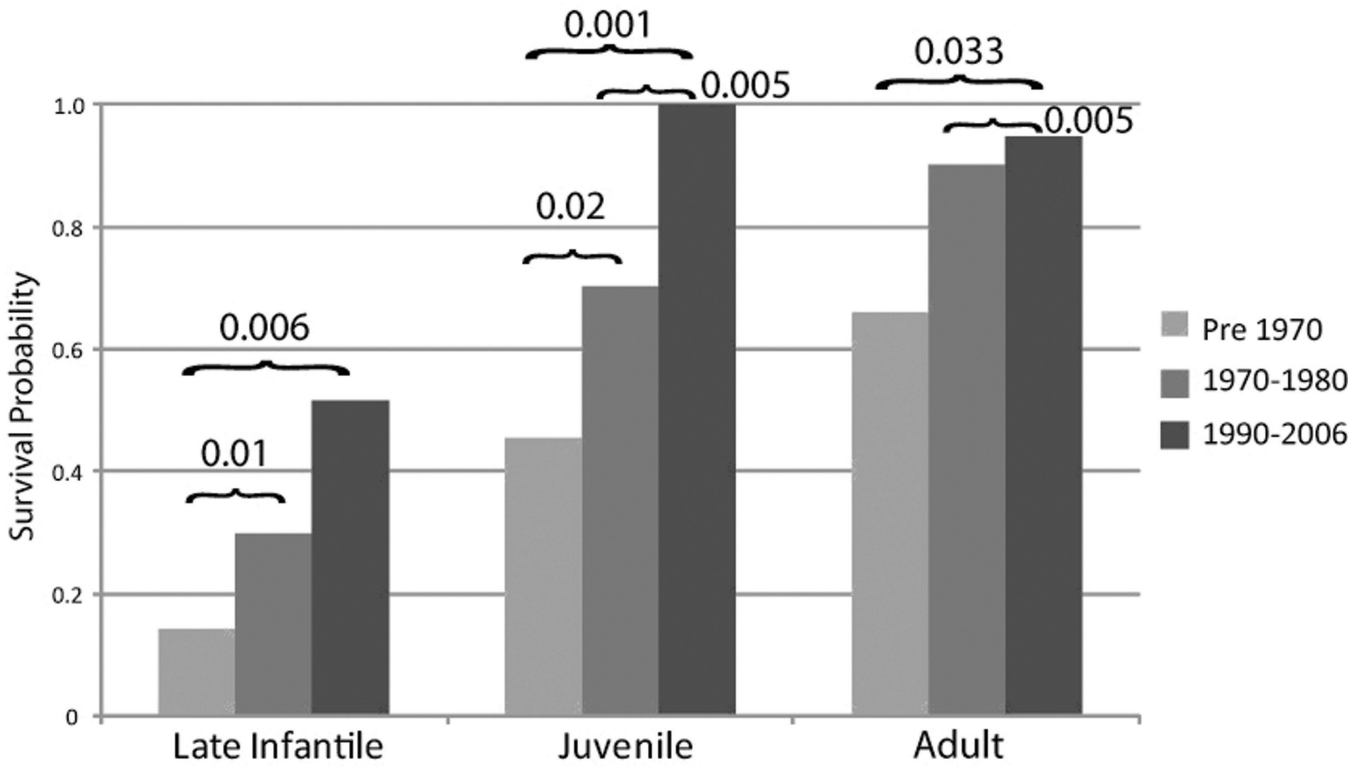

Figure 3.
Comparison of 5-year survival probability in three subtypes over time.

Table 1

Characteristics of three subtypes of Metachromatic Leukodystrophy.

Phenotype	N	Sex	Age of onset in Years		Follow-up Period in Years		Survival Probability**		
		# of Male(%)*	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Median	5-Year	10-Year
Late Infantile	98	36 (45%)	1.49 (0.5)	1.5 (0.69)	2.6 (1.8)	2.1 (2.3)	2.7	25.1%	0%
Juvenile	78	36 (49%)	10 (4.3)	10 (7)	6.3 (5.3)	5 (5)	9	70.3%	44.3%
Adult	127	67 (52.7%)	27.2 (10.1)	25 (14)	8.8 (8.4)	6 (8)	25	87.1%	69.6%

SD: Standard Deviation, IQR: Interquartile range

* Sex of 23 patients was not reported in the study.

** Survival as a function of years since onset of symptoms