

# Globoid Cell Leukodystrophy (Krabbe Disease): An Update

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**Abstract:** Globoid cell leukodystrophy or Krabbe is a disease that affects children as well as adults who have mutations in the gene encoding the enzyme galactosylceramidase/galactocerebrosidase (GALC), resulting in the deposition of the toxic lipid D-galactosyl-beta1-1' sphingosine (GalSph or psychosine). Several therapeutic modalities were used to treat patients with Krabbe disease, including hematopoietic stem cell transplantation, enzyme replacement therapy, autophagy activators, intravenous immunoglobulin, and inhibitors of the Pyroptosis process, among many other approaches. In this article, I will briefly discuss the disease in both human and animal model, describe recent clinical observations as well as methods utilizing genetic analysis for diagnosis, and finally review recent advances in treating this rare and devastating disease.

**Keywords:** Krabbe disease, globoid cell leukodystrophy, twitcher mice, GALC, treatment, diagnosis, genetics, cancer

## Introduction

About 20 years ago, we reported that D-galactosyl-beta1-1' sphingosine (GalSph, also known as psychosine), and D-glucosyl-beta1-1' sphingosine (GluSph) induced the in vitro apoptosis of human natural killer (NK) cells.<sup>1</sup> NK cells are part of innate lymphoid cells 1 (ILC 1), which play major roles in fighting cancer but are also involved in inflammation.<sup>2</sup> Globoid cell leukodystrophy (GLD) or Krabbe disease (KD), is an autosomal recessive disease that affects infants.<sup>3-5</sup> The disease is caused by the destruction of oligodendrocytes, reduced myelin formation, and leading to the accumulation of globoid cells.<sup>6,7</sup> The toxic lipid GalSph, which is not present in normal brain or other tissues,<sup>8</sup> accumulates at high concentrations in the brain of Krabbe patients, due to the deficiency of the enzyme galactosylceramidase/galactocerebrosidase (GALC). Although children are affected by the disease, adult-onset GLD is also prevalent but is usually neglected by clinicians.<sup>9</sup> GALC physiology, GLD pathophysiology, and therapeutic strategies for KD were recently reviewed.<sup>10</sup>

Demyelination was observed in infantile KD patients suffering from GALC deficiency. In addition, an increase of pathological CD8<sup>+</sup> T lymphocytes was observed, suggesting a linkage between clinical severity and neuroimmunology. Taken together, these findings support the interplay among proteins in KD brain white matter.<sup>11</sup> Microscopic analyses show profound neuro-axonal degeneration with a mild effect on myelin structure, indicating that GALC accumulating in the neurons is essential to protect the function of neurons regardless of myelin, which contributes to the pathogenesis of KD.<sup>12</sup> However, it must be noted that although the pathology of the infantile type of Krabbe disease exhibits atrophy of the brain and extensive loss of myelin in the white matter with massive gliosis and multiple globoid cells, in the few cases reporting adult-onset Krabbe disease, a focal and mild demyelination and a few globoid-like cells were observed.

## The Disease

### Krabbe Disease in Humans

Diagnosis of patients through newborn screening is essential for better quality of life.<sup>13</sup> During earlier years, the diagnosis was done by measuring GALC activity in leukocytes and cultured cells. Afterward, newborn screening (NBS) was used. One parameter for the disease diagnosis is the low GALC activity.<sup>14</sup> The KD NBS council suggested recommendations for successful

classification of NBS positive patients with a prediction of those at risk to progress towards late onset disease.<sup>15</sup> As predicted, these programs utilize GALC as an initial test, with an increase in psychosine levels as a confirmatory marker for predicting the onset of KD. Increased of psychosine activity results in the death of oligodendrocytes leading to a sequence of events in the nervous system that lead to the appearance of clinical symptoms associated with the disease.<sup>16</sup> However, these testes should be carefully evaluated as there might be a genuine risk of a false positive rate.<sup>17</sup>

Lactosylceramide metabolism is impaired in fibroblasts isolated from patients with KD in the absence of psychosine, suggesting that molecules other than psychosine might also be involved in the disease.<sup>18</sup> In a related matter, it was demonstrated that  $\alpha$ -synuclein which is involved in Parkinson's disease, might also have pathological similarities observed in KD. Consequently, KD brain accumulated  $\alpha$ -synuclein leading to fibrils aggregation, suggesting that  $\alpha$ -synuclein is involved in KD which could be a target for intervention.<sup>19</sup>

A KD pluripotent stem cells (iPSCs) line known as PUMCi002-A was generated from dermal fibroblasts of a Krabbe patient's father with a c.461C>A mutation in GALC gene. The pluripotency, in vitro differentiation potential and karyotype stability of this cell line were confirmed. This cell line can be used to better understand the mechanisms involved in GALC-associated KD, and more important it may provide plausible new therapeutic directions.<sup>20</sup>

## Globoid Cell Leukodystrophy (GLD) in Mice

A natural authentic model for human KD, is the twitcher mouse, which have mutations in their GALC gene,<sup>21,22</sup> associated with the deregulation of several proteins.<sup>23</sup> GalSph is increased in the kidneys, liver, spleen and highly accumulates in the brains of these animals. A heptahelical receptor that binds heterotrimeric G proteins, named T-cell-death-associated gene 8 (TDAG8), has been shown to bind GalSph and GlcSph.<sup>24,25</sup> Human TDAG8 exists in normal tissues and is restricted to lymphoid organs, such as spleen and lymph nodes, as well as its expression in peripheral blood lymphocytes. We previously demonstrated that NK cells express TDAG8 and reported that GalSph and GlcSph damage these cells after binding this receptor.<sup>1</sup> In addition, GalSph inhibited NK cell distribution into the spleens of twitcher mice, along with inducing their apoptosis.<sup>26</sup> In vivo electrophysiological recordings showed defective basic functional properties of twitcher mice primary visual cortex.<sup>27</sup>

One protocol describing the genotype determination of GALC mutation status in twitcher mice was based on the allele-discrimination RT-PCR reaction. This method diagnosed GLD accurately, and without ambiguity in homozygotes, wild type, and heterozygotes animals.<sup>28</sup> Another study investigated the mechanotransduction process in primary fibroblasts collected from twitcher mice. This study reported that focal adhesions, the protein clusters necessary to adhere and migrate were increased, and accordingly, cell migration and wound healing were affected in these mice.<sup>29</sup>

## Genetic Studies of Krabbe Disease

Heterozygous missense mutation: c.1658G>A (p.G553E) and c.1901T>C (p.L634S) were identified in the GALC gene by whole-exome sequencing. In this study, a certain novel mutation, namely c.1658G>A (p.G553E) was observed, which broadened the mutation spectrum in KD patients.<sup>30</sup> Using CRISPR-Cas9 gene editing, point mutations T513M observed in infants introduced in the murine GALC, resulting in GALC T513M/T513M mice. These animals suffer from a decrease in GALC activity, increased psychosine levels, leading to progress towards lethal neurological phenotype. In contrast, another variant, ie, GALC G41S/G41S mice have normal lifespan, modest decreases of GALC, and minimal psychosine accumulation.<sup>22</sup>

Changes in the gene expression of iPSCs and iPSC-derived neural stem cells (NSCs) from a patient with GLD designated as K-iPSCs/NSCs and normal control designated as AF-iPSCs/NSCs were investigated in order to determine the potential mechanism underlying GLD pathogenesis.<sup>31</sup> It was observed that mutations in the GALC gene affected the signaling pathways during neural development, suggesting that alterations in signaling pathways may contribute to GLD pathogenesis. These results also demonstrate that the model based on K-iPSCs may represent a novel tool that can be used to study the underlying molecular basis of GLD.<sup>31</sup>

Further, astrocytes collected from KD patients contain high levels of glucosylceramide and ceramide, suggesting that in certain cases the disease may not be always associated with the galactosylceramide and psychosine pathways.<sup>32</sup> Other neuroinflammatory genes were explored to understand their correlation with disease severity in the twitcher mouse. It was observed that kinases such as Ripk1 kinase does not play a role in KD.<sup>33</sup> Collectively, these data suggest that

although measuring the levels of GALC and psychosine is essential, other parameters must also be considered in order to reach a conclusive diagnosis therapy before is initiated.

## Clinical Observations

It is imperative for pediatricians to identify patients with the disease as soon as possible. However, this might be difficult due to misunderstanding of the disease symptoms.<sup>34</sup> Doctors may rely on genetic studies to diagnose the disease. For example, in patients who had a leukodystrophy associated with hypomyelination or delayed myelination on MRI, it was suggested that exome genome sequencing would be used to identify KD patients.<sup>35</sup> Further, KD patients with mitochondrial gene NDUFAF1 mutations were observed, suggesting that gene panel examination must be expanded in order not to miss pathogenic mutations.<sup>36</sup>

In one study, two siblings with atypical clinical and neuroimaging phenotypes of KD were examined, and it was reported that they carry biallelic loss-of-function GALC variants, including a recurrent 30 kb deletion.<sup>37</sup> In an infant boy with KD, the pathogenic variants of the disease were screened by whole-exome sequencing. These variants expressed different outcomes. For example, c.328+5G>T variant was predicted to alter splicing, whereas the variant c.658C>T indicates truncation of the protein.<sup>38</sup> A whole-exome sequencing identified a pathogenic homozygous missense mutation of the GALC gene in a young woman with an onset KD who was presented with generalized seizures, progressive cognitive decline, psychiatric symptoms, gait ataxia, and action-induced myoclonus.<sup>39</sup> Another polymorphic variant known as p.Ile562Thr over-represented in the KD population, was associated with reduced mature GALC protein and activity.<sup>11</sup>

A patient who developed KD in late infancy had a pathogenic genotype, showed reduced enzyme activity but surprisingly low psychosine levels, suggesting that measuring psychosine levels should be combined with other measurements, such as enzyme levels, as well as genotyping and correlation with the patient's clinical presentations.<sup>40</sup> Therefore, magnetic resonance (MR) images showing abnormal signals, as well as the presence of globoid cells must be done before final diagnosis of the disease.<sup>41</sup> For instance, MR imaging diagnosed A 32-year-old woman with headache as adult onset KB with two pathogenic variants in GALC.<sup>42</sup>

There was a high increase in psychosine levels in infants diagnosed with KD. This was corroborated with increased levels of acid ceramidase, a key enzyme for psychosine production, and hyperglycosylated lysosomal-associated membrane protein 1, a marker for lysosomal activation in periventricular white matter.<sup>11</sup> This patient suffered from neuropathological changes. It should be stressed that diagnosis of KB is highly important as the disease carries a tremendous financial burden. A study estimated that KD patients had over \$51 million in health care charges and hundreds of hospitalizations, demonstrating the health impacts of KD on the society.<sup>43</sup>

## Role of GALC in Cancer

Lysophospholipids play major roles in tumor microenvironment.<sup>44</sup> In this regard, GALC also plays a role in cancer.<sup>45</sup> Removal of  $\beta$ -galactose from  $\beta$ -galactosylceramide, leads to the formation of the oncosuppressor metabolite ceramide,<sup>46</sup> which may play a role in tumor growth and differentiation.<sup>47</sup> GalSph and GlcSph, lipids that disrupt the lysosomes, play definitive roles in cancer therapy.<sup>48</sup> Consequently, they may contribute to the development of multidrug-resistance by cancer cells. It was shown that GlcCer may provoke immune reaction and acts as a self-antigen in KD. On the other hand, GalCer was recognized as an important cellular receptor for HIV-1.<sup>49</sup>

## Therapeutic Approaches for Treatment of Krabbe Disease

Early studies showed that transplantation of hematopoietic stem cells from normal mice into syngeneic twitcher mice resulted in increased survival, but in these studies the success of the transplantation procedures did not go beyond 100 days.<sup>50,51</sup> In five patients with late-onset GLD, a high successful rate of recovery after hematopoietic stem cell transplantation was reported.<sup>52</sup> A comprehensive study examining the impact of hematopoietic stem cell transplantation (HSCT), demonstrated that this therapeutic regimen is associated with reduced mortality in KD patients.<sup>53</sup> In a case study of KD patient showing progressive spastic paraparesis who underwent HSCT, it was observed that GALC activity returned to a normal level and the lesions in the brain and spinal cord became faint on images.<sup>54</sup> Among patients between 24 and 40 days of age, HSCT therapy was successful and the patients were alive 30 to 58 months later.<sup>13</sup> However, HSCT must be done during the first weeks of life before symptoms develop.

Another regimen of therapy utilized recombinant adeno-associated virus (rAAV) vectors to infect Krabbe patient-derived neural stem cells (K-NSCs). Using several infected K-NSCs, this therapeutic regimen rescued GALC enzymatic activity in infected cells.<sup>55</sup> Another study successfully showed that human KD patients can be treated with high-dose AAVrh10 without blood stem cell transplantation.<sup>56</sup> The efficacy and safety of a single cisterna magna AAVhu68 administration to treat KD was also reported.<sup>57</sup> In twitcher mice, adenovirus gene therapy of the lysosomal enzyme GALC significantly ameliorated central and peripheral neuropathology, prolonged survival, and largely normalized motor deficits. These observations indicate that AAV-gene therapy may be considered an alternative mode of effective intervention.<sup>58</sup>

Rapamycin, an inhibitor of mTOR but autophagy activator, was used in twitcher mice in order to reduce the deposition of insoluble ubiquitinated protein, corroborated with the attenuation of astrogliosis and microgliosis.<sup>59</sup> This therapeutic modality was critical in inducing cortical myelination, neurite density, and rescued the neurological abnormalities of twitcher mice. Further, it induced cell migration and improved the clearance of focal adhesion in GALC-deficient fibroblasts.<sup>60</sup> Another therapeutic approach utilized lecithin/chitosan nanoparticles to prevent the cytotoxicity caused by psychosine in cultured human astrocytes *in vitro* suggesting a direct interaction between psychosine and the nanoparticles.<sup>61</sup>

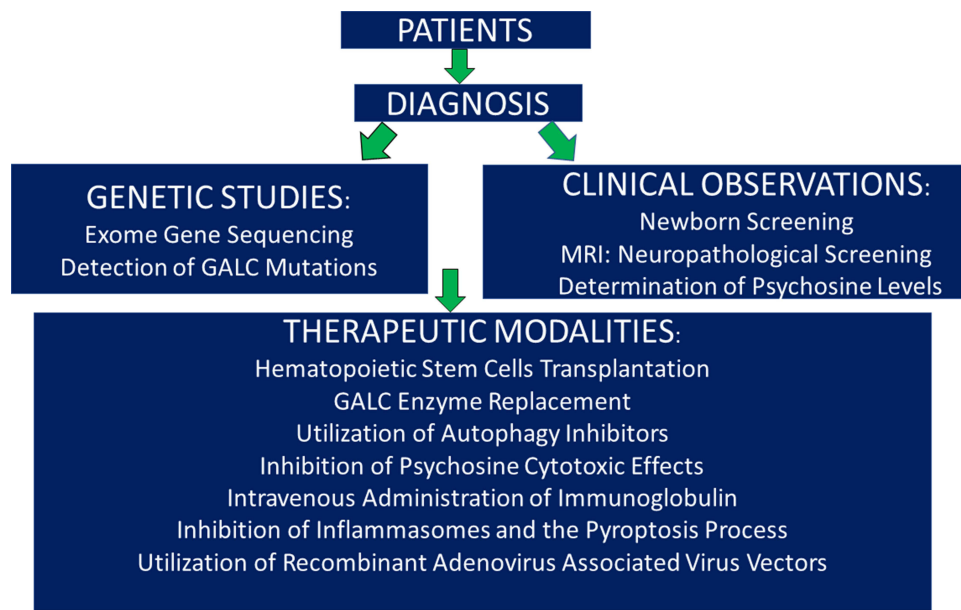
Enzyme replacement therapy is one of the initial approaches used to treat KD patients. However, it exerted limitations in relieving CNS lesions due to difficulties in passing the blood–brain barrier.<sup>62</sup> Administration of the enzyme GALC inserted into adeno-virus to twitcher mice resulted in the accumulation of this enzyme in the brains of these mice which consequently, led to prolong the mice lives.<sup>63</sup> Treating twitcher mouse with S202 amide, a galactosyltransferase inhibitor reduced GalCer and psychosine concentrations in the central and peripheral nervous systems, which significantly increased lifespan, although further studies are needed to understand the full therapeutic potential of such an inhibitor.<sup>64</sup> Substrate reduction therapy was also investigated utilizing RA 5557, a brain-penetrant inhibitor of GALC biosynthesis, in twitcher mice that lack GALC activity. This modality was effective and has an acceptable safety *in vivo* profile.<sup>65</sup>

Intriguingly, a novel approach for therapy was developed. Here, a young girl who was diagnosed with KD, received intravenous immunoglobulin (IVIg), and upon which her limb weakness improved. This was repeated when she reached 16 years old, and again her symptoms gradually improved. It was suggested that in certain KB cases, IVIg may be considered as a form of therapy.<sup>66</sup>

Pentraxin-3 (PTX3), a soluble pattern recognition receptor and a regulator of innate immunity,<sup>67</sup> was seen in the CNS of GALC-deficient Krabbe patients and twitcher mice. PTX3 may exert a protective role by reducing the neuroinflammatory response that occurs in the spinal cord of GALC-deficient animals. Regarding the role of innate immune system, *in situ* hybridization and immunohistochemical staining revealed that the expression of pro-inflammatory non-canonical caspase-11, canonical caspase-1, gasdermin D and cognate genes are induced in the nervous tissues. Caspase-11 was also found in reactive microglia/macrophages as well as in astrocytes, but caspase-1 and gasdermin D were restricted to reactive microglia/macrophages.<sup>68</sup> These results suggest that innate immune system might be involved in the inflammatory reactions associated with KB and twitcher mice. The role of the Pyroptosis process which utilizes gasdermin D and inflammasomes, in linking innate and adaptive immunity has been described.<sup>69,70</sup> It is therefore suggested that inhibitors of Pyroptosis such as those that inhibit inflammasomes, caspases, gasdermins, among others,<sup>71,72</sup> should be evaluated for effective intervention in Krabbe disease.

## Concluding Remarks

Although Krabbe disease was discovered by Dr Krabbe in the first twenty years of the last century, advances in understanding and treating this disease have been slow. When patients are presented in the clinic with a suspicious of disease occurring, neurologists and physicians rely on genetic studies in addition to the clinical observations in order to confirm the disease occurrence. Once this is validated, treatment can be started. Albeit early therapeutic modalities utilized hematopoietic stem cells transplantation and GALC enzyme replacement which are costly, recently several new therapeutic regimens have been successfully used to treat the disease, as shown in Figure 1. This figure also describes the algorithm of human disease from the time the patients enter the clinic until the time of therapy. The choice of the therapeutic modality should be agreed upon between the physicians and the parents of the patients diagnosed with the disease. Finally, the discovery of twitcher mice



**Figure 1** Algorithm of human Krabbe disease.

which resemble globoid cell leukodystrophy in humans, aided to some extent in certain aspects, particularly in generating novel therapeutic modalities. In this short review, I briefly touched on the nature of the disease and discussed novel approaches using genetic methods. I also discussed recent advances in treating KD.

## Disclosure

The author reports no conflicts of interest in this work.

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