# 조혈모세포 이식으로 치료한 Late infantile—onset globoid cell leukodystrophy 환자 1예

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# Late Infantile-Onset Globoid Cell Leukodystrophy: Treatment using Hematopoietic Stem Cell Transplantation

Globoid cell leukodystrophy is a rare autosomal recessive disorder of the brain white-matter caused by galactosylceramidase deficiency; the disorder is classified into four types based on the age of onset. Approximately 80-85% of patients have an early infantile form, while 10-15% has a late infantile form. Globoid cell leukodystrophy leads to a progressive neurological deterioration, and affected patients rarely survive more than 2-3 years. Although many different treatments have been investigated over several decades, further research is still needed. Hematopoietic stem cell transplantation is the standard treatment for globoid cell leukodystrophy. Here, we report a case of symptomatic late-infantile globoid cell leukodystrophy treated with stem cell transplantation. After transplantation, disease progression ceased and cognitive and motor function improved. And a 6 months follow-up study using brain magnetic resonance imaging showed white matter involvement was increased. After that, annual follow-up brain magnetic resonance imaging showed a stable status of disease.

Key Words: Krabbe disease, Late-onset globoid cell leukodystrophy, Hematopoietic stem cell transplantation

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#### Introduction

Krabbe disease, also called globoid cell leukodystrophy (GLD), is a rare autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC). The incidence of GLD is estimated to be approximately 1/100,000. Unlike other lysosomal storage diseases, psychosine (galactosylsphingosine) is the main compound underlying pathogenesis and cytotoxicity, not galactosylceramide<sup>1,2)</sup>. In 1970, Suzuki et al. identified GALC deficiency as the primary defect of GLD<sup>3)</sup>. The four forms of GLD are based on the age of onset. Early infantile GLD is diagnosed at first six months of life, late infantile GLD is diagnosed between 3 to 8 year of age, and adult GLD is diagnosed after 8 years of age<sup>1)</sup>. Early infantileonset GLD, the most common form, occurs in approximately 80–85% of all GLD patients, late infantile-onset GLD and juvenile onset GLD occur in approximately

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10-15% of GLD patients. Most patients with GLD have low GALC activity and mutations in the GALC gene<sup>4)</sup>. The current standard treatment of GLD is allogeneic hematopoietic stem cell transplantation (HSCT), which can stop disease progression and improve the neurodevelopmental outcomes of GLD patients<sup>5,6)</sup>. Other treatments(enzyme replacement therapy, gene therapy, and substrate reduction therapy) are under investigation for achieving better outcomes<sup>7)</sup>. Here, we present a case of late infantile GLD that was treated with HSCT.

## Case report

An 18-month-old girl without a specific medical history and family history presented with irritability and stiffness in both extremities that appeared at 1 year of age. Before clinical symptoms onset, her development was normal. Her symptoms were accompanied by developmental regression of gross motor and fine motor function at 1 year of age. Her developmental status seemed to be 6-7 months and she was only able to sit without arm support and reach and grab an object. Her head circumference was 46 cm (25-50 percentile), her height was 80 cm (50-75 percentile), and her weight was 11 kg (25-50 percentile). Neurological examination revealed an increased muscle tone and a loss of muscle strength (Grade 2-3) in all extremities and increased deep tendon reflexes. Initial magnetic resonance imaging (MRI) scans of the brain were normal. However, a follow-up brain MRI performed 4 months later showed an increased T2-weighted signal in the corona radiata, internal capsule and brain stem (Fig. 1). The GLD severity score of Loes et al. was 38. Nerve conduction studies were normal. The diagnosis of GLD was confirmed by an abnormal serum GALC level (0 nmol/hour/milligram of protein). Genetic analysis revealed a point mutation in one GALC allele (c,1901T)C;p,L634S) and a deletion in the other allele (c.686\_694del), which were previously reported as GALC gene mutations that cause GLD<sup>9,10)</sup>. Lumbar punctures, electroencephalography, visual evoked responses and brainstem evoked responses were not performed.

According to the staging system made by Maria et al. our patient belonged to stage 2111. We found an unrelated donor who was a full human leukocyte antigen match to the patient. Peripheral blood stem cell transplantation was performed when the patient was 21 months old after preparative myeloablation with busulfan, fludarabine, and thymoglobuline. HSCT was successfully completed without severe complications.

One month after the HSCT, the patient showed normalized

serum GALC levels (65.7 nmol/hour/milligram of protein). Additionally her developmental regression was stalled, and she showed static delayed development. After six months, her brain MRI scans showed an increased white matter involvement, And the GLD severity score was 10, Afterwards, the patient underwent annual follow-up brain MRI examinations; the regions of abnormal signal intensity remained stable status (Fig. 2).

At the last follow-up, the patient was 5-years-old and could make two-word sentences and stand up alone just a few seconds. She was not able to do independent walking. She can grasp objects with thumb and forefinger. Her head circumference was 51 cm (25-50 percentile), her height was 98 cm (below 3 percentile), and her weight was 16 kg (25-50 percentile). Her muscle strength has improved after the transplantation but she still shows rigidity in both lower extremities.

#### Discussion

GLD is a lysosomal storage disease caused by deficiency of GALC, which results in the accumulation of the cytotoxic metabolite psychosine; this accumulation arrests myelination

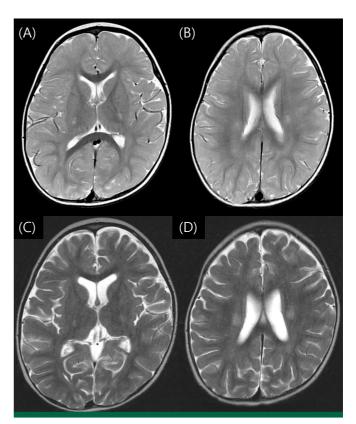


Fig. 1. Initial brain magnetic resonance imaging scans (Panels A and B) and 4 months follow-up brain magnetic resonance imaging scans (Panels C and D).

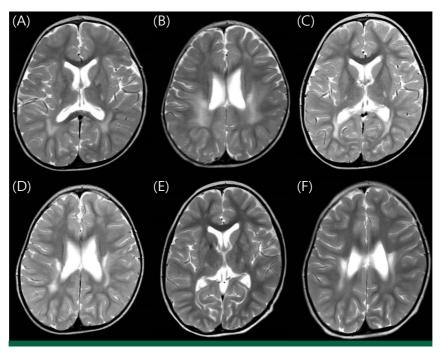


Fig. 2. Serial brain magnetic resonance imaging scans after transplantation; 6 months follow-up (Panels A and B), one-and-a-half years follow-up (Panels C and D), and three-and-a-half years followup (Panels E and F).

and destroys oligodendroglial cells<sup>12)</sup>. Children with early infantile-onset GLD experience severe neurological developmental regression and death at 2 or 3 years after the onset. The 1-year, 3-year, and 5-year survival rates of late infantile-onset GLD patients were 90%, 70%, and 50% of patients from onset of symptoms. And the longest survival of late infantile-onset GLD patient is more than 12.5 years<sup>13)</sup>. Allogeneic HSCT is the firstline treatment and can favorably change the course of the disease, especially in early infantile-onset GLD<sup>6</sup>. There are no indication criteria to evaluate patients with GLD for HSCT<sup>14)</sup>. Better outcomes are expected after transplantation when the transplantation is performed before the onset of severe clinical symptoms<sup>11)</sup>. As a result, New York state began analyzing GALC activity in all newborns to screen for infantile-onset GLD<sup>15)</sup>. There has been controversy about the efficacy of HSCT in patients with later-onset GLD<sup>16</sup>. The untreated patients with later-onset GLD have longer life expectancies, making interpretation of the results of transplantation difficult<sup>13)</sup>. Nevertheless, some articles' authors say that transplantation can make arrest of disease progression and improvement in neurological disability<sup>13,17)</sup>.

The most common signs and symptoms of infantile-onset GLD are crying and irritability, followed by poor feeding, poor head control, stiffness, loss of milestones, fisting of the hands, arching, loss of vision and seizures<sup>18)</sup>. Lumbar punctures, MRI scans, nerve conduction velocities, electroencephalography,

visual evoked responses and brainstem evoked responses are used for neurodiagnostic studies, but the diagnosis of GLD must be confirmed based on a low GALC level, Although patients with symptomatic GLD are expected to show abnormalities on brain magnetic resonance images, only 76% of these patients show brain MRI abnormalities<sup>18)</sup>. The severity score system of Loes et al, can be used to evaluate brain MRI scans in patients with GLD<sup>8)</sup>. The severity score (0 to 32, average of 8.1 for infantileonset GLD) is calculated based on the location and extent of involvement and the presence of focal and/or global atrophy. The staging system of Maria et al. for predicting outcome after HSCT for infantile Krabbe disease, classifies patients into 4 stages; stage 1-2 patients have minimal symptoms and are predicted to have better post-transplantation outcomes than stage 3-4 patients who show advanced symptoms. The patients of stage 1 appear to be normal or have some minor inconclusive neurologic symptoms such as weak feeding, hypotonia of shoulder girdle, and gastroesophageal reflux. The patients of stage 2 show obvious neurologic symptoms such as fixed thumb clasp, spasticity of extremities, trunk hypotonia, and abnormal tongue, lip or chin movements. The signs of moderate to severe neurologic involvement such as clinical seizure, visual tracking difficulty, and jerky eye movement were seen in patients of stage 3. The patients of stage 4 exhibit severe weakness with partial or complete loss of primitive weakness and sensory impairment<sup>11)</sup>. Our patient's disease stage was 2

because the following clinical symptoms were observed; spasticity on extremities; trunk hypotonia; mild thumb clasp; hypotonia of shoulder girdle; and weak feeding.

Our initial clinical impression of the patient in the present case was GLD because her initial symptoms and neurological examination results were consistent with GLD. However, her initial brain MRI findings and nerve conduction velocities were normal; therefore we were not completely convinced regarding the diagnosis of the GLD. A 4 month follow-up brain MRI revealed leukodystrophy, which is consistent with a diagnosis of GLD. The GLD severity score of patient was 3 because the following regions were observed to be involved: the corona radiate; internal capsule; brain stem. After HSCT was successfully performed, the patient showed static delayed development and improved symptoms. But on the six months follow-up brain MR images, progression of white matter involvement was detected. Severity score was 10 because the following regions were observed to be involved: the corona radiata; internal capsule; brain stem; periventricular, central, and subcortical frontal white matter; and periventricular, central, subcortical, and parieto-occipital white matter. Mild global atrophy was also observed. After that, the patient underwent annual follow-up brain MRI examinations; progression of leukodystrophy was stopped and showed stable status of diseases.

In conclusion, patients with symptoms that are suspicious for GLD should be screened early on the basis of their galactosylcerebrosidase level, despite normal findings on other neurodiagnostic tests such as brain MRI and nerve conduction velocities. Furthermore, HSCT should be performed as early as possible for better outcomes.

## 요약

GLD는 지질 침착 질환 중 하나로 라이소좀 효소인 GALC의 결핍 에 의해 나타난다. GLD 환자에서 적절한 치료가 빠르게 이뤄지지 않 으면, 증상 시작 후 2-3년 안에 사망할 수 있어 빠른 진단과 치료가 중요한 질환이다. GLD 환자는 뇌 자기공명영상에서 뇌실 주변 백질의 탈수초, 말초 신경에서 운동 신경 전도 속도 감소, 뇌척수액 검사에서 단백 양의 증가 등의 소견을 보이며, 확진은 GALC level의 감소를 통 해서 한다. 치료로서는 조혈모세포이식이 질병의 진행을 막을 수 있 는 것으로 알려져 있다. 이 증례는 보챔과 사지 강직, 정신 운동 발육 지연을 주소로 내원한 1세 여아에 대한 보고이다. 환아의 신경학적 진 찰상 근긴장도가 저하된 소견을 보이고, 건반사는 증가되어 있었다. 환아의 초기 뇌 자기공명영상 및 운동 신경 전도 속도는 정상 소견을 보였었다. 4개월 후 시행한 뇌 자기공명영상에서는 뇌실 주변 백질의 demyelination이 확인되어 GALC level을 검사하여 GLD을 진단하였

다. 환아는 조혈모세포이식을 통해 치료 후 증상이 호전되었으며, 지 속적인 인지 및 운동발달을 보이고 있다. 또한 시행한 추적관찰 뇌 자 기공명영상에서 백질의 demyelination의 범위가 감소하는 소견을 보 였다. 이 증례를 통해 본 보고에서는 환아와 같이 GLD를 의심할 수 있는 증상이 진행된 환자임에도 뇌 자기공명영상, 운동 신경 전도 속 도는 정상 소견을 보일 수 있기에, 초기에 GALC level을 같이 확인하 여GLD를 진단하는 것이 중요함을 강조하였다. 또한 저자들은 Late infantile-onset GLD 환자에서는 조혈모세포이식을 빠르게 시행하여 성공적으로 치료된 증례를 보고하고자 한다.

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