Improved outcomes in early treated GAMT deficiency: A sibling study

Liora Caspi[1], Robin Hayeems[2,3], Andreas Schulze[1,4,5]

1 Genetics and Genome Biology, Hospital for Sick Children, Toronto, Canada
2 Child Health Evaluative Sciences Program, Hospital for Sick Children, Toronto, Canada
3 Institute of Health Policy Management and Evaluation, University of Toronto, Canada
4 Department of Biochemistry, University of Toronto, Canada
5 Department of Paediatrics, University of Toronto, Canada

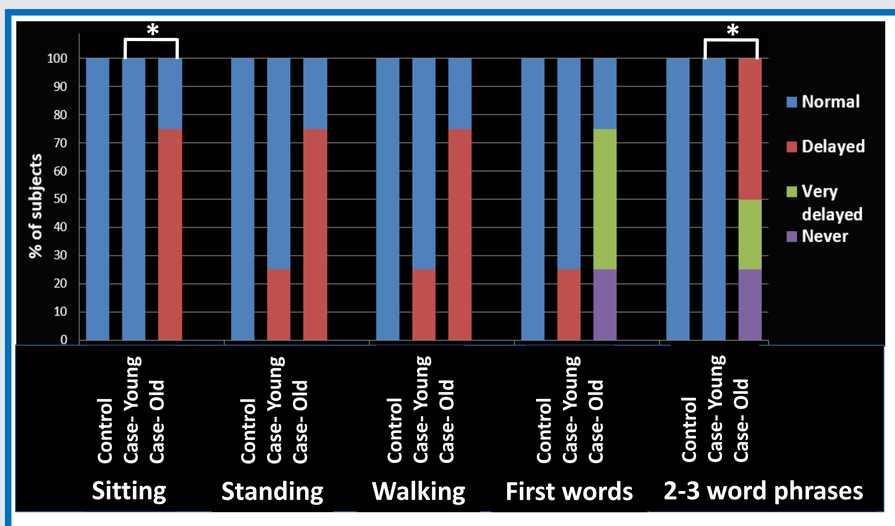
Background

- Guanidinoacetate Methyltransferase (GAMT) deficiency is an autosomal-recessive condition that presents in the first years of life with global developmental delays and severe epileptic seizures refractory to seizure medication. It is one of the Creatine Deficiency Syndromes.
- Without early treatment, individuals with GAMT deficiency develop severe intellectual disability. These patients often present with features of autism, speech delay, failure to thrive, hypotonia, seizures and movement disorders.
- The current standard of care appears to enable affected children to achieve normal development when the treatment starts shortly after birth.
- The treatment for GAMT deficiency includes oral creatine monohydrate, an arginine/protein restricted diet, and/or the supplementation with pharmacological doses of L-ornithine. This treatment attempts to replenish creatine levels in the brain and to reduce the toxic levels of circulating guanidinoacetate.

Methods

- Four sibling pairs with GAMT deficiency (n=8, age range- 9-18.7y, 4 males, 4 females) and eight age-matched control healthy sibling pairs (n=16, age range- 4.9-16y, 8 males, 8 females) were enrolled.
- Based on structured interviews with the four GAMT deficiency families, a questionnaire was constructed and administered to the parents of all sibling pairs (case and control groups).
- In each sibling pair with GAMT deficiency the younger sibling received standard treatment for GAMT deficiency at a younger age compared to the older sibling.
- Parents were asked to indicate whether and when their child achieved specific milestones, achieved them with support, or did not achieve them. The questionnaire included questions about developmental milestones, fine motor-, cognitive-, self-care-, and social skills, behavior, coordination, and therapy/support.
- Descriptive statistics and thematic analysis were used to synthesize the data.

Developmental milestones



001- *"her body strength seemed to be ok initially and then decreased.""..it was the speech that really stood out, it was really delayed."*

002- *"...he had such poor balance... " ".. had low muscle tone" "He is non verbal, uses his communication device."*

Figure 1: % of subjects who achieved early developmental milestones within the normal age range (normal development), achieved them at an older age (delayed/ very delayed) or never achieved them.
* p-value <0.05

**001-004- older siblings in four case families

003- *"...started missing milestones pretty early on." "He couldn't sit up" "he was not able to lift his head up until after he got creatine"*

004- *"..everything that involved the lower body was delayed, because she had no strength in her legs at all."*

Cognitive skills and school program

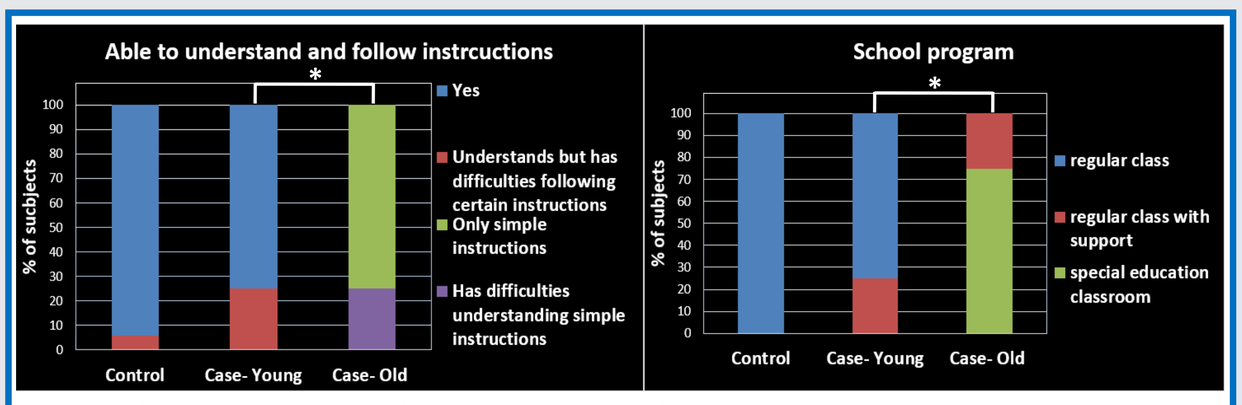


Figure 2: Ability to understand and follow complex and simple instructions.
Figure 3: % of subjects who attend regular class, regular class with support or special education classroom.
* p-value <0.05

001- *"She doesn't have the understanding of language or thought to be able to learn a lot."*

003- *"School is difficult, speech, writing and reading comprehension."*

002- *"He is intellectually delayed"*

004- *"..developmentally she is like a 5y old (chronological age of 14y), she is very trusting, she is very vulnerable, she has no danger awareness. Academically she cannot read and write."*

**001-004- older siblings in four case families

Fine motor skills

001- *"she needs some help with cutting her food" "she had a little bit of tremor...and I would only see it when she was trying to do something very fine motor"*

Figure 4: % of subjects who are able to perform these fine motor tasks with no help ('Yes'), with help ('Needs help') or unable to do it ('No').
* p-value <0.05

**001, 003- older siblings in two of the case families

003- *"he didn't have the pincer grasp.." "He struggles with fine motor skills, moving the toothbrush around is difficult for him. Shaving,... I think he has difficult time moving the razor around."*

Seizures and behavior

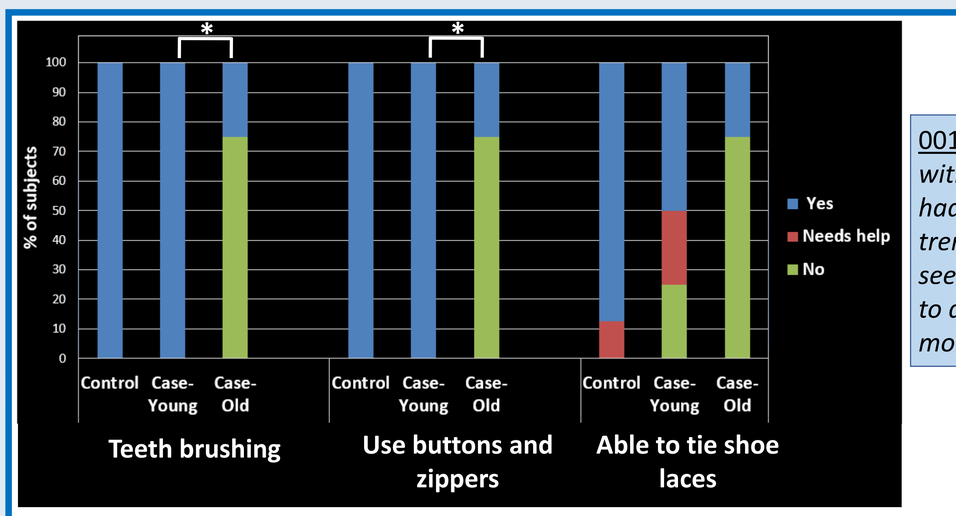
Figure 5: % of subjects who had ('Yes') or never had ('No') seizures in the past and those who are still having seizures ('Yes') or do not have seizures anymore/ never had seizures ('No').
Figure 6: % of subjects who have ('Yes') or do not have ('No') these behaviors.
* p-value <0.05

**002, 004- older siblings in two of the case families

002- *"...he was on 3 different kinds of seizure medications, he was almost intoxicated from all the medications, that for several years he was just roll on the ground... I think that his development was interrupted not only by his seizures but by his seizure medications."*

004- *"She went through various seizure medications but none of them ever did anything really other than make her drowsy... She had seizures hundreds of times a day."*

Differences between siblings



001- *"The biggest thing that is different about them is their intellectual abilities, their ability to understand complex conversations, to speak clearly, speak about complex topics, understand instructions. They are very different socially in their ability to engage with people, have friends."*

Figure 7: Differences between the siblings in each family (case and control) from the parents' point of view.
* p-value <0.05

**001-004- four case families

002- *"The difference is physical...Their ability to communicate, my son wants to communicate but has the challenges that hold him back."*

003- *"She (younger sibling) hit all of her milestones on time, she is very socially aware, self-care is very easy for her, she doesn't seem to have any behavioral issues, she can follow multi step directions."*

004- *"The boy looks like a normal child, you cannot tell that he has GAMT deficiency, she looks like a child with learning disability and that she is disabled." ".. the difference between the two of them is huge and it breaks my heart when I see how much more capable he is compared to his sister, because she could have been like that too."*

Conclusion

- This study supports the notion that early initiation of treatment in children with GAMT deficiency results in improved outcomes.
- Early treatment, ideally in the pre-symptomatic phase of the disease is indicated.
- To facilitate early treatment, early identification of affected individuals through universal newborn screening warrants consideration.

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