

Classic Galactosemia Neurological Complications: An Overview

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Abstract

Classic galactosemia is an autosomic recessive disorder that leads to increase galactose 1 phosphate and galactitol intracellular levels; with clinical manifestations that arise from the ingestion of galactose from the diet but can be reverted when restricted. Yet about 90% of the patients develop neurological complications. Because of that we evaluate the impact of the diet on the generation of such complications, like the strict galactose restriction and the glycosilation impairment, galactosemia and social interactions as factors that influence neurodevelopment, oxidative stress secondary to galactosemia and its influence on neuroinflammation, epigenetics modifications secondary to the diet and the social interactions and other causes that can affect neurodevelopment on galactosemia.

Keywords: Galactosemia, galactose, lactose-galactose restriction diet.

Background

Classic galactosemia (OMIM 230400) is an autosomic recessive disorder resulting from the decreased activity of Galactose 1-phosphate uridylyltransferase enzyme (GALT), leading to increasing galactose 1 phosphate and galactitol intracellular levels. Clinical manifestations arise from the ingestion of lactose-galactose, can be reverted when restricted; yet chronic neurological symptoms are present nearly in 90% of the galactosemia population [1,2].

Speech disorders are classified in childhood apraxia of speech, dysarthria or not specified motor-speech disorder, motor disorders or cognitive impairment [2,3]. Speech and motor disorders have a higher frequency of co-existing than in normal infants with only speech disorders; although not present a proper motor disorder the children with classic galactosemia that develop childhood apraxia of speech have poorer hand dexterity and coordination [3].

Classic galactosemia patients have impaired language secondary to decreased conceptualization at the early phase of syntactic processing, less efficient syntactic planning, increase time and word usage to express themselves, causing decreased language comprehension, interpretation and manipulation what they are taught; a posterior delay on attaining the literacy skills necessary to achieve a proper academic outcome, and a cause for the observed cognitive impairment [4,5].

Prenatal exposure to galactose 1-phosphate instead of post-natal milk days the infant has been exposed is linked to increased risk of

diverse neurological complications [3].

Treatment and its impact

Galactosemia treatment is a galactose-restricted diet where dairy products are restricted and galactose content (galactose content below 25mg/100g) determine the type of food ingested with the objective of maintaining galactose 1-phosphate levels below 5 mg/dl, is started with the suspicion of the disease and no diagnose or when diagnosed by newborn screening or prenatally. Treatment prevents the appearance of cataracts, liver and renal failure and growth delay, yet more than 90 percentages of the galactosemia patients present with neuro-developmental delay symptoms and if women will present with hypergonadotrophichypogonadism [2,3,6,7].

It has been suggested that after infancy increasing the amount of galactose a patient ingest does not cause an adverse outcome on the patient and could probably decrease long-term complications [8].

Neuroimaging findings and complications

White matter synthesis is declined because of impaired synthesis of galactocerebrosides, altering diverse the corpus callosum and diverse tracts such as arcuate, inferior longitudinal and superior longitudinal fasciculus that is responsible for language processing functions and would explain the presence of speech disorders and cortico-spinal tracts explaining motor disturbances [9,10]. Cerebellar atrophy has been observed in patients with co-occurrence of motor and speech disorders yet that finding is not very common [3,10].

Neuroimaging in galactosemia is not recommended unless a proper neurological symptom is present (motor disturbance, seizures), and findings are not present in most of the patients [2,10].

Glycosylation impairment

An over restricted galactose diet impairs myelin synthesis secondary to a deficit of galactolipids (galactocerebrosides) and glycoproteins, that is hypoglycosylated because of increased production of non-galactosylated or mono-galactosylated proteins [4,9,11-13]. It has been observed In Vivo that the increased levels of galactose 1-phosphate inhibit glucose pyrophosphorylase reducing UDP-glucose/galactose and responsible for impaired glycosylation of proteins and lipids, such problems are different between individual, because the activation of secondary pathways to metabolize galactose can be epigenetic regulated and depend on the individual's genetic characteristics [9,12].

Epigenetics and Galactosemia

Epigenetic modifications originate from external factors such as maternal care observed on the infant by the quality of care needed that could or could not be given by the caregiver causing changes on cortical thickness mainly on the prefrontal area and diet properties, as the infant requires a specific lactose-galactose restriction diet that would impact on the production of intestinal neurotransmitters responsible for epigenetic modifications [2,14-16].

Early life stressors influence white matter development, therefore affect IQ scores, attachment, EEG activity, executive functions on the infant; patients with Galactosemia report with lower levels on quality of life questionnaires and characterize the disease as an stressor [2,15].

Oxidative Stress in Galactosemia

Increased levels of galactose cause NADPH oxidase impairment decrease activity of Glutathione Peroxidase facilitating an increase oxidative stress on the host [17].

Reactive Oxygen Species (ROS) and other free radicals inhibit Golgi derived vesicles that carry proteins in charged of axonal integrity a decrease mitochondrial production of ATP leading to posterior axonal degeneration and neuroinflammation, activate microglia leading to a neuro-immune active state and cause dopaminergic neurotoxicity [18, 19].

Other causes of the complications

Presynaptic dopaminergic neuronal degeneration has been associated with the development of tremor or movement disorders; such findings can be related or not to anatomic MRI findings [20]. There is a need to determine if the degeneration is directly related to the disease or can be an outcome related to the oxidative stress and dopaminergic neurotoxicity.

Winter et al observed a patient with galactosemia that develops severe neurologic deterioration during a sepsis infection with the Ashkenazi Jews 5.5kb GALT gene mutation, asides from causing diminish GALT synthesis impaired receptors of interleukin 11a generating neuronal inflammation and toxicity when an infection occurs [21]. This patients presented with a severe infectious disease so it can be theorized that asides from the interleukin toxicity there could be a severe impairment on the immune response secondary to the NADPH oxidase impairment that leads to the severe infectious disease.

Conclusion: Over restricted diet or not

The treatment goal to maintain galactose 1-phosphate levels below 5 mg/dl with food containing with galactose content of less than

25 mg/100 gr is the backbone of the over restricted diet but is responsible for the impaired glycosylation of proteins leading to decreased white matter synthesis and the posterior neurological symptoms; and increased levels of galactose 1-phosphate are prone to induce oxidative stress and caused neurotoxicity [2-4,11-13,17-19].

Because of that, increasing the levels of galactose on children above the age of 5 has been proposed to decreased the long-term outcomes with positive effects, what is needed is to determine what would be the threshold for galactose levels in such population that does not induce oxidative stress nor limits the glycosylation of proteins [8].

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