Developmental and Functional Outcomes in Children with a Positive Newborn Screen for Krabbe Disease: A Pilot Study of a Phone-Based Interview Surveillance Technique

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Objective To assess the utility of a telephone-based interview system in providing ongoing monitoring of the developmental and functional status of children with both positive newborn screens for Krabbe disease and low galactocerebrosidase activity on confirmatory testing, and to determine whether this approach provides improved compliance with follow-up compared with formal neuropsychological testing.

Study design Infants with low galactocerebrosidase activity (as detected by the New York State newborn screening program) were eligible for this longitudinal prospective cohort study. Consenting families were interviewed by telephone at infant ages of 4, 8, 12, 18, and 24 months. Designated instruments were the Ages and Stages Questionnaires, the Clinical Linguistic and Auditory Milestone Scale, the Gross Motor Quotient, the Warner Initial Developmental Evaluation of Adaptive and Functional Skills 50, and the WeeFIM II 0-3 instrument. Assessments with the *Bayley Scales of Infant and Toddler Development, Third Edition* (Bayley III) were scheduled at age 12 and 24 months.

Results Seventeen patients were enrolled; 16 were assessed at age 12 and 18 months, and 15 were assessed at age 24 months. Scores were within the normal range on all tests of developmental and functional status, with the exception of expressive language. Only 7 patients completed the *Bayley Scales of Infant and Toddler Development, Third Edition* assessments; all their scores were in the normal range.

Conclusion This telephone-based technique allows close monitoring of the developmental and functional status of children with a positive newborn screen for this neurometabolic disease, with special attention to detecting plateauing or regression of developmental milestones. Compliance is improved compared with formal neuropsychological testing. *(J Pediatr 2012; ■: ■-■).*

Determining the developmental and functional outcomes of children with inherited metabolic diseases who have been identified by newborn screening should be an essential component of all longitudinal follow-up programs. Unfortunately, in New York State and elsewhere, outcomes are not being assessed, because of the high cost of neuropsychological testing (often not reimbursed by insurance companies) and fragmentation of developmental and behavioral surveillance techniques in early childhood. The New York State program of newborn screening for Krabbe disease is unique in that it involves a statewide consortium of child neurologists, geneticists, neuroradiologists, transplantation physicians, and newborn screening providers who are committed to evaluating and following all children with both positive newborn screening tests and confirmatory testing using a specific schedule of agreed-upon neurodiagnostic and neurologic tests. When the program began in 2006, the predicted (based on the literature) incidence of Krabbe disease was 1/100 000 live births, with 90% of identified infants having the early infantile phenotype.[1] By the end of the second year of testing, however, it became clear that the majority of infants with positive newborn screens and very low galactocerebrosidase (GALC) activity were clinically normal during infancy.[2] Whether these children would develop later-onset forms of the disease or remain clinically unapparent indefinitely was unclear. It also was unknown whether children with very low GALC activity would have learning or other neurodevelopmental disorders in the absence of frank disease. Consequently, we sought to document the developmental and functional status of a cohort of children who had a positive newborn screening test for Krabbe disease and low GALC activity on confirmatory testing. The children

ASQ 2	Ages and Stages Questionnaire, 2nd edition
BAILEY II	*Bayley Scales of Infant and Toddler Development, Second Edition*
BAILEY III	*Bayley Scales of Infant and Toddler Development, Third Edition*
CLAMS	Clinical Linguistic and Auditory Milestone Scale
GALC	Galactocerebrosidase
GMQ	Gross Motor Quotient
WIDEA-FS 50	Warner Initial Developmental Evaluation of Adaptive and Functional Skills, 50 Items

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were studied at intervals through a combination of parent questionnaires, a telephone-based data collection technique, and formal neuropsychological testing.

Methods

In this longitudinal, prospective cohort study, all infants born in New York State identified as having a positive newborn screen for Krabbe disease and confirmatory low GALC activity were eligible for enrollment. Institutional Review Board approvals were obtained at the University at Buffalo, Upstate Medical Center, Strong Memorial Hospital, Albany Medical Center, Montefiore Medical Center, and State University of New York at Stony Brook Medical Center. Families of confirmed affected infants were invited to participate in the telephone-based interview study of developmental and functional skills. For each family who consented in writing, contact information was transmitted to the interviewer, who then conducted telephone interviews when the child was 4, 8, 12, 18, and 24 months old. Only one interviewer participated in this study, a certified pediatric nurse practitioner with >30 years experience in developmental and behavioral assessments.

The family was sent the age-appropriate Ages and Stages Questionnaire-II (ASQ 2) to complete before the telephone interview.[3] Responses on the questionnaire were reviewed on the telephone with the parent/caregiver. The interviewer then conducted the following criterion reference assessments: the Clinical and Linguistic Auditory Milestone Subscale (CLAMS) of the Capute Scales,[4] the Gross Motor Quotient (GMQ) of Capute and Shapiro,[5] the WeeFIM II 0-3,[6] and the Warner Initial Developmental Evaluation of Adaptive and Functional Skills, 50 Items (WIDEAS-FS 50).[7] (For both the CLAMS and the ASQ 2, parents were requested to attempt the task in question with their child if it was not something that was observed routinely.) Results were discussed with the parent/caregiver, and appropriate developmental resource information was provided when indicated. Results of the developmental and functional assessments were also sent to the referring neurologist. The *Bayley Scales of Infant and Toddler Development, Third Edition* (Bayley III) test was administered at age 12 and 24 months.[8] Children considered at risk for developmental delays were referred to an early intervention program in their geographic area.

Developmental Assessments

The ASQ 2 is a parent-completed child monitoring system consisting of 30 developmental items at each age assessed.[3] It is divided into 5 areas each comprising 6 questions: communication, gross motor, fine motor, problem solving, and personal social. Items were chosen that reflected skills that could easily be observed by parents and those likely to occur in a home setting. The questions are worded simply and do not require a reading comprehension beyond the sixth grade level. The questionnaire can be completed in 10-15 minutes. This instrument is scored as pass or fail.

The ASQ 2 was validated with the *Bayley Scales of Infant and Toddler Development, Second Edition* (Bayley II) in a low-risk sample of children at age 24 months. Scores on the ASQ 2 communication domain were found to significantly correlate with the Bayley II ($P = .001$), as did the scores on the ASQ 2 gross motor ($P = .01$), but the ASQ 2 problem solving and fine motor domains did not correlate.[9] The ASQ 2 was found to have a sensitivity of 100% and specificity of 87% at 24 months (n = 40) for severely delayed status, using a Bayley II score cutoff of <70.

The Capute Scales are designed to assess the language and visual-motor streams of development that underlie cognitive skills in children aged 1-36 months. Specifically, the CLAMS measures expressive and receptive language development.[4] Because most children do not consistently manifest their complete verbal expressive abilities when interacting with unfamiliar adults, the expressive language skills score relies on parental report. The CLAMS includes 26 criterion-specific expressive language items that extend over the age range of 1-36 months. Receptive language milestones of the CLAMS subscale combine historical information from the parent as well as the child's demonstration of language understanding by an action. From these items, a CLAMS Developmental Quotient can be calculated.

The Capute Scales have been validated in a normal population of children aged ≤36 months compared with the Bayley II.[4] The criteria used for comparison were CLAMS and Bayley II scores of <75, which would qualify the child for early intervention services.

Capute and Shapiro[5] also developed a gross motor milestone scale, the GMQ, to complement the CLAMS. The GMQ is calculated by dividing the child's motor age by the chronological age. Both the CLAMS and the GMQ can be completed in 5 minutes. Scores on both the CLAMS developmental quotient and motor quotient >85% are considered normal (pass), 70%-85% are considered mild delay, <70% are considered severe delay.

Functional Assessments

The WeeFIM II 0-3 instrument is designed to assess precursors to function that children aged newborn to 36 months need to acquire to perform basic daily living skills. The measure has been validated in a normal and an impaired population.[6] The instrument includes 36 items in 3 domains: motor (16 items), cognition (13 items), and behavior (7 items). The motor and cognitive domains comprise items that measure physical and cognitive functioning. The behavior domain includes items intended to reflect difficulties during parent/caregiver–child interactions rather than a hierarchy of behaviors intrinsic to the child; thus, it could serve as an early warning of suboptimal parent/caregiver interaction. Each item is rated on a 3-level ordinal scale to indicate frequency of occurrence, with 1 representing "rarely/never," 2 representing "sometimes," and 3 representing "usually". Because each item is intended to reflect the parent or caregiver's perceptions, the preferred method of data collection is report by

the parent(s) or primary caregiver(s) most familiar with the child. The assessment takes 10 minutes to complete.[6]

The WIDEA-FS 50 is a 50-item criterion-specified assessment of basic activities for children aged 1-29 months. It was designed to capture essential mobility, self-care (eg, feeding, drinking, diaper awareness), communication, and social cognitive skills. Interviews are conducted with either the child's parents or individuals who have observed the child's performance during daily routines. The WIDEA-FS 50 requires 15 minutes to administer by telephone.[7,10,11] Normative data for the WIDEA-FS 50 was obtained by evaluations of both unaffected and neurologically at-risk children. There was a robust correlation between chronologic age and WIDEA-FS 50 total score ($R^2 > 88$; $P < .001$) over the first 15 months of life.[12,13]

Neuropsychological Assessment

The Bayley III is a formal neuropsychological assessment that includes cognitive language, motor, social-emotional, and adaptive behavior scales.[8] The test takes more than 1 hour to administer. The normative sample of the Bayley III involved 1700 children aged 1-42 months that were stratified to reflect the demography of the 2000 US census. Validation studies included explicit concurrent measures of motor, communicative, and adaptive skills as well as construct validity in 622 children with or at high risk for neurodevelopmental disabilities.[8]

Statistical Analysis

All data analyses were done using SPSS version 14.0 (SPSS Inc, Chicago, Illinois). Common domains among the WeeFIM II 0-3, the ASQ 2, the CLAMS, the GMQ, the IDEA-FS 50, and the Bayley III were identified, and similar items within the domains between instruments were matched and cross-walked to determine percent agreement between measures. Pearson correlations were performed on the WIDEA-FS 50 total score, WeeFIM 0-3 total score and ASQ 2 composite scores at age 4, 8, 12, 18, and 24 months to identify any significant correlations at each age interval. Because functional and adaptive skills in motor, self-care, and communicative domains may be indicators of neurologic integrity, individual domains over time were compared with the normative sample of typically developing children.

Results

A total of 17 children (8 males and 9 females) were enrolled in the study. Two participants were lost to follow-up, one after 8 months and the other after 18 months. All 17 children were assessed at age 4 and 8 months, 16 of 17 were assessed at age 12 and 18 months, and 15 of 17 were assessed at age 24 months. The Bayley III test was scheduled to be performed at age 12 and 24 months; 7 children underwent the Bayley III, 4 at age 12 months, 1 at 18 months, and 5 at 24 months.

Five children were considered at moderate risk for Krabbe disease based on GALC activity of 0.16-0.29 nmol/hour/mg protein, and 12 were considered at low risk based on GALC activity 0.3-0.5 nmol/hour/mg protein. The study group contained no high-risk children.[2]

A comparison of ASQ 2 communication scores (pass/fail) versus CLAMS communication scores (>85 = pass) found that at least 94% of patients had passing scores at 4, 8, and 12 months, but by 18 months, the percentage of passing scores had dropped to 56% for the ASQ 2 and 63% for the CLAMS (Figure 1). At 24 months, the percentage of passing scores increased, to 73% on the ASQ 2 and 67% on the CLAMS. The difference between the 2 instruments was not statistically significant. Four of the children had scores in the severely delayed category on the overall CLAMS communication score. In an effort to better understand the

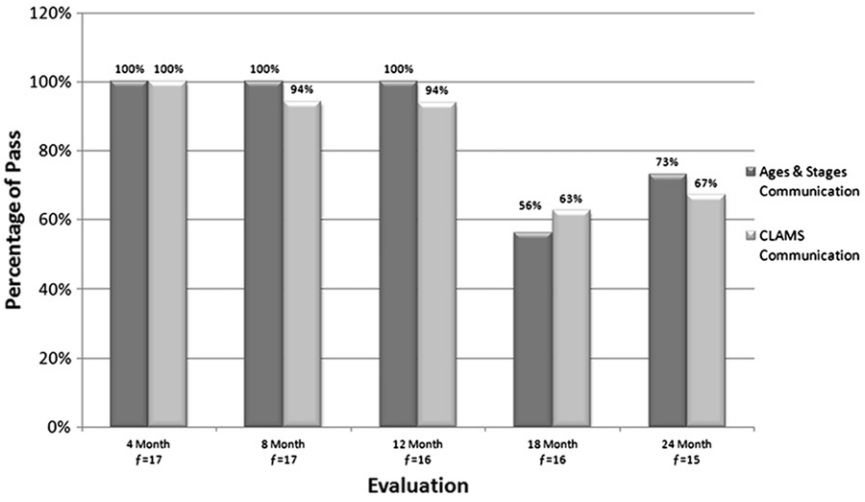

Figure 1. Comparison of ASQ 2 communication and CLAMS communication scores. For both tests, the percentage of passing scores declined by age 18 months and age 24 months. The results did not differ significantly between the 2 tests.

potential issues with language, we compared the CLAMS receptive and expressive language scores (Figure 2). In this analysis, expressive language declined to a score of 50% by 18 months. In most cases (>90%), receptive language was normal. No child scored in the severely delayed category for receptive language on the CLAMS, but 4 scored in the severely delayed category for expressive language on at least one assessment. One child scored in the severely delayed range on 2 assessments. Three of these 4 children were in the low-risk category.

A comparison of the ASQ 2 gross motor score (pass/fail) and the GMQ (>85 = pass) at the 4-month evaluation found a difference between the 2 instruments, with only 77% of children passing the GMQ compared with 100% on the ASQ 2. Subsequent GMQ passing rates were 88% at 8 months and 100% at 12 and 18 months; the passing rate on the ASQ 2 motor score was 100% at all examined intervals (Figure 3). None of the GMQ scores were in the severely delayed range. Two of the moderate risk children at age 4 and 8 months had atypical motor findings, including persistent fisting and increased axial tone when pulled to a sitting position. In both cases, the findings had resolved by age 12 months.

Results for the WIDEA-FS 50 revealed ongoing progression of motor, communicative, self-care, and social domain skills. There was an identical trajectory at age 4 months and age 24 months for the total WIDEA-FS 50 score when the children at risk for Krabbe disease (based on positive newborn screening and confirmatory testing) were compared with the normative WIDEA-FS 50 cohort.

Results for the WeeFIM II 0-3 motor and cognition domains revealed normal values at all tested intervals, demonstrating progressive improvement in functional independence over time, as would be expected in typically developing children.

The total scores for the WIDEA-FS 50, WeeFIM 0-3, and ASQ 2 composite were compared at age 4, 8, 12, 18, and 24 months. All measures were significantly correlated with one another ($r < 0.51$; $P < .01$) at all ages except 4 months, when only the ASQ 2 and the WeeFIM 0-3 were significantly correlated ($r = 0.84$), and at 24 months, when only the WIDEA-FS 50 and ASQ 2 were significantly correlated ($r = 0.71$).

Bayley III

The Bayley III was administered to 7 children. Four children were tested at 12 months and had the following scores: cognition, 3 high average, 1 average; language, 1 average, 3 low average; motor, 3 average, 1 low average. Five children were tested at 24 months and had the following scores: cognition, 3 high average, 2 average; language, 1 high average, 4 average; motor, 1 high average, 4 average. One child was tested at 18 months and scored in the average range in all categories. Three children were tested at both 12 and 24 months; in all 3 children, scores improved from the 12-month assessment to the 24-month assessment. No child had a score in the abnormal range.

Referral for Early Intervention Programs

Four children were referred for early intervention evaluation. Only one of these children qualified for services based on genetic risk and expressive speech delay.

Discussion

When this study began, it was unknown whether all children with low GALC activity would develop clinical signs of Krabbe disease over time or whether some of them might remain unaffected indefinitely. None of the children enrolled in this pilot study was in the high-risk category, and thus the risk of early infantile Krabbe disease was considered remote. Alternatively, there are several later-onset phenotypes (ie, late infant onset, later onset, adolescent, adult onset) for which these children might be at risk. It was anticipated that the

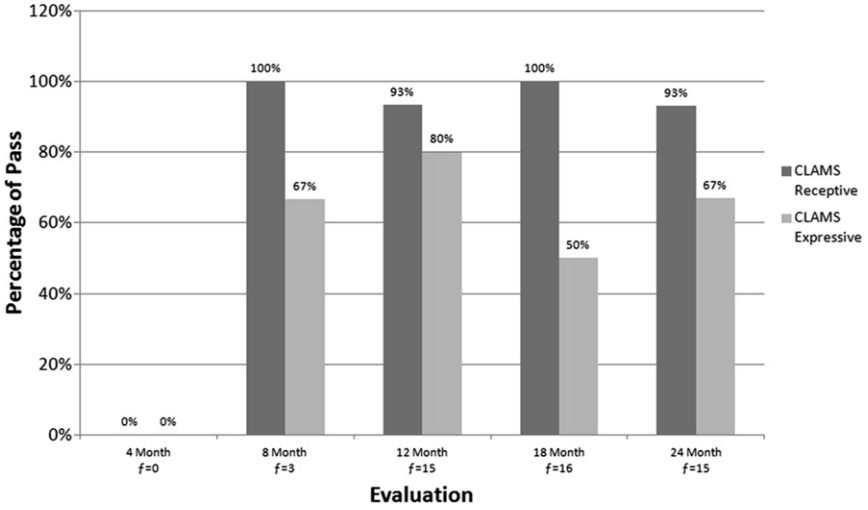

Figure 2. Comparison of CLAMS receptive and CLAMS expressive language scores. Although receptive language scores were normal, expressive language scores declined to 50% pass by 18 months.

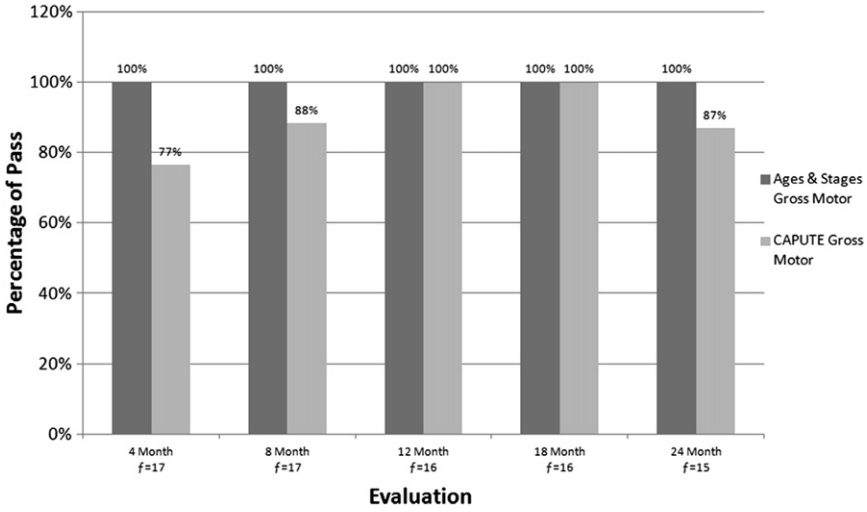

Figure 3. Comparison of ASQ 2 gross motor scores and GMQ scores. After the 4-month evaluation, no child scored in the abnormal range on either instrument.

telephone-based approach would allow both good compliance and close follow-up between medical visits. The protocol was based on a previous Children's Oncology Group study of infants and very young children with medulloblastoma, in which infants were scheduled to receive cranial irradiation very early in the course of treatment. Even though 3-dimensional conformal rather than standard irradiation was to be delivered, the risk of radiation-induced cognitive deficits was considered high. Thus, close developmental follow-up was essential to reassure investigators that the radiation had no untoward consequences. Previous studies of children with brain tumors reported poor compliance with neuropsychological testing. In an effort to address the need for close monitoring of development and improve compliance with scheduled testing, a telephone-based interview technique using the ASQ 2, the Capute CLAMS, and GMQ, and the WeeFIM 5.0 was developed and administered.[14] The results of that study revealed 100% compliance with the telephone-based technique (in contrast to a 46% compliance rate at 2 years for neuropsychological testing) and excellent intertest reliability.[14]

Thus, when newborn screening for Krabbe disease began in New York State, this telephone-based approach appeared to be an ideal way to follow at-risk children. There are some differences in the 2 patient populations, however. The children with medulloblastoma received therapeutic interventions, including surgery, chemotherapy, and radiation; were often neurologically impaired at baseline; and were older than the children in our study group. In addition, whereas the children with medulloblastoma had a clearly defined diagnosis, the likelihood of clinical manifestations of Krabbe disease appearing in 24 months in this population of infants identified by neonatal screening was unclear.

Like the medulloblastoma study, the present study used standardized questionnaires from the ASQ 2 as well as criterion-specific activities, which assessed communication (CLAMS), motor milestones (GMQ), adaptive abilities (WIDEA-FS 50), and function (WeeFIM II 0-3). Because the WeeFIM instrument used in the medulloblastoma study is most appropriate at children aged 2-6 years, the WeeFIM II 0-3 was used to assess the needs of children in the first 2 years of life.

One aim of the present study was to identify early indicators of later-onset forms of Krabbe disease. Because prompt diagnosis is essential if hematopoietic cell transplantation is to be considered, the interviews focused on the most common symptoms of the various Krabbe phenotypes, including loss of milestones, irritability, feeding difficulties, loss of smiling, visual and auditory deficits, changes in gait, and atypical motor development. Thus, the purpose of these interviews extended beyond routine assessment of developmental status. Given the variable frequency of medical follow-up, the telephone contacts provided additional information on each child's status that could trigger an immediate medical referral if necessary.

The results of our developmental, functional, and formal cognitive tests, although limited in number, reveal a generally normal cohort of children. Even though only mild abnormalities were identified, severe delays in expressive language were seen in a minority of patients. This finding is of particular interest because most children with early infantile Krabbe disease who undergo hematopoietic cell transplantation have expressive language deficits. Whether this is a chance finding or reflects the influence of low GALC on motor aspects of language is uncertain. Additional studies in children up to age 5 years will help clarify this issue, and identify preschool developmental trajectories.

A major strength of the present study is the multiple longitudinal assessments obtained in a cohort of asymptomatic children identified by newborn screening. In addition, all data were collected by a single experienced individual, thereby

eliminating interrater variability. Although the telephone-based system was not meant to replace formal face-to-face testing, the high compliance with multiple telephone-based assessments is a strength of this approach. Unfortunately, compliance with formal neuropsychologic testing was poor, even though no cost was incurred by the families or insurance companies. Communication advancements, such as Skype, could provide direct observation of children, which should enhance the accuracy of the parental reports.

Although this study has demonstrated the feasibility of the telephone-based interview approach, whether the functional tests provide sufficient meaningful data to merit both the extra interview time (20 minutes per call) and the associated increased cost is unclear. The answer likely rests with the population to be studied. For children who are at risk but have no evidence of active neurologic disease, developmental screening in the pediatrician's office is likely adequate. If this screening reveals an abnormality or the parents are concerned about a developmental problem, then both a neurologic exam and a developmental assessment using the Capute or Battelle scales are required.[15,16] In contrast, children identified on newborn screening with other lysosomal storage diseases, as well as those considered at neurologic risk (due to, eg, extreme prematurity, perinatal hypoxia-ischemia, complex congenital heart disease) are likely to develop clinical signs of static or progressive neurologic dysfunction. In these cases, the added information on motor, communicative, and adaptive function will be useful both to monitor neurodevelopmental integrity and to assess the role of biomedical interventions on developmental trajectories. ■

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