Mullen Scales of Early Learning Adaptation for Assessment of Indian Children and Application to Tuberculous Meningitis

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Introduction: Tuberculous meningitis (TBM) results in significant morbidity and mortality among children worldwide. Associated neurocognitive complications are common but not well characterized. The Mullen Scales of Early Learning (MSEL), a well-established measure for assessment of neurodevelopment, has not yet been adapted for use in India. This study's goal was to adapt the MSEL for local language and culture to assess neurocognition among children in India, and apply the adapted measure for assessment of children with TBM.

Methods: Administration of MSEL domains was culturally adapted. Robust translation procedures for instructions took place for three local languages: Marathi, Hindi and Tamil. Multilingual staff compared instructions against the original version for accuracy. The MSEL stimuli and instructions were reviewed by psychologists and pediatricians in India to identify items concerning for cultural bias.

Results: MSEL stimuli unfamiliar to children in this setting were identified and modified within Visual Reception, Fine-Motor, Receptive Language and Expressive Language Scales. Item category was maintained for adaptations of items visually or linguistically different from those observed in daily life. Adjusted items were administered to six typically developing children to determine modification utility. Two children diagnosed with confirmed TBM (ages 11 and 29 months) were evaluated with the adapted MSEL before receiving study medications. Skills were below age-expectation across visual reception, fine motor and expressive language domains.

Conclusions: This is the first study to assess children with TBM using the MSEL adapted for use in India. Future studies in larger groups of Indian children are warranted to validate the adapted measure.

KEYWORDS: cultural competency, developmental neuropsychological assessment, tuberculous meningitis, India

INTRODUCTION

Tuberculous meningitis (TBM), a form of meningitis caused by *Mycobacterium tuberculosis*, is characterized by inflammation of the meninges. It is a life-threatening disease resulting in significant morbidity and mortality among children worldwide, particularly in developing countries [1–3]. Neurological complications of TBM, such as seizure, hydrocephalus, vision impairment and hearing impairment are common and are large contributors to long-term morbidity in those affected by this disease [4]. TBM affects young children during important neurodevelopmental stages, resulting in neurological complications and sequelae in about 50–60% of affected children, despite anti-tubercular therapy [5, 6]. Motor disability and intellectual impairment are long-term complications in survivors of TBM [7–9]. Longitudinal neurocognitive assessment starting at the time of diagnosis with baseline measurement to monitor recovery over time; however, has not been previously reported.

Key motor and language milestones are achieved during the span of life ranging from birth to 5 years of age, making it an important period in early child development [2]. The developing brain is adversely affected by TBM due to the combined effects of increased intracranial pressure resulting from hydrocephalus and ischemic infarction related to periarthritis nodosa. Further, *M. tuberculosis* resides in microglia in the brain, and these cells play a key role in neurocognitive development [10]. TBM arises from the formation of a metastatic lesion in the meninges. This initial lesion increases in size and discharges small numbers of tubercle bacilli into the

subarachnoid space. The resulting gelatinous exudate infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction and subsequent infarction of cerebral cortex. Brain regions most commonly affected by such ischemia are the cerebral cortex or meninges, brainstem, basal ganglia and thalamus [2, 3, 11, 12]. This obstruction due to the inflammatory infiltrate in cerebrospinal fluid (CSF) leads to hydrocephalus, and vasculitis which contributes to infarction, causing potentially irreparable neurological damage and cognitive disabilities [13].

In the pediatric population, TBM has generally occurred in children following infection and between the ages of 6 months to 5 years of age [14]. A Study done in India found that 57% of children with TBM in India survived with disability sequelae; however, no study has reported psychosocial or behavioral results of assessment and intervention in these children and no single tool has been utilized to assess neurocognitive function [6]. The completed retrospective research on children with TBM in South Africa, used a caregiver rating form of behavior, The Child Behavior Checklist [15], to assess their long-term behavioral outcomes, with the mean age at follow-up assessment being 10 years, 7 months. They found behavioral disinhibition and internalized emotional difficulties to be common long-term complications of the survivors of TBM [12].

In 2014, a completed systematic review of developmental screening tools used for assessment of any population in lower middle income countries (LMICs), only 20 tools were identified, with 6 developed in high-income countries and 14 developed in LMICs, and they varied significantly in their

psychometric properties and feasibility to administer [16]. Similarly, researchers reviewed 90 screening tools used for identification of developmental delays with various age groups worldwide. They found a lack of consensus for screening tool efficacy, particularly where tools were used in cultures other than those in which they were created [17].

Limited studies have evaluated neurodevelopmental skills in children with TBM using one inclusive scale of measurement. In India, The Developmental Assessment Scale for Indian Infants (DASII) is one such tool, and it is frequently used in the Indian clinical setting [18, 19]. It is an Indian adaptation and standardization of the Bayley Scales for Infant Development (BSID) [19]. Despite its sound psychometric properties and use in research, its application is limited to ages 3–30 months [20]. Assessment of developmental skills in infants and young children in a reliable and valid way is important for the planning and provision of effective rehabilitative interventions. It is believed that early identification and intervention, such as through rehabilitative interventions (speech-language, occupational, and physical therapies etc.) this may help to minimize the long-term impact of these problems [21, 22].

The Mullen Scales of Early Learning (MSEL) is a tool commonly used to assess developmental milestones in children between birth to 68 months of age in western and other multicultural populations that is well validated in this setting [23–25]. It measures a child's gross and fine-motor skills, visual reception, expressive and receptive language skills, all of which may be adversely impacted by TBM. Although the MSEL has previously been adapted for use in children in Africa, Francophone countries, and for children with Rett syndrome, it has not been used to assess neurocognitive outcomes in children with TBM nor has it been used in the Indian setting [26–28]. India is a highly diverse country with varied languages and cultural practice. With 2.8 million of tuberculosis cases reported annually, it is also the country with the highest incidence of tuberculosis in the world [29]. In total, 10–20% of all cases of tuberculosis in high burden countries are estimated to be comprised of pediatric tuberculosis. Of these, about 25% of cases are extrapulmonary, with TBM being the most severe form [30, 31]. The purpose of this

study was to adapt the MSEL for local language and culture to use in a population of Indian children with TBM.

MATERIALS AND METHODS

Participants

TBM-KIDS parent trial

The use of MSEL is a component of a multicenter clinical trial, 'A Phase I/II Randomized, Open-label Trial to Evaluate the Pharmacokinetics, Safety and Treatment Outcomes of Multidrug Treatment Including High Dose Rifampicin with or without Levofloxacin versus Standard Treatment for Pediatric Tuberculous Meningitis' [32, 33]. The main objective of the trial is to assess the effects of optimized antimicrobial treatment on functional and neurocognitive outcomes in children with TBM. Trial details are described elsewhere [32], but in brief, those children with possible, probable or definitive TBM who are between the ages of 6 months to 6 years undergo serial neurocognitive assessments, in addition to other evaluations. A tool for comparing neurocognition and recovery across treatment arms at various time points was needed. The MSEL results we report here are from two children with definite TBM enrolled in TBM-KIDS at baseline. Baseline in this context refers to assessment of skills prior to the time of study treatment administration.

Measure of neurocognitive development

The MSEL measure provides an overall assessment of cognitive ability in five domains and is intended for use in children from birth to 68 months. Assessment scores are provided for the developmental domains of Gross Motor (birth through 33 months), Visual Reception, Fine-Motor, Receptive Language, and Expressive Language [23]. The Early Learning Composite provides a general measure of fluid intelligence believed to underlie cognitive ability in general. The Early Learning Composite is derived from the transformed sum of the standardized scores of four scales and does not include the Gross Motor scale.

Adaptation of MSEL for Indian languages and culture

Adaptation refers to the processes of translation and item modification to reduce errors when applying a test in a culture other than the one in which it was developed. We adapted the five components of the MSEL culturally and linguistically into three local languages, including Tamil, Marathi and Hindi, commonly spoken languages in the western and southern regions of India using a robust translation procedure for instructions. A series of steps was carried out to ensure the effective translation of instructions and fair cultural adaptation of the measure. The original English MSEL administration manual was carefully and independently reviewed by two experienced psychologists and two pediatricians in India to identify carefully items concerning for cultural bias. Following their advice, items of concern from the stimulus book were shown to 12 healthy children. Each psychologist and pediatrician provided suggestions on items where modifications were required. The details about adaptations are provided in attached [Supplementary Appendix](#).

Linguistic translation of instructions

Instructions for MSEL were professionally translated into Tamil, Marathi and Hindi languages, which are the prominent local languages spoken in the study location regions. The translation of instructions was checked item by item by multilingual testing staff who reviewed and compared the translated instructions against the original version for accuracy. Additional translation verification took place via a review by psychologists proficient in the study's Indian languages who did not have access to the original version. Beyond that review, study neurocognitive team members reviewed all instructions. Discrepancies were discussed, resolved and incorporated into the assessment measure by consensus. Equivalence across languages was also ensured by all reviewers.

Substitution of culturally inappropriate stimuli and materials

Toys and stimuli that were deemed inappropriate or unfamiliar to children in this setting were identified. These included items that were not commonly

observed (e.g. a chimney) or were visually different (e.g. a Western style purse) in the Indian context. When selecting substitutions for stimuli, efforts were made to maintain the category of the item (e.g. household object, currency).

Training

Neurocognitive study team members who would be field testers were selected based on background in testing or working with young and medically fragile children. These individuals were also fluent in English and either Marathi, Hindi, or Tamil. Testers were trained in MSEL administration by an experienced pediatric neuropsychologist, with training consisted of watching videos, live demonstrations of item administration, group practice and discussion of scoring criteria. Subsequently, they practiced administering the assessment to non-study children. Supervision was provided both by their peers in the training group and the pediatric neuropsychologist. Practice testing sessions were video-recorded, and testers were provided in-depth feedback on their administration and scoring prior to being deemed fully trained for study purposes. Refresher training took place every 3–6 months and as needed throughout the course of the study.

RESULTS

MSEL stimuli unfamiliar to children in this setting were identified and modified within Visual Reception, Fine-Motor, Receptive Language, and Expressive Language Scales. Adaptations were made for items that were visually or linguistically different from those observed in daily life. When selecting substitutions for pictures, letters, words and phrases, item category was maintained. Adjusted items were administered to six typically developing children to determine utility of modifications.

We describe use of the adapted tool for two children, ages 11 and 29 months. Both cases tested were females admitted to a tertiary care hospital for seizure-like events as well as complaints of fever, irritability, altered sensorium lasting 1 day, lethargy and reduction in playfulness. The CSF was Gene Xpert positive for *M. tuberculosis* along with clinical entry criteria as per Uniform Research Case definition for TBM [34]. The MSEL was administered to

these children in the pediatric ward. Specific test results are described in Table 1. Given that normative data do not exist for India for the MSEL, scores for this measure were adjusted for age using existing USA norms. A standard score has a mean of 100 and a SD of 15.

Case 1

An 11-month-old participant with confirmed TBM was individually administered the MSEL. Her overall cognitive performance was below expectation for

age, and her performance varied between scales. Strongest skills were in the area of expressive language, which were broadly within the average range (within 1 SD of the normative mean). Visual reception, expressive language and fine-motor skills were more than 2 SDs below the normative mean, and gross motor skills were 3 SDs below the normative mean, all representing areas of significant weakness for age.

Gross motor skills were at a 4-month-old equivalent, and the participant was able to roll over and

Table 1. Demographic characteristics and MSEL performance at study enrollment

Variables	Case 1		Case 2	
Age at testing (months)	11		29	
Sex	Female		Female	
Residence	Urban		Urban	
Family type	Nuclear		Extended	
Parent education	High School		Primary	
Native language	Marathi		Marathi	
Gestational age	40 weeks		35 weeks	
Birth weight (kg)	2750 kg		2000 kg	
Onset of symptoms prior to testing (days)	7		4	
Type of meningitis	Definite TBM		Definite TBM	
Neurodiagnostic findings based on computed tomography	Hydrocephalus		Hydrocephalus	
Non-study medications	Ceftriaxone, Phenytoin, Ondansetron, Phenobarbitone, Dexamethasone and Pantoprazole		Ceftriaxone, Phenytoin, Amikacin, Acyclovir, A to Z syrup, Ondansetron, Mannitol, Dexamethasone, Vitamin A and Ranitidine	
MSEL performance (standard score for age using US norms)				
Scale/early learning composite	Case 1 Standard score	Age equivalent (months)	Case 2 Standard score	Age equivalent (months)
Gross Motor Scale	55	4	88	25
Visual Reception	66	6	55	16
Fine Motor	58	7	55	20
Receptive Language	63	5	55	14
Expressive Language	85	9	64	16
Early Learning Composite	61	–	51	–

MSEL, Mullen Scales of Early Learning. MSEL scores were adjusted for age using an American-based normative group, given that no normative data are available for India for this measure.

support herself using her forearms; however, she was unable to pull herself to sit or stand on her feet with assistance. Visual reception skills were at a 6-month-old age equivalent. She was able to search for a stimulus taken out of immediate view and pulled a cord to obtain a stimulus; however, she was unable to make item associations or attend to a picture. Fine-motor skills were at a 7-month-old equivalent, and she could grasp a block, transfer, bang, and drop a stimulus, but she could not use a pincer grasp to pick up small items. Receptive language skills were equivalent to a 5-month-old. The participant was able to recognize her name and was responsive to voice and faces; however, she was unable to recognize familiar names and words. Expressive language skills were at a 9-month-old age equivalent. The participant could babble voluntarily and vocalized sounds comprised of more than one syllable, but she was unable to two syllable sounds or say first words.

Case 2

A 29-month-old participant was individually administered the MSEL. Her overall cognitive performance was below expectation for age, and her performance also varied between scales. Strongest skills were in the area of gross motor functioning, which were broadly within the average range (within 1 SD of the normative mean). Expressive language skills were more than 2 SDs below the normative mean, and visual reception, fine motor, receptive language skills were 3 SDs below the normative mean, all representing areas of significant weakness for age.

Gross motor skills were at a 25-month-old equivalent, and the participant was able to kick a ball and walk up a staircase; however, she was unable to walk on her tiptoes, walk on a line or walk down stairs by herself. Visual reception skills were at a 16-month-old age equivalent. She was able to discriminate an object on a form board but she was unable to nest cups. Fine-motor skills were at a 20-month-old equivalent, and she could use two hands together and turn pages of a book one at a time; however, she could not draw a horizontal line or put coins into slots. Receptive language skills were equivalent to a 14-month-old. The participant was able to understand simple verbal commands but she could not comprehend simple questions or identify body parts.

Expressive language skills were at a 16-month-old age equivalent. The participant was able to combine words and jargon but was unable to name objects or pictures.

DISCUSSION

This study describes the process of cultural adaptation of a tool to assess early development in a population of Indian children with confirmed TBM. In India, currently available tools exist for screening purposes in community clinics, such as the Baroda Developmental Screening Test for Infants (BDST-1961) [18], the Trivandrum Developmental Screening Chart (TDSC) [35], and the Indian Council of Medical Research Psychosocial Screening Test [36]. Although they may be used to screen for children who may be at risk for developmental delays, they are not comprehensive and do not provide sufficient measurement of these skills [20]. In contrast, the Developmental Assessment Scale for Indian Infants [18], is a more comprehensive tool frequently used in the Indian clinical setting [19]. The DASII is an Indian adaptation and standardization of the BSID and is used to assess general cognition, language, motor skills and socio-emotional skills in detail. Although it has sound psychometric properties and has been used in research, its application is limited to infants and it assesses the children with age 3–30 months [20]. Assessment of developmental skills in both infants and young children in a reliable and valid way is important for the creation and provision of effective interventions as it is believed that early identification and intervention may help to minimize the long-term impact of these problems. As such, the adaptation of a more comprehensive tool was necessary.

This investigation was the first to implement an adapted version of the MSEL for use with children in India. Given the diversity that exists within the Indian culture, including languages and regional expression, adaptation was an important and necessary process of the present study. A cultural adaptation is a complex process and the characteristics of the original version need to be preserved. In this process, we substituted specific stimuli (e.g. pictures, local names) and adapted instructions via translation for local Indian languages. As a whole, only a few items

were substituted, which may reflect current globalization such as impact related to access and exposure to internet, cellular phones and television, for example. This method was multifaceted and required a large-scale collaborative process to be culturally fair in assessment, to reduce language barriers along with adjustment of items to be culturally appropriate. Through this method, appropriate measurement of the impact of TBM in early brain development among Indian children was made possible as no other measures were appropriate to adapt for children within the age group of the primary study, which predominantly includes children 6 years of age and younger.

Age and severity of disease at the time of diagnosis are important factors affecting outcome of childhood TBM. The cases which are presented each have a definite TBM diagnosis and the main impact of TBM in these cases at baseline is in the area of cognition. In this study, the most severely affected developmental areas at study enrollment for the two cases presented were related visual reception, fine motor and receptive language skills. These findings are consistent with reported literature on neurodevelopmental outcomes among children with TBM which showed difficulties in these areas [7, 37].

Challenges in these areas have been reported to occur even after the completion of TBM treatment. As such, early identification of affected cognitive domains through adequate assessment and early intervention to target weaknesses is encouraged. Early rehabilitative intervention, such as physical, occupational, and speech-language therapies along with medical treatment has strong potential for positively impacting a child's quality of life. Children who have sustained traumatic brain injury (TBI) and have been treated with such interventions have responded well, suggesting that early initiation of these rehabilitation therapies improves functional outcomes in children with TBI [2, 38]. Literature on post-acute and long-term care in children with brain injuries has demonstrated ongoing need for rehabilitative therapies as well as psychosocial intervention. One study, completed in Amsterdam on pediatric survivors of brain tumors, reported long-term sequelae in the areas of general cognitive ability, physical, emotional, social, and parenting problems in these children

[39]. A review of predominantly child and adolescent survivors of bacterial meningitis, including TBM, showed overall reduced intellectual ability and adverse development across multiple domains including cognitive, social, language and motor skills [40]. Survivors were deemed likely to have poorer health outcomes, educational attainment and employment opportunities. However, studies of children exposed to and/or infected with HIV have shown that even within 1 year of disease onset, rehabilitative intervention can improve cognition, speech and language skills, and motor functioning, and interventions targeting the caregiver can improve cognitive performance and behavior of the affected child [41].

This is the first study to adapt the MSEL for use in Indian languages and culture. This is also the first study to measure neurodevelopmental skills in children soon after they have been diagnosed with TBM, at a point in which we could obtain a baseline for which to make future comparisons, for the purposes of comparing affected domains in the context of TBM treatment over time. It is hoped that information obtained from the use of measurements from the adapted MSEL may be serve as guidance to clinicians or health care providers to plan the therapy along with treatment.

Limitations and future directions

In this study, we were able to measure developmental skills of children with TBM in India using a culturally adapted MSEL; however, measurement interpretation should be interpreted with caution given absence of an Indian normative group. Presently, no normative data exist for this measure in Indian children; however, the MSEL has been adapted in other languages/cultures and tends to measure cognitive domains well among these settings. This scale has been culturally and linguistically adapted in francophone and South African countries and showed to measure cognitive domains in these settings successfully among children at different developmental levels [24, 27]. Although we have demonstrated a method of adaptation of the MSEL for use in India, future studies are necessary to compare it with DASII to see if there are any differences with the results given the same age group and for the

validation of its use in this setting. In order to do so, in addition to language proficiency of the tester, extensive face to face training and live demonstrations with routine refresher training, essential factors for training and competency in this measure include the flexibility and ability to address challenging behaviors in young and medically fragile children in the moment on a case-by-case basis.

ETHICAL APPROVALS

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Byramjee Jeejeebhoy Government Medical College and Johns Hopkins University Ethics Committees.

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SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

AUTHOR CONTRIBUTIONS

K.D., A.A., S.N., V.M., A.K. and S.J. conceived the study idea. A.A., S.N. A.K., S.J., N.S., C.V. and N.G., framed the research question and provided scientific input on methodology. A.A., S.N., M.B., M.P., S.K., B.D., K.K. and M.I. helped in adaption, A.A., K.D., K.T., A.K. and N.G. provided technical expertise on the scale, A.A., K.D., V.M., A.G., K.T., M.P., B.D. and N.G. provided clinical scientific input to contextualize the study findings. S.N. and A.A. drafted preliminary article. K.D., V.M., S.J., A.K., A.G., N.S., D.B.D. and C.V., revised the article critically for important intellectual content. All authors approve of the final revised version submitted for publication.

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