2014

Neurodevelopmental outcomes of duarte galactosemia: an exploration of cognitive development and special needs in duarte galactosemia patients

Tran, Catherine T.
NEURODEVELOPMENTAL OUTCOMES OF DUARTE GALACTOSEMIA:
AN EXPLORATION OF COGNITIVE DEVELOPMENT AND SPECIAL
NEEDS IN DUARTE GALACTOSEMIA PATIENTS

by

CATHERINE T. TRAN

B.A., University of California, Berkeley, 2009

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2014
DEDICATION

I would like to dedicate this work to my parents, my brother, and my partner Davis for their unwavering support in my endeavors throughout the years.
ACKNOWLEDGMENTS

I would like to acknowledge and thank the many professionals who have helped me in the successful completion of this thesis:

To Dr. Susan Waisbren, Ph.D., I would like to express my immense gratitude for welcoming me into her field of work from which my thesis arose. She has been an extraordinary mentor. Her patience and positivity throughout this process have been constant boosts of confidence. She has fostered the development of my passion for this thesis topic and has provided endless guidance along the way.

To Dr. Gerard Berry, M.D., I would like to thank for getting my thesis project started. His willingness to talk to me about his field of work in pediatric metabolism and genetics sparked the initial idea to study galactosemia. The way he shared his ongoing medical questions during our meetings was inspiring and encouraged me to strive towards life-long learning.

To Dr. Cynthia Gubbels, M.D., Ph.D., I would like to express how grateful I am for her everlasting patience and for taking me under her wing. As a visiting researcher, she took time out of her work to provide additional assistance in creating, finishing, and editing this project and my thesis. She has constantly pushed me to excel and I am extremely thankful not only for her mentorship but for her friendship.

To Dr. Fernando Garcia-Diaz, Ph.D., I would like to thank for his guidance and advice throughout my graduate school years. His honesty as an advisor and
a teacher has been truly humbling and a driving force behind striving to always do better.
NEURODEVELOPMENTAL OUTCOMES OF DUARTE GALACTOSEMIA:
AN EXPLORATION OF COGNITIVE DEVELOPMENT AND SPECIAL
NEEDS IN DUARTE GALACTOSEMIA PATIENTS

CATHERINE T. TRAN

ABSTRACT

Duarte galactosemia is a variant form of galactosemia that on average results in a reduction of the galactose-1-phosphate uridylyltransferase enzyme to 25% activity. This enzyme is involved in the metabolism of galactose in the body. On the contrary, patients diagnosed with the classic form of galactosemia have a galactose-1-phosphate uridylyltransferase enzyme activity of zero or near-zero. As a result, classic galactosemics are placed on galactose-restricted diets to prevent acute neonatal signs of disease that can ultimately lead to death. These diets are instituted for the rest of the patients' lives. However, even with dietary treatment, classic galactosemia patients go on to experience long-term neurodevelopmental outcomes, most notably cognitive defects and speech and language delay.

Duarte galactosemia patients, as a result of their residual enzyme activity, experience much milder disease symptoms. Many specialists agree that these patients have a benign disease and therefore treatment is not consistently agreed upon nor prescribed. Most Duarte patients follow an unrestricted diet and if a diet is prescribed, it is only for the first year of life. While these patients have
enough enzyme activity to prevent acute neonatal signs of disease, there is still limited information regarding any long-term neurodevelopmental outcomes in the Duarte galactosemia population.

This study examined developmental outcomes and need for special services of a sample of Duarte galactosemia patients. The outcome data were compared to the general population as well as to a classic galactosemia group. A convenience cohort of clinical charts for patients seen for neuropsychological evaluations from 1978 to 2013 was reviewed. Developmental scores, neuropsychological outcomes, and need for special services for patients diagnosed with a form of galactosemia were entered into an electronic database.

Recorded developmental information on twenty-two Duarte galactosemia patients were found. All of the 22 Duarte patients were found to have developmental test scores within normal range. However, 38.9% of Duarte patients containing information regarding special services were found to participate in early intervention, 71.4% of which received speech therapy. Furthermore, 22.2% of Duarte patients containing information regarding special services were found to participate in special education, and 100% of these children received speech therapy.

In conclusion, despite Duarte galactosemia patients not exhibiting lower learning test scores, there was a large proportion of them participating in special services, particularly in speech therapy. This indicates some speech and language difficulties in children with Duarte galactosemia.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE PAGE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>v</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>viii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>What Is Galactosemia?</td>
<td>1</td>
</tr>
<tr>
<td>Classic Galactosemia</td>
<td>2</td>
</tr>
<tr>
<td>Duarte Galactosemia: A Variant Form</td>
<td>4</td>
</tr>
<tr>
<td>Genetics and Testing of Classic and Duarte Galactosemia</td>
<td>7</td>
</tr>
<tr>
<td>A Further Look at Long-Term Complications of Galactosemia: Known</td>
<td></td>
</tr>
<tr>
<td>Neurodevelopmental Outcomes of Classic vs. Duarte Galactosemia</td>
<td>9</td>
</tr>
<tr>
<td>The Enigma of Duarte Galactosemia</td>
<td>11</td>
</tr>
<tr>
<td>SPECIFIC AIMS AND OBJECTIVES</td>
<td>13</td>
</tr>
</tbody>
</table>
METHODS ........................................................................................................................................... 15
Participants ......................................................................................................................................... 15
Procedure ........................................................................................................................................... 15
Statistical Analysis ............................................................................................................................. 18
RESULTS ........................................................................................................................................... 21
Description of the Study Sample ......................................................................................................... 21
Special Services: Early Intervention ...................................................................................................... 22
Special Services: Special Education ...................................................................................................... 25
Developmental Testing Outcomes ........................................................................................................ 27
“Any” Developmental Outcomes and Diet .......................................................................................... 31
Indications of Speech or Language Problems in the Duarte Galactosemia
Cohort .................................................................................................................................................. 32
DISCUSSION .................................................................................................................................... 34
CONCLUSION .................................................................................................................................... 42
REFERENCES ..................................................................................................................................... 44
CURRICULUM VITAE .......................................................................................................................... 47
<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Basic Description of Study Sample</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Early Intervention Needs for Duarte Galactosemia and Classic Galactosemia</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Special Education Needs for Duarte Galactosemia and Classic Galactosemia</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Bayley Scales of Infant Development: Duarte Galactosemia</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>Bayley Scales of Infant Development: Classic Galactosemia</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>Intelligence Quotient Scores: Duarte Galactosemia</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>Any Developmental Problem and Diet in the Duarte Cohort</td>
<td>32</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

D/G ............................................. One Duarte Gene and One Classic Galactosemia Gene
DQ ................................................................................. Developmental Quotient
Gal-1-P ................................................................. Galactose-1-Phosphate
GALE .................................................................... Uridine Diphosphate Galactose-4-Epimerase
GALK ........................................................................ Galactokinase
GALT ................................................................. Galactose-1-Phosphate Uridyltransferase
IQ .............................................................................. Intelligence Quotient
MDI ........................................................................... Mental Developmental Index
PDI ......................................................................... Psychomotor Developmental Index
POI .............................................................................. Primary Ovarian Insufficiency
INTRODUCTION

What Is Galactosemia?

Galactosemia is a disorder in which there is a disruption in how the body processes galactose (Louis J Elsas, 1993; “Galactosemia - Genetics Home Reference,” 2008). Patients with this rare genetic disorder have an impaired ability to utilize galactose from their diet (Berry & Walter, 2012). The primary pathway of galactose metabolism is known as the Leloir pathway (Fridovich-Keil & Walter, 2013). The Leloir pathway involves 3 main enzymes: galactokinase (GALK), uridine diphosphate galactose-4'-epimerase (GALE), and galactose-1-phosphate uridyltransferase (GALT). Impairment in any of the important enzymes in the Leloir pathway can result in a form of galactosemia (Fridovich-Keil & Walter, 2013).

Galactose is a part of the disaccharide lactose which is found predominantly in milk (Berry & Walter, 2012; Fridovich-Keil & Walter, 2013). Ingested lactose is broken down in the intestine to galactose and glucose and these monosaccharides are then absorbed. Once galactose has been absorbed, it can be further converted into glucose-1-phosphate and subsequently be used as an energy source. Thus, particularly in infants where milk is the primary food source, galactose is an essential nutrient (Berry & Walter, 2012; Fridovich-Keil & Walter, 2013).
**Classic Galactosemia**

The most profound form of galactosemia is described as classic galactosemia and is caused by severe galactose-1-phosphate uridyltransferase (GALT) deficiency (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013). Currently, there are 266 recorded GALT gene mutations that result in various forms of enzyme deficiency and consequently different severities of the disorder. Of the recorded mutations however, 85% are known to be pathogenic and associated with classic galactosemia (Calderon, Phansalkar, Crockett, Miller, & Mao, 2007). The biochemical consequences of the pathogenic GALT deficiency are abnormal accumulations of galactose and its metabolites such as galactose-1-phosphate (gal-1-P), galactitol, and galactonate in the blood, tissues, and urine of patients (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013).

Classic galactosemia occurs in about 1 in every 40,000-60,000 births in the United States and is detected by newborn screening (Berry & Walter, 2012; Louis J Elsas, 1993). The inheritance pattern for classic galactosemia is described as autosomal recessive where both copies of the gene in each cell of the child must have the mutation. As an inherited genetic disease, classic galactosemia is passed down among families (Berry & Walter, 2012; Louis J Elsas, 1993; “Galactosemia - Genetics Home Reference,” 2008). However, parents of galactosemic children each carry one copy of the autosomal recessive gene with a normal gene and generally do not manifest any symptoms.

In places where newborn screening is not available or does not include screening for galactosemia, physicians must remain vigilant towards newborns presenting with clinical symptoms of galactosemia. Infants with classic galactosemia have zero or barely detectable GALT enzyme activity (Berry & Walter, 2012; Louis J Elsas, 1993). Thus, classic galactosemia is a medical emergency in the newborn infant as it can result in life-threatening signs of disease after the exposure to lactose (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013). At birth, these infants present with normal weight, but as they begin consuming milk, acute symptoms of the disorder can manifest in the first days of life. These symptoms include failure to thrive, trouble feeding, vomiting, jaundice, and lethargy. Damage of the liver and kidney, bleeding, cataracts, and bacterial infections can follow, ultimately leading to death if left untreated. If a galactose disorder is suspected, milk-feeding should be stopped immediately (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013).

Once classic galactosemia is confirmed, the dietary therapy remains with a diet restricted from galactose and ultimately lactose. Typically, there is an exception to fruits and vegetables that contain small amounts of galactose and those foods are often allowed in the diet (Berry & Walter, 2012). With this treatment, the detrimental symptoms in early infancy can rapidly resolve and the
further complications of liver problems, bacterial infections, and death can be prevented. This galactose-restricted diet is instituted for the rest of the patient’s life (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013; Waisbren, Norman, Schnell, & Levy, 1983).

The majority of patients with classic galactosemia, even with prompt treatment, still experience life-long complications as they develop and grow (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013). While complications in intellectual development and growth are much more likely if treatment is delayed, infants with classic galactosemia remain at risk for further long-term complications. Generally, these long-term outcomes include developmental delays, speech deficits, fine motor function problems, cataracts, poor growth, and overall intellectual disabilities (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013). Females with classic galactosemia are also at a greater risk for primary ovarian insufficiency (POI) and overall ovarian dysfunction (Berry & Walter, 2012; Fridovich-Keil et al., 2011).

**Duarte Galactosemia: A Variant Form**

With the numerous gene mutations of the GALT enzyme that exist, not all of them transpire into a classic galactosemia diagnosis. Duarte galactosemia is a disorder resulting from a variant form of GALT deficiency (Berry & Walter, 2012; Fridovich-Keil & Walter, 2013). The Duarte variant of galactosemia presents with milder clinical outcomes and is in fact the most frequent variant of GALT mutation
(Berry & Walter, 2012; Fernhoff, 2010; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013). It is most commonly found in newborn screening because of moderately elevated amounts of blood galactose and lower, but not zero, GALT activity (Berry & Walter, 2012).

Despite the abnormality of the GALT enzyme, patients with the Duarte gene, even if paired with the classic galactosemia gene, are usually healthy. These patients with one Duarte gene and one classic galactosemia gene, commonly referred to as D/G patients, retain about 25% of normal GALT enzyme activity (Berry & Walter, 2012; Louis J Elsas, 1993; Fernhoff, 2010; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013). With just 25% of enzyme activity, D/G patients seem to remain without clinical symptoms, especially the acute symptoms characteristic of classic galactosemia (Berry & Walter, 2012; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013).

Currently, there is no general consensus as to whether or not Duarte galactosemia patients should be treated via diet-therapy (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013). Even though the majority of D/G patients often present without classic galactosemia symptoms, infants can accumulate some mild to moderately elevated levels of galactose metabolites early in life, particularly red blood cell gal-1-P from ingesting lactose (Fernhoff, 2010). Along with the elevated gal-1-P levels, other metabolites like galactitol, galactonate, and urine galactitol also show higher values during early infancy (Ficicioglu et al., 2008). Thus, some medical facilities and centers have instituted
a practical treatment plan towards Duarte patients. This plan starts with a galactose-restricted diet, as that prescribed to classic galactosemia patients, in the first 1 to 4 months of life, and is then followed by a transition to a galactose-containing diet as the blood gal-1-P levels normalize (Berry & Walter, 2012). Other centers, however, choose to maintain a galactose-restricted diet through the first year of life until the gal-1-P levels normalize (Berry & Walter, 2012; Fernhoff, 2010). Still, there are many facilities where no dietary treatment is prescribed to Duarte galactosemia patients at all (Fridovich-Keil & Walter, 2013).

Long-term complications of Duarte galactosemia in older children and adults have been reported only minimally (Badik et al., 2011; Powell et al., 2009). Since treatment varies across the United States, Duarte patients are often lost to follow-up once they enter early childhood, whether or not they were on treatment (Badik et al., 2011; Fernhoff, 2010). Unlike the known long-term outcomes in classic galactosemia, there is no consensus regarding the complications that may be experienced in Duarte galactosemia. Thus, the questions of any long-term complications in this group are still left unanswered (Badik et al., 2011; Fernhoff, 2010). In regards to another long-term outcome comparable to classic galactosemia, female reproductive problems, Badik et al (2011) has studied ovarian function in Duarte galactosemia. All of their 57 female D/G patients were found not to have any increased risk for premature ovarian insufficiency, a stark difference from the known complication of POI in female classic galactosemia patients (Badik et al., 2011).
**Genetics and Testing of Classic and Duarte Galactosemia**

The most common genotype for classic galactosemia that presents with severe outcomes of the disease is a homozygous Q188R mutation, where an arginine is substituted for a glutamine at the amino acid position 188. As a result, the catalytic activity of the GALT enzyme complex is absent or greatly reduced (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013). In North Americans, the frequency of the Q188R allele is between 60-70% in individuals with galactosemia (Fridovich-Keil & Walter, 2013).

The Duarte galactosemia variant is characterized by the substitution of an aspartate for an asparagine at the amino acid position 314 and is known as the N314D mutation (Louis J Elsas, 1993; Fernhoff, 2010; Ficicioglu et al., 2008). The Duarte allele actually exists in two different forms: Duarte-1 and Duarte-2 (Louis J Elsas, 1993; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013). While both forms of Duarte allele mutations exhibit the same amino acid substitution at position 314, the Duarte-2 allele also has a 4 base pair deletion. The Duarte-1 allele, known as the Los Angeles variant, does not have the additional 4 base-pair deletion, but rather a second L218L mutation and the GALT enzyme activity actually is elevated (Louis J Elsas, 1993; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013). In Duarte-2 alleles where there is the 4 base-pair deletion on the promoter region, GALT enzyme activity is depressed (Louis J Elsas, 1993; Fernhoff, 2010). On average, the activity is 25% of normal (Berry & Walter, 2012; Louis J Elsas, 1993; Fernhoff, 2010; Ficicioglu et al., 2008; Fridovich-Keil &
Walter, 2013). In the United States population, the Duarte-2 variant mutation has about a 5% incidence, meaning 1 in 20 people carry this Duarte allele. When the Duarte-2 variant and a classic galactosemia mutation coexist on different alleles, the patient is diagnosed with Duarte galactosemia (L. J. Elsas et al., 1994; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013).

In the United States where newborn screening is widely used, the standard and primary method in screening for galactosemia is by a determination of the GALT enzyme activity and by analysis of total galactose and/or gal-1-P in the blood. Furthermore, GALT gene mutation analysis can also be obtained to assist the neonatal screening using patient DNA from a blood sample (Berry & Walter, 2012; Louis J Elsas, 1993; Fridovich-Keil & Walter, 2013). For classic galactosemia, the alleles that are most frequently seen and that are targeted for in gene mutation analysis are Q188R, S135L, K285N, and L195P (Louis J Elsas, 1993; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013). The S135L is a unique mutation of African origin where a serine is substituted for leucine at amino acid position 135. This mutation is mostly found in Africans and African-Americans and has been found to account for 50% of the GALT allele mutations in African-Americans (Fridovich-Keil & Walter, 2013). For Duarte galactosemia, patients are screened for the N314D mutation (Louis J Elsas, 1993; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013).
A Further Look at Long-Term Complications of Galactosemia: Known Neurodevelopmental Outcomes of Classic vs. Duarte Galactosemia

There have been numerous studies detailing the depths of the neurodevelopmental outcomes of a classic galactosemia diagnosis such as impaired intelligence quotients (IQ), problems with speech, and deficits in language development (Antshel, Epstein, & Waisbren, 2004; Nelson, 1991; Potter, Lazarus, Johnson, Steiner, & Shriberg, 2008; Ridel, Leslie, & Gilbert, 2005; Schadewaldt et al., 2010; Schweitzer, Shin, Jakobs, & Brodehl, 1993; Waggoner, Buist, & Donnell, 1990; Waisbren et al., 1983). These patients have also been found to have tremors, small brain size, and ataxia or uncoordinated muscle movements (Schweitzer et al., 1993). There are also records of early intervention services in classic patients to assist in specific learning delays (Potter et al., 2008). Interestingly, these various neurodevelopmental outcomes have been found not to be associated with how early or how well the patient has been treated nor with the severity of the classic galactosemia disease (Antshel et al., 2004; Nelson, 1991; Schadewaldt et al., 2010; Schweitzer et al., 1993; Waisbren et al., 1983).

Many studies have made evident that the severity and persistence of the cognitive impairments in IQ, speech, and language development can also vary across the classic galactosemia population (Potter et al., 2008). Sometimes classic galactosemia can result in near-normal or even normal mental ability in those less affected by the disease but can also result in a lifetime’s struggle due
to large mental disability in patients that are highly affected (Schadewaldt et al., 2010). Still, all together the studies on the long-term outcomes of classic galactosemia indicate a relatively consistent profile of neurodevelopmental delay and intellectual deficits (Antshel et al., 2004).

Compared to the vast amount of literature for the classic galactosemia population, only few studies have been conducted on the Duarte population and among those, even fewer on the long-term neurodevelopmental outcomes of the variant (Badik et al., 2011; Powell et al., 2009). Since Duarte patients are recognized in newborn screening programs, the question remains whether the reduced GALT enzyme activity is a risk factor for patients to acquire outcomes similar to those of classic galactosemia (Ficicioglu et al., 2008). There were strides in answering these questions when Ficicioglu and colleagues (2008) showed that their cohort of D/G patients had good and unaffected developmental outcomes whether or not they were treated with a diet in their first year of life (Ficicioglu et al., 2008). They found that even though untreated D/G patients had increased levels of metabolites due to galactose ingestion, those levels did not compare to levels seen in classic galactosemia and did not cause any developmental disability in early childhood. This was an indication that Duarte galactosemia metabolite levels may not be in a toxic range. Finally, neither group of D/G patients (treated or untreated) developed any symptoms associated with the classic form of galactosemia (Ficicioglu et al., 2008).
Contrary to the studies of Ficicioglu and colleagues (2008), Powell and colleagues (2009) found some indications of possible developmental problems in the Duarte galactosemia patients (Powell et al., 2009). They examined a population-based sample of school-age Duarte patients for long-term speech and language developmental problems that required special education services. They found that despite dietary treatment up to 1 year of age, there were in fact some developmental problems among some children with Duarte galactosemia. Speech and language problems were evident and the requirement of special education was higher for older children with this variant than for the general population (Powell et al., 2009).

**The Enigma of Duarte Galactosemia**

While there have been steps towards examining the long-term outcomes of Duarte galactosemia, more studies are needed. Even though Ficicioglu and colleagues (2008) found no developmental delay in their Duarte cohort, they only examined patients from 1 to 6 years of age (Ficicioglu et al., 2008). On the other hand, Powell and colleagues (2009) did find developmental problems in their Duarte population but the significance appeared in older children and only the treated patients were examined (Powell et al., 2009). More examinations about how Duarte galactosemia patients compare to their classic counterparts may help more definitively point towards whether Duarte galactosemia can be characterized as a benign or more harmful disease. Studies that look at cognitive
development, language acquisition, motor ability and early intervention services in Duarte galactosemia patients over time can help increase the knowledge of delays regarding if and when they might arise. Even if Duarte patients may not be found to have deficits similar to the classic patients, perhaps they still exhibit developmental delays and learning complications compared to population norms. Finally, more studies to document any consistent future outcomes in untreated Duarte patients can help calm the debate of whether treatment is needed for a Duarte galactosemia diagnosis.
SPECIFIC AIMS AND OBJECTIVES

This thesis aims to study and compare the mental development, intelligence quotients, and special developmental needs of Duarte galactosemia patients to the general population. The results will also be compared to a group of individuals with classic galactosemia. This study will examine any possible long-term neurodevelopmental outcomes among the Duarte galactosemia population within the context of the long-term complications in classic galactosemia.

There are four study objectives that will help explore the cognitive development and possible neuropsychological complications of Duarte galactosemia patients seen for psychological evaluations during infancy, childhood, or adolescence.

The first objective is to examine the mental development, intelligence quotients, and special developmental needs of Duarte patients compared to established population norms of children unaffected by disease. The goal is to determine if overall, Duarte patients might experience developmental delays and increased need for special services more often than unaffected children yet less than what is observed for the classic galactosemia control group.

The second objective is to determine to what extent Duarte galactosemia patients might have other neurodevelopmental complications, such as the specific needs in early intervention and special education services. The goal is to
examine these complications and determine which services, if any, demonstrate a greater use. This may be an indication of common developmental problems within the Duarte galactosemia population.

The third objective is to compare the cognitive and language development to the motor development in Duarte galactosemia patients during early infant and toddler years. The goal is to determine if there is an observed significance in the difference of these scores first within the Duarte population and then comparatively to the classic population. This can be an indication of the areas in development in which Duarte galactosemics start to excel or struggle.

The final objective is to examine the cognitive development of the Duarte galactosemia group and compare these results to a group of individuals with classic galactosemia. The goal is to determine if Duarte patients exhibit a pattern of deficits similar to those in the classic galactosemia group, albeit to a lesser degree.

Overall, this thesis attempts to complete a consistent profile for the long-term outcomes of Duarte galactosemia and ventures to answer the larger question of whether Duarte galactosemia has any problems at all.
METHODS

Participants

108 patient profiles were reviewed and examined in this study. These subjects were obtained from an entire sample of completed neuropsychological clinic visits at a university-affiliated outpatient metabolism clinic at Boston Children’s Hospital. The patients were seen from 1978 to 2013. The inclusion criteria were a confirmed diagnosis of either Duarte galactosemia, classic galactosemia, or other variant galactosemia and an IQ test or an infant developmental test.

Procedure

The study conducted was a cross-sectional retrospective chart review. The convenience cohort of actual patient clinical charts derived from neurodevelopmental psychological evaluations was reviewed. The outcome variables collected from the review included demographic information, baseline diagnosis information, and scores on developmental tests, as well as reports of early intervention services, developmental delay or special education services.

A database was created to suit the needs for the information collected in this study. For every subject, information available in the clinical charts was recorded. Type of galactosemia, diet, and genotype were recorded under diagnosis information. Genotype was collected for the classic or other variant
galactosemia diagnosis if available in the chart. For the primary study group of Duarte galactosemia patients, the genotypes were also recorded by further examination in hospital electronic records.

Other neuropsychological outcomes were recorded once for each subject of the review if available. These outcomes included early intervention services, special education services, age at which services started, any noted signs of autism or attention deficit disorder, and tremors. Early intervention services were any therapies or other developmental assistance used by patients from birth until the age of 3. Special education services were the same such therapies or other developmental and academic assistance used by patients greater than age 3 at which they are entering school-attending age. The specific types of services used were also recorded if subjects were documented to participate in early intervention and/or special education. All of these outcomes were put into the database if recorded in visit reports or included by parent or patient report.

For the neurodevelopmental battery of the subjects, all subjects of the study had at least one evaluation but some subjects had more than one neurodevelopmental or psychological evaluation. For each visit, the age at which the examination was performed was recorded as well as the resultant scores of the developmental or IQ tests of the visit. Each evaluation included had either an infant test for cognitive, language, and/or motor ability or a test for intelligence that included a verbal comprehension, perceptual performance, and/or full scale intelligence score. Other tests that may have been in the clinical chart, but that
were not required for the database, were behavioral and adaptive skills assessments and visual-motor integration tests. These scores, if available, were also entered into the database if they were present during an evaluation with intelligence tests for completeness of the chart review.

The largest amount of data on neurodevelopmental tests that was attained were scores from the Bayley Scales of Infant Development, either the Second or Third Edition (Bayley, 1993, 2006). The Bayley Scales of Infant Development Second Edition provides a Mental Developmental Index (MDI) and a Psychomotor Developmental Index (PDI) (Bayley, 1993). The Bayley Scales of Infant Development Third Edition provides a Cognitive composite score, a Language composite score, and Motor composite score (Bayley, 2006). For purposes of this study, the MDI and Cognitive composite score were used to describe the overall developmental level, referred to as a Developmental Quotient or DQ. This has a mean of 100 and a standard deviation of 15 (Bayley, 2006). The PDI and Motor composite score were also examined together. This also has a mean of 100 and a standard deviation of 15 (Bayley, 2006). Test scores from before the age of 1 year and test scores at an age equal to or after 1 year were examined separately as age groups within each diagnosis.

For developmental tests beyond the Bayley Scales of Infant Development, the tests that were performed within the Duarte group were the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 2002), the Wechsler Intelligence Scale for Children, Third or Fourth Edition depending on what
version was most current at the time of testing (Wechsler, 1991, 2003), or the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). These tests provide a Verbal Comprehension score, a Perceptual Performance Score, and a Full Scale IQ score. These have a mean of 100 and a standard deviation of 15 (Wechsler, 2003).

Exclusion criteria included subjects in which no intelligence or mental developmental tests were found as well as individual visits within subject profiles without intelligence or mental developmental tests. Subject charts were reviewed for history of any significant, yet unrelated, medical problems that might influence the performance in their evaluation but none were found to have any other condition. This retrospective chart review was performed with the approval of the Boston Children’s Hospital Institutional Review Board (IRB-P00010681).

**Statistical Analysis**

The data analysis for this study used the SPSS statistics program (IBM SPSS Statistics Version 21) along with an in-depth non-program analysis and discussion of the data collected. Trends, points of interests, and tests for statistical significance comparing Duarte patients to the general population norms and to the classic galactosemia group were the specific aims of the data analysis. Descriptive statistics of the subject population as well as of the outcome variables collected were attained.
The distribution of the outcome variables were examined using histograms, box-plots, and tests for normality. Special services needs for the Duarte study group were examined in comparison to the population values of such services. Sex, diet, developmental problems, and neuropsychological complications such as early intervention and special services between the study groups were further examined using chi-squared analyses.

Cognitive developmental differences between the Duarte study group and classic galactosemia group were compared using their means and standard deviations. To account for the small number of patients in which repeated measures were attained, the average of developmental scores from either infant or IQ tests for those patients with more than one examination was used. Tests were also performed using all scores instead of averages and no difference or change in significance was found. The results remained the same. Because the majority of the subjects in the study presented with at least an infant test for development, infant test scores from before 1 year of age and infant test scores at 1 year of age or older were described separately as age groups within each diagnosis for some analyses. To examine the differences between cognitive and/or language developmental scores versus motor development scores within test groups, t-tests for paired samples were used where data had normal distribution. Wilcoxon Signed-Rank tests for paired samples were used where data sets had non-normal distribution. Independent samples t-tests were used to compare infant tests scores between age groups before and after 1 year old for
the Duarte and classic galactosemia populations where data followed a normal
distribution and Mann-Whitney U independent samples tests were used for data
that were of non-normal distribution.

While data were collected for all patients in the convenience sample that
had some form of galactosemia, those with some other variant form of the
disease were not considered in the formal analysis. The reasons for this are that
the Duarte galactosemia patients were the primary group of the study, the classic
galactosemia patients represented a control group, and the other variant group
had a very small sample size and was less homogenous.
RESULTS

Description of the Study Sample

Among the 108 study subjects, there were 22 patients diagnosed with Duarte galactosemia, 73 patients diagnosed with classic galactosemia, and 13 patients diagnosed with some other variant form of galactosemia. There were 3 clinical charts reviewed but excluded from the study since these charts were found without any developmental tests—2 patients were diagnosed with classic galactosemia and 1 patient was diagnosed with Duarte galactosemia. The patients ranged in age from 6 months to 40 years at the time of their visit or visits. Table 1 depicts the counts of males, females, and diets followed within the Duarte and classic galactosemia groups. Among the 22 Duarte galactosemia patients, there were 9 (40.9%) males and 13 (59.1%) females. Within the 73 classic galactosemia patients, there were 39 (53.4%) males and 34 (46.6%) females. There was no significant difference between the number of males and females within the Duarte or classic galactosemia groups.

In regards to diet history, 4 (18.2%) of the 22 Duarte galactosemia patients were recorded to be on a galactose-restricted diet at the time of the examination. However, 2 of the 4 patients on a galactose-restricted diet were on such a diet because of milk allergies or lactose intolerance and not because of their Duarte galactosemia diagnosis. There were 15 (68.2%) Duarte galactosemia patients recorded to have never been on a galactose-restricted diet
while 3 (13.6%) Duarte galactosemia patients were on a galactose-restricted diet for only a brief time of their lives. In the classic galactosemia group, 72 (98.6%) of these patients were on a galactose-restricted diet, 1 of which was on a true galactose-free diet and was strictly restricted from all lactose-containing foods including fruits and vegetables with the sugar. Only 1 (1.4%) classic galactosemia patient was recorded to be on a galactose-restricted diet briefly.

Within the Duarte galactosemia cohort, 20 (90.9%) patients were found to have a heterozygous genotype with one Duarte gene and one classic galactosemia gene for a genotype of N314D/Q188R. There was 1 (4.5%) patient with a different heterozygous genotype of one Duarte gene and one African-American galactosemia gene described as N314D/S135L. Lastly, 1 (4.5%) patient included in this group had a homozygous Duarte genotype described as N314D/N314D.

Table 1 Basic Description of Study Sample

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>On Diet</th>
<th>On Diet Briefly</th>
<th>Never on Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duarte Galactosemia</td>
<td>22</td>
<td>9</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40.9%</td>
<td>59.1%</td>
<td>18.2%</td>
<td>13.6%</td>
<td>68.2%</td>
</tr>
<tr>
<td>Classic Galactosemia</td>
<td>73</td>
<td>39</td>
<td>34</td>
<td>72</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53.4%</td>
<td>46.6%</td>
<td>98.6%</td>
<td>1.4%</td>
<td></td>
</tr>
</tbody>
</table>

Special Services: Early Intervention

Table 2 shows how many patients needed early intervention in the Duarte and classic galactosemia groups. Early intervention services were any therapies or other developmental assistance used by patients from birth until the age of 3.
In the Duarte galactosemia cohort, 18 of the 22 patients contained recorded information regarding the participation or non-participation of early intervention services. Of those 18 Duarte galactosemia patients, 7 (38.9%) patients confirmed participation in early intervention services and 11 (61.1%) patients did not use these services. Among the 7 patients that participated in early intervention, 2 patients were on a galactose-restricted diet, 2 patients were on a diet for a brief time in their lives, and 3 patients were never on a diet. Among the 11 patients that did not participate in early intervention, 1 patient recorded to be on a diet and 1 patient recorded to be on a diet briefly.

In the classic galactosemia group, 51 patients were known to either participate or not participate in early intervention services. Among those 51 classic galactosemia patients, 37 (72.5%) patients confirmed participation in early intervention services while 14 (27.5%) patients did not use these services. All 37 classic patients that participated in early intervention were on a galactose-restricted diet.

In a chi-squared analysis for diagnosis and early intervention, it was found that disease and early intervention variables were significantly dependent (p=0.005). There were less Duarte galactosemia patients participating in early intervention and more classic galactosemia patients participating in early intervention than would be expected if early intervention and disease group were not correlated.
Table 2 also illustrates what services were used for those participating in early intervention within the Duarte and classic galactosemia groups. Among the 7 Duarte patients that used early intervention services, the number of patients exceeded 40% in all categories of the type of early intervention used. Speech therapy was the most frequent type of early intervention used as 5 (71.4%) of the 7 Duarte patients in early intervention needed it for speech. This is comparable to the percentage of classic galactosemia patients where 26 (70.3%) of 37 classic patients were in early intervention for speech therapy. The next frequent type of early intervention used in the Duarte group was physical therapy where 4 (57.1%) of the 7 Duarte patients used it. Only 10 (27%) of the 37 classic patients in early intervention used physical therapy. For occupational therapy or other developmental therapy, 3 (42.9%) of the 7 Duarte patients were recorded in each of these services. For the classic group, 14 (37.8%) of the 37 and 11 (29.7%) of the 37 classic patients in early intervention used occupational therapy and other developmental therapy respectively.

Table 2 Early Intervention Needs for Duarte Galactosemia and Classic Galactosemia.

<table>
<thead>
<tr>
<th>Early Intervention</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duarte Galactosemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>38.9%</td>
<td>61.1%</td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>71.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic Galactosemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>14</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>72.5%</td>
<td>27.5%</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Count</td>
<td>Percentage</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td>26</td>
<td>70.3%</td>
<td></td>
</tr>
<tr>
<td>Physical Therapy</td>
<td>10</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>14</td>
<td>37.8%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>29.7%</td>
<td></td>
</tr>
</tbody>
</table>

Note: count and percentages for each type of service calculated from the count of “yes” to early intervention.

**Special Services: Special Education**

Table 3 presents the numbers of patients in special education within the Duarte and classic galactosemia groups. Special education services were any therapies or other developmental and academic assistance used by patients greater than age 3 at which they are entering school-attending age. For the Duarte patients, 18 of the 22 subjects were known to either have participated or not participated in special education. Of those 18 patients, 4 (22.2%) participated in special education services while 14 (77.8%) did not. Among the 4 patients that participated in special education, 2 were recorded to be on a diet while the other 2 were never on a diet.

In the classic galactosemia group, 57 patients contained known information regarding the use of special education services. Among those 57 classic galactosemia patients, 43 (75.4%) patients were recorded to have participated in special education and 14 (24.6%) patients did not. All but one of the 43 classic patients that had special education were on a diet. The one that was not on a diet at the time of the visit had been on a diet previously.
In a chi-squared analysis for diagnosis and special education, it was found that the two variables were also significantly dependent (p<0.001). There were less Duarte galactosemia patients in special education and more classic galactosemia patients in special education than would be expected if special education and disease group were not correlated.

Table 3 also demonstrates the specific services used for special education among the Duarte and classic galactosemia groups. Within the Duarte cohort, those found to participate in special education and the resulting types of special education decreased to 4 patients. Among those 4 patients, all (100%) of them participated in special education services for speech. These means that 4 (22.2%) of the 18 Duarte patients whose participation in special education services was known needed speech therapy. In the classic group, 35 (81.4%) of the 43 classic patients partook in special education services for speech. For special education services in physical therapy and occupational therapy, only 1 of the 4 and 2 of the 4 Duarte patients in special education used physical and occupational therapy. In the classic group, there were 15 (34.9%) and 26 (60.5%) of the 43 classic patients in special education that needed physical and occupational therapy. Finally, none of the Duarte galactosemia patients in special education required any special services for academic problems. In comparison, 25 (58.1%) of the 43 classic galactosemia patients required special education for academic problems.
Table 3 Special Education Needs for Duarte Galactosemia and Classic Galactosemia

<table>
<thead>
<tr>
<th>Special Education</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duarte Galactosemia</strong></td>
<td>4</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Speech</td>
<td>4</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Physical Therapy</td>
<td>1</td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>2</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Other (Academics)</td>
<td>0</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td><strong>Classic Galactosemia</strong></td>
<td>43</td>
<td>14</td>
<td>57</td>
</tr>
<tr>
<td>Speech</td>
<td>35</td>
<td></td>
<td>81.4%</td>
</tr>
<tr>
<td>Physical Therapy</td>
<td>15</td>
<td></td>
<td>34.9%</td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>26</td>
<td></td>
<td>60.5%</td>
</tr>
<tr>
<td>Other (Academics)</td>
<td>25</td>
<td></td>
<td>58.1%</td>
</tr>
</tbody>
</table>

Note: count and percentages for each type of service calculated from the count of “yes” to special education.

Developmental Testing Outcomes

For Bayley Scales of Infant Development, the Cognitive/MDI score distributions were found to be non-normal and thus non-parametric tests were used for any analysis involving cognitive/MDI scores. The language and motor/PDI scores were found to have normal distribution.

Table 4 describes the Bayley scores from before 1 year of age and from equal to or after 1 year of age for the Duarte galactosemia patients. There were 19 of 22 Duarte patients that had at least one recorded Bayley test. Some of these Bayley tests were given prior to the age of 1 and some at or after the age of 1. At the age of less than 1 year, the mean cognitive/MDI score was 109.5
(Standard deviation (SD) =6.26; n=8), the mean language score was 105.57 (SD=12.18; n=7), and the mean motor/PDI score was 98.25 (SD=12.54; n=8). At the age of greater than or equal to 1 year, the Duarte galactosemia cohort presented with a mean cognitive/MDI score of 108.74 (SD=13.95; n=15), a mean language score of 104.5 (SD=15.81; n=12), and a mean motor/PDI score of 100.58 (SD=18.69; n=15). Overall, the scores from the Duarte patients were within average range of the Bayley Scales of Infant Development demonstrating no problems in early developmental testing.

Table 4 Bayley Scales of Infant Development: Duarte Galactosemia
Average Bayley Scales of Infant Development scores for the Duarte cohort before 1 year of age and equal to or after 1 year of age.

<table>
<thead>
<tr>
<th>Duarte Galactosemia</th>
<th>n</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive/MDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;1</td>
<td>8</td>
<td>109.50</td>
<td>6.26</td>
</tr>
<tr>
<td>Age ≥ 1</td>
<td>15</td>
<td>108.74</td>
<td>13.95</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;1</td>
<td>7</td>
<td>105.57</td>
<td>12.18</td>
</tr>
<tr>
<td>Age ≥ 1</td>
<td>12</td>
<td>104.50</td>
<td>15.81</td>
</tr>
<tr>
<td>Motor/PDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;1</td>
<td>8</td>
<td>98.25</td>
<td>12.54</td>
</tr>
<tr>
<td>Age ≥ 1</td>
<td>15</td>
<td>100.58</td>
<td>18.69</td>
</tr>
</tbody>
</table>

Table 5 describes the Bayley scores from before 1 year of age and from equal to or after 1 year of age in the classic galactosemia group. There were 44 of the 73 classic patients that had at least one recorded Bayley test. Some of these tests were given prior to the age of 1 year and some given at equal to or after the age of 1 year. For the age of less than 1 year, the mean cognitive/MDI score was 106.32 (SD=16.38; n=28), the mean language score was 111.4 (SD=19.58; n=5), and the mean motor/PDI score 96.48 (SD=18.52; n=25). For the classic galactosemia group at an age of greater than or equal to 1 year, the
mean cognitive/MDI score was 98.33 (SD=16.58; n=35); the mean language score was 99.92 (SD=12.55; n=12), and the mean motor/PDI score was 97.34 (SD=20.22; n=26).

Table 5 Bayley Scales of Infant Development: Classic Galactosemia
Average Bayley Scales of Infant Development scores for the classic cohort before 1 year of age and equal to or after 1 year of age.

<table>
<thead>
<tr>
<th>Classic Galactosemia</th>
<th>n</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive/MDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;1</td>
<td>28</td>
<td>106.32</td>
<td>16.38</td>
</tr>
<tr>
<td>Age ≥ 1</td>
<td>35</td>
<td>98.33</td>
<td>16.58</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;1</td>
<td>5</td>
<td>111.40</td>
<td>19.58</td>
</tr>
<tr>
<td>Age ≥ 1</td>
<td>12</td>
<td>99.92</td>
<td>12.55</td>
</tr>
<tr>
<td>Motor/PDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;1</td>
<td>25</td>
<td>96.48</td>
<td>18.52</td>
</tr>
<tr>
<td>Age ≥ 1</td>
<td>26</td>
<td>97.34</td>
<td>20.22</td>
</tr>
</tbody>
</table>

A longitudinal analysis was done for the disease groups to compare the differences in the scores from before 1 year old to scores equal to or after 1 year old. For the cognitive/MDI scores, the Mann-Whitney U tests for the separate age groups were used. There was no significance difference in the Duarte galactosemia group between the cognitive/MDI scores from before 1 year and equal to or after 1 year of age. There was a significance difference in the classic galactosemia group between the cognitive/MDI scores from before 1 year and equal to or after 1 year of age (p=0.028). For the language and motor/PDI scores, comparisons of the differences between these scores before and equal to or after 1 year of age were found using independent samples t-tests. In both the Duarte and classic groups, there was no significant difference between the language scores or between the motor scores before and equal to or after the age of 1.
Paired comparisons within the disease groups were also performed to examine the differences between cognitive/MDI scores versus motor/PDI scores as well as language scores versus motor/PDI scores. These comparisons were separated at age before 1 and at age equal to or after 1. To compare the cognitive/MDI and motor/PDI scores, Wilcoxon Signed-Rank tests for paired samples were used. Paired-samples t-tests were used for the language and motor/PDI comparisons. In the Duarte group, there existed a significance difference between the cognitive/MDI score and the motor/PDI score at an age less than 1 (p=0.028). This was the same for the classic galactosemia group (p<0.001). The cognitive/MDI mean scores were 11.25 (Duarte) and 9.84 (classic) points higher than the motor/PDI mean scores. There was no significant difference between the language and motor/PDI scores for the Duarte or the classic groups at the age of less than 1.

At an age equal to or greater than 1, the Duarte group continued to show a significant difference between the cognitive/MDI score and the motor/PDI score (p=0.017). The cognitive/MDI mean score was 8.16 points higher than the motor/PDI mean score. However, there was no longer a significant difference between the cognitive/MDI and motor/PDI scores within the classic group at an age equal to or greater than 1. The difference between the cognitive/MDI and motor/PDI mean scores in this age group for the classic cohort was just 0.99. In both the Duarte and classic groups, there remained no significant difference
between the language and motor/PDI scores at the age of greater than or equal to 1.

For developmental tests beyond the Bayley Scales of Infant Development, 6 Duarte galactosemia patients had an IQ test. As noted in Table 6, the mean verbal comprehension score was 109.11 (SD=11.39; n=6), the mean perceptual performance score was 112.45 (SD=10.49; n=6), and the mean full scale score was 111.4 (SD=11.99; n=5). The Duarte patients' scores were within average range of normal values.

**Table 6 Intelligence Quotient Scores: Duarte Galactosemia**
Average verbal comprehension, perceptual performance, and full scale IQ scores for the Duarte cohort.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Comprehension</td>
<td>6</td>
<td>109.11</td>
<td>11.39</td>
</tr>
<tr>
<td>Perceptual Performance</td>
<td>6</td>
<td>112.45</td>
<td>10.49</td>
</tr>
<tr>
<td>Full Scale</td>
<td>5</td>
<td>111.40</td>
<td>11.99</td>
</tr>
</tbody>
</table>

“Any” Developmental Outcomes and Diet

Within the Duarte cohort, a variable was created using the data to examine whether any developmental problem was associated with an adherence to a diet at any point in life. Duarte patients in this study were separated into a group for any developmental problem based on whether they had at least one of the following: early intervention, special education, or a difference of at least +10 between the average cognitive/MDI and motor/PDI score either before or after the age of 1. Table 7 presents the number of Duarte patients with any developmental problem cross-tabulated with diet history. It was found that 6 (85.7%) of the 7 Duarte subjects recorded to either have been on a diet or were
currently on a diet fell under the category of having any developmental problem.

Of the 15 Duarte patients that were never on a diet, 7 (46.67%) patients were also found to have one of the developmental problems. Upon chi-square analysis, the variables of diet and any developmental problem were found not independent and not significant.

Table 7 Any Developmental Problem and Diet in the Duarte Cohort

<table>
<thead>
<tr>
<th>Diet</th>
<th>Has either early intervention, special education or at least 10 point difference between Cognitive/MDI and Motor/PDI</th>
<th>Has no problem</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>On diet currently or at some point</td>
<td>6 (85.71%)</td>
<td>1 (14.29%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>Never on diet</td>
<td>7 (46.67%)</td>
<td>8 (53.33%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (59.09%)</td>
<td>9 (40.91%)</td>
<td>22 (100%)</td>
</tr>
</tbody>
</table>

Indications of Speech or Language Problems in the Duarte Galactosemia Cohort

Since speech therapy is the most prevalent service used among the Duarte population, a closer examination was performed on the data with a focus on any complications in speech or language. As mentioned above, there were records of Duarte patients that had speech therapy in early intervention or special education. However, there were also Duarte patients with other chart findings in relation to speech and language, such as speech and language skills that were less developed than cognitive or motor skills. In total, 11 (50%) of the
22 Duarte patients had either speech therapy or a chart note expressing that the speech or language skills were less developed at the time of testing. Among the 11 patients, 4 patients did not have speech therapy but did have lower language scores and a note of less-developed speech and language skills in comparison to their cognitive and motor skills. Developmental testing showed all the scores were within average range, but that the language score fell lower in the average range. The remaining 7 patients had speech therapy and corresponding speech and language difficulties or delays in the chart notes, with the exception of one who was noted to have very well developed language skills. Additionally, 4 of the 11 patients had a diet history and 7 patients were never on a diet.
DISCUSSION

In the cohort of Duarte galactosemia patients, the results were both surprising in certain areas and consistent with prior literature in other areas. In the primary study group, the Duarte galactosemia patients were found not to show decline in their developmental scores. For the Bayley Scales of Infant Development, none of the scales in this test fell below 98.25. This was the mean motor/PDI score for Duarte subjects before the age of 1. Even so, the cognitive/MDI and language scores before and equal to or after 1 year of age as well as the motor/PDI score equal to or after 1 year of age were at least 100. At older ages in which subjects were given IQ tests, the mean verbal comprehension, perceptual performance, and full scale scores were each over 108, well within average range. Ficicioglu et al (2008) found that their Duarte subjects all had normal range developmental quotients (Ficicioglu et al., 2008). While the findings in this study are consistent with the study by Ficicioglu et al (2008) it remains difficult to discern a developmental problem solely from these test scores. The test scores used suggest normal development but, since the majority of the test scores were performed at a very early age, they may not be an accurate reflection of the complete neurological development in these patients. Some Duarte patients in this study did have intelligence tests at an older age. However, with the small Duarte sample in this study and even fewer of that sample with developmental tests at an older age, it is still difficult to
definitely eliminate any developmental problems based on all the test scores alone.

The classic group had results similar to previous studies. To summarize, the classic group was found to have high incidences of early intervention and special education. There was need for speech therapy both early in development as well as later in the school-age years. This corroborates past findings indicating that classic galactosemia patients are at a higher risk for speech and language disorders throughout childhood, adolescence, and adulthood (Hoffmann, Wendel, & Schweitzer-Krantz, 2011; Potter et al., 2008; Ridel et al., 2005; Waisbren et al., 1983). The classic galactosemia patients in this study also experienced declines, even early on, in developmental quotients after 1 year of age. The motor/PDI scores in the classic galactosemia toddler years remained under 100 before and after 1 year of age and their cognitive and language scores followed suit in tests after 1 year of age. In intelligence tests at older ages, the classic group had a majority of low verbal comprehension (mean of 85.21±17.16), perceptual performance (mean of 86.25±18.36), and full scale scores (mean of 85.21±19) but showed some variability. Finally, these results were found despite the adherence to a galactose-restricted diet. These cognitive findings are consistent with previous studies documenting cognitive impairment and generalized reduced IQ (Antshel et al., 2004; Nelson, 1991; Ridel et al., 2005; Schadewaldt et al., 2010; Waggoner et al., 1990).
Comparing the infant scores of the Duarte group to the classic group, it was interesting to see the longitudinal differences before a year old and after a year old. Both the Duarte cohort and classic group had similar significant differences between the mean cognitive scores and mean motor scores before 1 year of age. However, once patients were 1 year old or after, the classic galactosemia group started to separate as expected. They now had cognitive and motor scores that were lower overall and the cognitive and motor scores were no longer significantly different. The Duarte group still had significantly higher cognitive scores than motor scores. This suggests that based on developmental tests, the Duarte group develops consistently in early infancy and toddler years and does not show declines in development like the classic group. Again, at the young age in which these tests are performed, the scores are subject to variability and may be unable to depict learning problems. Taken all together, it remains difficult to distinguish issues in development just from these test scores.

The study results did, however, depict some possible developmental issues in Duarte galactosemia patients from the information acquired of the need and use of special services, such as early intervention and special education. Powell et al (2009) found in their study that a high percentage of Duarte galactosemia patients in the Atlanta, Georgia area were receiving special education, particularly for speech and language disorders (Powell et al., 2009). When they restricted their study to subjects of age 8, they found that the
percentage of Duarte subjects receiving special education was 2.5 times that of the general population in Atlanta (Powell et al., 2009). Similar to the study by Powell et al (2009), this study also found high percentages in special services but in the use of both early intervention services and special education services. Where participation in early intervention was known, almost 40% of the Duarte patients were confirmed for these services. Among those patients, the majority of them (71%) needed speech therapy and greater than 40% required physical therapy, occupational therapy, or other help during their infant and toddler years.

A high percentage of the Duarte patients were also confirmed to participate in special education. While the number of patients in special education was below that for early intervention (22%), it was found that some learning problems still existed as these patients reached school age. There was less of a need for physical therapy and occupational therapy as well as no need for academic help. However, what is remarkable among the Duarte patients in special education is that all (100%) of them were in speech therapy. This suggests that the need for speech therapy remained high throughout the infant and toddler ages to school-attending ages in this Duarte population. Even though developmental testing indicated consistent cognitive development, these data on early intervention and special education show that developmental problems may have been masked by the within-average test scores.

Compared to the general population, the findings of special services for the Duarte population in this study are striking. While the chi-squared analysis
showed that Duarte patients were expected to participate less in these services due to their milder disease form compared to the classic patients, there was no indication that the Duarte patients needed the services less than the unaffected population. Perhaps the correlation indicates a developmental problem in the Duarte population that is less severe than the classic group but existent nonetheless. A recent report found that 2.4% of infants and toddlers in the general population were reported to receive early intervention services (Blackorby et al., 2010). This study showed that the Duarte group exhibited much higher percentages than 2.4% in early intervention. The same report found that 12.9% of school-age children in the general population receive special education (Blackorby et al., 2010). This study showed again that the percentage of Duarte patients in special education remained higher than the general population. With such a rare disease and a resultant small sample size, it was difficult to make statistical conclusions as to whether the prevalence of services in this Duarte population was higher than what would have been expected by chance among the national population. However, the findings are described and discussed compared to found population percentages and are consistent with the findings by Powell et al (2009)—more Duarte patients used special services compared to the general population. Therefore, this study suggests Duarte galactosemia patients exhibit an increased need of special services compared to those children of the general population. Developmental problems in Duarte galactosemia may
be more evident in the education services that are used rather than the test scores that are attained.

Classic galactosemia patients are known to be at risk for speech delays and language impairments (Hoffmann et al., 2011; Potter et al., 2008; Ridel et al., 2005; Waisbren et al., 1983). Among the general population, there is 8-9% prevalence of speech and language disorders (“Quick Stats for Voice, Speech, and Language [NIDCD Health Information],” 2010). In this study, the proportion of Duarte patients in speech therapy was high. It was found that 5 (27.8%) of the 18 Duarte patients whose information regarding early intervention was known needed speech therapy and 4 (22.2%) of the 18 Duarte patients whose information regarding special education was known needed speech therapy. The patients needing speech therapy had recorded notes of speech and language difficulties and/or delays. Compared to the national percentage, the prevalence of speech therapy in this study suggests that the percentage of Duarte galactosemia patients with speech and language disorders is about 3 times higher than the general population. Thus, there may be developmental problems particularly in the areas of speech and language for Duarte galactosemia patients. This problem may not be similar in severity to the classic group but can be a significant problem in comparison to children without this disease.

Furthermore, the data suggest that speech problems may arise during the infant and toddler years for Duarte galactosemia patients but that these problems do not appear to be coupled with an overall intelligence test decline like the
classic galactosemia counterparts. There were Duarte patients in this study which did not have speech therapy but had Bayley language scores that were less-developed compared to the other areas of measurement yet still within an average range. Hence, not only may Duarte patients experience some delays in the speech and language area, but these delays may be evident early in development and despite normal range test scores.

Lastly, diet therapy for the Duarte cohort continues to remain puzzling in its positive or negative effects. The Duarte patients that were found to have developmental problems or less-developed speech or language were those with and without a diet. There was no indication or statistical significance that diet correlated with a developmental outcome or special service. This study is unable to determine if diet affected the use of services or developmental scores.

One limitation of this study was the small sample size of Duarte galactosemia patients from the convenience sample of patient charts. Since this study relied on the patient files among a stored record of neuropsychological or developmental testing, it is possible that Duarte patients whose charts were never placed in these files were missed. Another limitation to this study was that the review was limited to what was available within the clinical charts. Therefore, it was difficult to discern if the Duarte patients had other reports or measurements regarding any developmental history prior to their visits. An inclusion bias was a limitation of this study. Since the review was from a convenience sample of charts, it is possible that these patients only came into
the metabolism clinic because they already showed problems. Other patients might have come in only because of a suggestion from their pediatrician and were otherwise fine after just one examination. Classic patients typically undergo neuropsychological evaluations because of the high risk of developmental problems. Thus, it is possible that some Duarte patients might have come in after parents learned of the outcomes of classic galactosemia and wanted to confirm that their Duarte child did not have similar symptoms. Finally, there were no siblings of Duarte galactosemia patients with homozygous normal alleles among the convenience cohort that could have represented a normal control group.

Despite these limitations however, this study did have important strengths. The test results and clinic reports of the Duarte population were from actual in-person psychological evaluations. The visits involved conversations between patients and their guardians and the senior psychologist. Patient testing, test results and visit evaluations were performed, tabulated and reported by the senior psychologist. Consequently, this study was able to gather valuable data among the Duarte cohort and a beneficial database was created for Duarte galactosemia patients. Furthermore, a compilation of certain outcomes within the Duarte population provided an opportunity to examine the Duarte patients as a whole.
CONCLUSION

Most of the patients found to have the Duarte form of galactosemia often do not show any clinical signs of a disease and many specialists in the metabolic field believe that Duarte galactosemia is not a disease entity (Berry & Walter, 2012; Louis J Elsas, 1993; Ficicioglu et al., 2008; Fridovich-Keil & Walter, 2013). This study found some developmental problems in the Duarte population in the areas of the need for special services. While the Duarte group did not experience large deficits in the test scores compared to their classic counterparts, they did demonstrate the need for help and therapies in early infant and toddler ages as well as when they were of school-attending age. The severity of the long-term outcomes does not seem to match those of the classic galactosemia patients. Yet, the Duarte group showed a higher incidence in both early intervention and special education than the general population, particularly in the area of speech therapy. Thus, the Duarte galactosemia population appears to be at a higher risk for speech and language problems compared to a child without the disorder. Additionally, this study also showed no evidence that the use of diet-therapy for this group prevented problems. Treating a Duarte galactosemia patient did not prevent any need for special services but not treating a Duarte patient did not result in not needing those services either.

These findings challenge the belief that Duarte galactosemia is a benign disease. Consequently, a continuation of routine examinations for Duarte
patients may need to be implemented to more closely monitor these patients. Future studies involving a larger sample size of Duarte galactosemia patients would provide more insight to the network of possible problems that these patients may experience throughout life. Additionally, an effort to study the adult population of Duarte galactosemia would be a worthwhile study objective since a large number of unstudied Duarte patients may now be adults. Finally, a long-term prospective study can further confirm the prevalence of developmental problems and when they arise. This would help determine whether Duarte galactosemia patients can be expected to adapt to the problems, will continue to need services, or are at risk for other problems in behavior and socialization. Ultimately, it can help provide a more definitive consensus about the perplexing issues in Duarte galactosemia.
REFERENCES


galactosemia allele. *American Journal of Human Genetics, 54*(6), 1030–1036.


developmental issues among children with Duarte galactosemia. *Genetics in Medicine, 11*(12), 874–879. doi:10.1097/GIM.0b013e3181c0c38d


CURRICULUM VITAE

CATHERINE T. TRAN

6 Worcester Square ▪ Boston, MA ▪ 02118
catherine.tran87@gmail.com
(408) 693-4624
1987

EDUCATION

Boston University, Boston, MA ▪ Expected: 2014
Candidate for Master of Science in Medical Sciences

University of California, Berkeley, Berkeley, CA ▪ 2009
Bachelor of Arts in Molecular and Cell Biology

RESEARCH EXPERIENCE

University of California, San Francisco and the San Francisco Injury Center, San Francisco, CA
June 2009 – August 2011
Research Assistant, Mental Health Study
- Conducted needs assessment and psychiatric interviews to eligible patients
- Correspond with over half of the subjects to complete follow-up interviews
- Review subject charts for past and present hospital visits

PUBLICATION

Dicker, Rochelle A. MD; Mah, Jennifer BS; Lopez, Dahianna MSN, MPH; Tran, Catherine BA; Reidy, Rosemary BS; Moore, Megan BA; Kreniske, Phil BA; Crane, Ian BA; Knudson, M. Margaret MD; Li, Moon NP; Menza, Rebecca NP; Shumway, Martha PhD; Alvidrez, Jennifer PhD. Screening for Mental Illness In A Trauma Center: Rooting Out A Risk Factor For Unintentional Injury. The Journal of Trauma, Injury, Infection and Critical Care 70(6): pp 1337-1344, June 2011

PROFESSIONAL EXPERIENCE

Steven A. Harrison, M.D. APL. Walnut Creek, CA
June 2009 – July 2012
Ophthalmic Technician, Retinal Photographer, Surgery Scheduler
• Prepare patients and evaluate accurate patient medical history and symptoms for ophthalmologists
• Operate a fundus camera to photograph detailed images of the retina
• Coordinate with surgery centers and county hospitals to schedule surgery for patients

Recreational Sports Facility, University of California, Berkeley
April 2007 – July 2012
CalFit Tennis Instructor
• Develop a five-week course curriculum for beginner and low-intermediate tennis enthusiasts
• Modify lesson plans to accommodate individual student needs
• Engage Berkeley community members in appreciating tennis fundamentals and rules

VOLUNTEER EXPERIENCE

Boston Health Care for the Homeless Program, Boston, MA
February 2014 – Present
Foot Clinic Assistant
• Assess patients’ feet for injuries or problems and prepare foot baths for cleaning
• Obtain vital signs such as body temperature, blood pressure, pulse, and blood sugar
• Maintain open communication with nurses and doctors regarding health, needs, and allergies of patients

Rosie’s Place- A Sanctuary for Poor and Homeless Women, Boston, MA
December 2013 – Present
Dining Room Server
• Assist in the preparation of meals in advance to scheduled dining times
• Provide a comfortable environment for patrons with polite and welcoming interactions
• Clean and re-stock the dining area and kitchen at the end of a meal time

Coaching Corps- A Team-Up for Youth Program, Oakland, CA
October 2008 – May 2009
Team-Up for Youth Sports Coach
• Created an environment of youth empowerment through sports education and physical activity
• Established customized lesson plans to help youth accomplish the goals of the program
Instituted an innovative system of responsibility to promote individual youth development

**Oakland Children’s Hospital**, Oakland, CA  
August 2007 – March 2009  
Pediatric Rehabilitation Volunteer, 80.25 Hours  
- Assisted physical therapists in equipment transportation and clean-up during their appointments  
- Maintained an organized gym area for therapist and patient safety  
- Filed and retrieved patient charts upon request by physical therapists

**ACADEMIC ORGANIZATIONS**

**Health and Medical Apprenticeship Program**, University of California, Berkeley  
January 2008 – May 2009  
Public Health 116 Course Teaching Assistant  
- Lead students in weekly discussions about current major public health issues  
- Encouraged students to speak their minds and to broaden their perspectives on the topics presented  
- Participated in weekly Teaching Assistant meetings to prepare for discussion sessions

**Professional Pre-Health Sorority—Kappa Gamma Delta**, University of California Berkeley  
August 2007 – May 2009  
President, Fall 2008 – Spring 2009  
- Guided fellow sisters by demonstrating the sorority values of professionalism, service, and support  
- Delegated tasks and supervised active members to accomplish the goals of each semester  
- Cooperated with sisters to address concerns and suggestions in order to facilitate the progress of the organization