

# A Rare Presentation of Childhood Pompe Disease: Cardiac Involvement Provoked by Epstein-Barr Virus Infection

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**ABSTRACT.** Myocarditis attributed to Epstein-Barr virus (EBV) as the sole cause is a rare manifestation. Myocarditis ascribed to EBV infection in combination with other factors has been reported in a few more cases. We report a child who experienced active EBV infection and later, at 19 months of age, received a diagnosis of Pompe disease (acid  $\alpha$ -glucosidase deficiency) with predominant cardiac involvement. The cardiac symptoms resolved at the end of the EBV infection. When the patient was recently seen, at 8 years of age, she had an increased left ventricular wall thickness but normal cardiac function. DNA analysis identified this patient as compound heterozygote for a mutant Tyr292Cys and a null allele. In light of genotype-phenotype correlation, it is notable that a Spanish patient with a functionally similar genotype (Tyr292Cys/Arg854Stop) also had childhood Pompe disease with peripheral muscular involvement. *Pediatrics* 2002;109(4). URL: <http://www.pediatrics.org/cgi/content/full/109/4/e65>; *cardiomyopathy, Pompe disease, Epstein-Barr virus, acid alpha-glucosidase.*

ABBREVIATIONS. EBV, Epstein-Barr virus; IgM, immunoglobulin M; IgG, immunoglobulin G; EBNA, Epstein-Barr B nuclear antigen.

Myocarditis is a rare manifestation of Epstein-Barr virus (EBV) infection. To our knowledge, only 3 cases of myocarditis in which EBV infection was thought to be the sole cause have been reported.<sup>1-3</sup> In a few more cases, the myocarditis was ascribed to other factors in combination with EBV infection.

We present a child who experienced active EBV infection and later received a diagnosis of Pompe disease (acid  $\alpha$ -glucosidase deficiency) with predominant cardiac involvement. When the EBV infection resolved, the heart improved dramatically and the clinical picture became that of childhood Pompe disease with predominant peripheral muscle involvement.<sup>4</sup> Mutation detection of the gene for acid  $\alpha$ -glucosidase identified the patient as compound heterozygote for a mutant Tyr292Cys and a null allele.

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## CASE REPORT

In March 1995, a 19-month-old native Dutch girl was admitted to our hospital because of persistent high serum transaminases thought to be attributable to infectious mononucleosis. She was well until September 1994 (13 months of age), when she was seen by a pediatrician, because of splenomegaly, discovered during a routine examination at a welfare center. At that moment, the immunoglobulin M (IgM) titer against EBV was 128, the immunoglobulin G (IgG) titer was 1250, and the IgG anti-Epstein-Barr B nuclear antigen (EBNA) was <20. During the next 6 months, she tired easily and developed muscular weakness. She had no fever. The serum transaminases were persistently high (aspartate aminotransferase, 299–384 U/L; alanine aminotransferase, 220–248 U/L) with the following EBV titers: IgM, <32; anti-capsid IgG, 2500 to 5000; anti-EBV early antigen IgG, 1250; and anti-EBNA IgG, 160 to 320.

On admission to our hospital, she had normal heart sounds and no hepatic or splenic enlargement. She had muscular weakness, especially of the shoulder muscles, and weak tendon reflexes. On palpation, the muscles were normal. No dysmorphic features, including macroglossia, were found. Creatinine-phosphokinase levels were repeatedly high (918 and 646 U/L, with a normal muscle-brain fraction). A thoracic radiograph showed cardiomegaly (cardiothoracic ratio 0.6, see Table 1). The electrocardiogram showed a short P-R interval (0.065 seconds at a cardiac frequency of 100/min) and massive left ventricular hypertrophy (S in V1 28 mm and R in V6 38 mm). Echocardiography revealed an enlarged, diffuse, hypertrophic left ventricle with decreased contractility (see Table 1). Systolic and diastolic left ventricular dimensions were far above the 95th percentile for normal Dutch children.

Both muscle ultrasound and electromyogram were normal. Because of progressive muscular weakness, initially thought to be attributable to polymyositis, a biopsy of the quadriceps muscle was taken. The histologic picture showed predominant lysosomal storage of glycogen, which is characteristic of Pompe disease. This diagnosis was confirmed by measurement of acid  $\alpha$ -glucosidase, which showed enzyme activity below detection level in both leukocytes and cultured skin fibroblasts using glycogen (respectively) glycogen and 4-methylumbelliferyl  $\alpha$ -D-glucopyranoside as substrate.<sup>5</sup>

DNA analysis was performed to establish the patient's  $\alpha$ -glucosidase genotype. DNA analysis in leukocytes from this girl did not show any of the 3 most common mutations in the Netherlands (IVS1 [-13 G], 525 del T, and del exon 18 allele).<sup>6,7</sup> Full-length cDNA sequence analysis by reverse transcriptase-polymerase chain reaction<sup>7</sup> led to detection of a single, apparently homozygous, A to T transversion at position 875 in exon 5, resulting in amino acid substitution Tyr292Cys. However, confirmation of this mutation by polymerase chain reaction sequence analysis of genomic DNA indicated that the patient was actually heterozygous for 875A→T. The combination of both sequence data sets indicates that the seemingly normal 875A allele is not expressed at the mRNA level. Compound heterozygosity of this type is not unusual in Pompe disease.<sup>6</sup>

$\alpha$ -Glucosidase cDNA harboring the 875T mutation and wild-type cDNA were cloned in the eukaryotic expression vector pSHAG5 and expressed in COS cells to study the functional effect. Transfection of the wild-type cDNA to COS cells showed normal activity of acid  $\alpha$ -glucosidase, whereas transfection of the mutated cDNA to COS cells did not. The Tyr292Cys substitution fully abolishes the catalytic activity of acid  $\alpha$ -glucosidase for the arti-

**TABLE 1.** Radiographic Cardiothoracic Ratio and Echocardiographic Parameters

Date	Radiographic Cardiothoracic Ratio	Left Ventricular Inner Diameter, Diastolic/Systolic (mm)	Posterior Wall Thickness, Diastolic/Systolic (mm)	Interventricular Septal Diameter, Diastolic/Systolic (mm)	Fractional Shortening	Body Weight (kg)
March 1995	0.60	37/28	7/10	7.5/10	0.22	10
January 1996	—	32/26	7/10	7.5/9	0.20	12
March 1997	—	36/24	8/11	8/9.5	0.33	13
October 1998	0.45	36/23	8/13	8/11	0.35	14
May 2001	0.48	32/22	8/12	14/15	0.31	19

Left ventricular inner diameter, posterior wall thickness, and interventricular septal diameter were measured by echocardiography in the parasternal short axis view.

cial substrate 4-methylumbelliferyl  $\alpha$ -D-glucopyranoside, but, interesting, approximately 10% of the activity is left with glycogen as the natural substrate.

During follow-up of this patient, the peripheral muscular power diminished further. The girl became wheelchair dependent and has needed ongoing artificial ventilation since April 2001. Initially, the dimensions and the contractility of the left ventricle of the heart returned to normal, as did the cardiothoracic ratio on radiograph (see Table 1). Recent echocardiography revealed an increased ventricular wall thickness, with still normal contractility. EBV titers stayed high for 1 year but normalized later (IgM, <32; anti-capsid IgG, 256; anti-EBV early antigen, < 32; and anti-EBNA, 64).

### CONCLUSION

At the age of 7 years, the patient meets all criteria for a typical presentation of childhood Pompe disease.<sup>4,8</sup> The transient cardiomegaly is a remarkable finding. In classic infantile-onset disease, cardiomegaly presents at birth and aggravates. In late-onset disease, cardiomegaly is absent. Skeletal muscle weakness, by contrast, is a common feature of all clinical subtypes.

The acid  $\alpha$ -glucosidase activity in leukocytes and fibroblasts of our patient was below detection level, but mutation analysis indicated that some residual activity for the natural substrate persisted. It might have been just enough to prevent cardiomegaly under normal circumstances but just too little under the challenge of an EBV infection. We realize that this theory for explaining the transient cardiomegaly builds heavily on the value of mutation analysis. The latter, however, seems justified in light of a recent report of a Spanish patient with childhood/juvenile Pompe disease.<sup>9</sup> This Spanish patient, too, was compound heterozygote and carrier of the Tyr292Cys allele but combined with the silent Arg854Stop allele.<sup>9,10</sup>

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