SPECIAL ISSUE ARTICLE

General Movements: A Behavioral Biomarker of Later Motor and Cognitive Dysfunction in NICU Graduates

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ABSTRACT

Infants who have graduated from a neonatal intensive care unit require close follow-up because they have a greater chance of experiencing later motor and cognitive difficulties; however, these difficulties are often challenging to identify at an early age. The General Movement Assessment is a low-cost and highly reliable tool that can indicate abnormal neurological development in young high-risk infants, but it has not yet been widely implemented in the United States. In this review, we discuss the literature about the use of the General Movement Assessment in high-risk infants and how to implement the tool in a clinical setting. **[*Pediatr Ann*. 2018;47(4):e159-e164.]**

Graduates of a neonatal intensive care unit (NICU) have an increased risk of developing motor, visual, auditory, and intellectual disabilities. Accurate diagnosis of these conditions currently requires long-term follow-up and they are notoriously difficult to predict in infancy. Advanced brain imaging techniques have been used at term-equivalent age to identify subtle structural markers associated with later cognitive and motor impairment; however, these neuroimaging methods are not widely available or often used clinically. The General Movement Assessment (GMA) is a nonintrusive, highly sensitive, and reliable method to evaluate the young nervous system and has been internationally recommended as the best clinical tool to predict cerebral palsy in infants who are younger than age 5 months.[1] In this review, we discuss the evidence surrounding the GMA and clinical application with the high-risk infant population.

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WHAT ARE GENERAL MOVEMENTS?

Behavior is a representation of neural activity and gives insight into the developing brain. In the case of the fetus or young infant, spontaneous movements can be considered a behavior that is an expression of neural function. Without being triggered by a specific sensory input, the fetal and neonatal nervous system endogenously generate a variety of motor patterns including, yawns, stretches, startles, sucking, side-to-side movements of the head, eye movements, breathing movements, and general movements.[2] These early movement patterns are produced by central pattern generators (a specific neural network), located in the brainstem.[3]

General movements during the preterm and term age period are defined as variable movements of the entire body with a fluctuating sequence of arm, leg, neck, and trunk movement. They wax and wane with changing intensity, speed, and range of motion, and they have a gradual onset and ending. The changing of direction and rotations around the limb axes produce a fluent and elegant quality. The general movements have a similar appearance from early fetal life until the end of the second month after term. Prior to term age, the general movements are

named "preterm general movements," and from term age and beyond they are termed "writhing movements."[3]

The perinatal period is a continuum of development interrupted by the event of birth. Compared to nonhuman primates, with the exclusion of vital functions, the human infant is less equipped to adapt to extra-uterine life, and there is a continuation of fetal behavior that extends to the first 2 months of life after term age.[4] This is also noted in the similarity between preterm and writhing general movements.

At approximately the end of the second month of life, many behavioral changes occur in the infant that allow for adaptation to the extra-uterine environment, including increasing muscle power, the beginning of social smiling and cooing vocalization, a change in sucking pattern, and focused visual attention and binocular visual development.[4,5] It is also at this time a new pattern of general movements, termed "fidgety movements," occur. Fidgety movements are defined as tiny movements of the neck, trunk, and limbs that occur in all directions and with variable acceleration.[3] These movements are observable between 3 and 5 months post-term age, with their peak at age 12 to 16 weeks post-term. Fidgety movements are only seen when the infant is awake, and they disappear when the infant is crying, fussy, or asleep.

Notably, fidgety movements appear as the infant brain is shifting from subcortical to cortical mechanisms of metabolism,[6] coinciding with several other behavioral changes in the infant.[4] Prechtl and Hopkins[4] originally described the presence of fidgety movements and theorized that their ontogenic adaptive function may be a postnatal calibration of the proprioceptive system, as fidgety movements are directly followed by voluntary manipulative movements with visual regard.[4] Almost all infants will develop normally if fidgety movements are present and normal, especially if they occur with other smooth and fluent movement.[7]

THE QUALITY OF GENERAL MOVEMENTS CHANGE WHEN THE NERVOUS SYSTEM IS IMPAIRED

Supraspinal projections and sensory feedback most likely modulate the central pattern generator activity that produces variable movement. When there is an abnormality in the nervous system, the general movements lose their variable and complex quality. Therefore, the presence of normal and variable general movements indicates normal development, whereas abnormal and monotonous general movements presage neurologic impairment. During preterm and term age, abnormal general movements are described as (1) poor repertoire, in which the sequence of movements is monotonous and the intensity, speed, and range of motion lack regular variability; (2) cramped synchronized, in which movements appear rigid as the limb and trunk muscles contract and relax almost simultaneously and lack the ordinary smooth and fluent quality; and (3) chaotic, in which there are large amplitude movements of high speed that are abrupt and tremulous. Fidgety movements can be abnormal (exaggerated in amplitude and speed), sporadic (confined to a few body parts and never lasting longer than 3 seconds between the ages of 9 and 16 weeks post-term age), or 3 absent (fidgety movements are not present between 9 and 16 weeks post-term ages).[2,3]

THE GENERAL MOVEMENT ASSESSMENT IS THE STRONGEST PREDICTOR OF CEREBRAL PALSY IN HIGH-RISK INFANTS

Systematic review evidence (from large cohort trials of mainly preterm infants) shows that the GMA, specifically the absence of fidgety movements, is the best predictor of cerebral palsy in high-risk infants, with summary estimates of 98% sensitivity and 91% specificity.[1,8,9] Additionally, the specific subtype, anatomical distribution, and eventual level of self-mobility skills can be appreciated with the GMA and detailed observation (**Table 1**). Early markers of spastic cerebral palsy include consistent cramped synchronized general movements, followed by absent fidgety movements at 3 to 5 months. In fact, the earlier that cramped synchronized general movements are observed in the preterm infant, the worse the eventual motor impairment.[10] Furthermore, a cramped-synchronized movement character, repetitive kicking, repetitive opening and closing of the mouth, and abnormal finger postures at age 3 to 5 months identified children who would later exhibit poor self-mobility.[11] Infants who eventually developed unilateral cerebral palsy displayed asymmetrical wrist segmental movements and reduction in independent upper limb digit movement contralateral to the lesioned hemisphere.[12] Children who developed dyskinetic cerebral palsy were noted to have an absence of fidgety movements but also circular arm movements with or without spreading of the fingers at age 3 to 5 months.[3]

GENERAL MOVEMENTS IN INFANTS WITH GENETIC SYNDROMES AND AUTISM SPECTRUM DISORDERS

Although the majority of research has been done on infants at risk for cerebral palsy, several authors have looked at general movements in children with other developmental disabilities, including genetic syndromes and autism spectrum disorders. One case report describes a boy diagnosed with Cornelia de Lange syndrome who had abnormal general movements during term age.[13]

TABLE 1.

Developmental Trajectories of General Movements in NICU Graduates

GMs During Preterm Age	GMs During Term Age to 6 Weeks Post-Term Age	GMs from 9-16 Weeks Post-Term Age	Neurological Outcome
Normal or poor repertoire	Normal writing movements or poor repertoire	Normal fidgety movements	Normal[3,7,12,23]
Poor repertoire or cramped synchronized	Poor repertoire or cramped synchronized	Absent fidgety movements	Bilateral spastic cerebral palsy[3,7,10,30]
Poor repertoire	Poor repertoire or cramped synchronized	Absent fidgety movements and asymmetrical segmental movements and individual digit movements	Unilateral spastic cerebral palsy[3,7,12]
Poor repertoire	Poor repertoire	Absent fidgety movements, absence of foot-to-foot contact; circular arm movements, finger spreading	Dyskinetic cerebral palsy[3,7]
Poor repertoire	Poor repertoire	Can have normal, abnormal, or absent fidgety movements	Various genetic disorders[3,13-18]
Poor repertoire	Poor repertoire	Abnormal fidgety movements or normal fidgety movements with monotonous character	Autism spectrum disorders[18,19]
Poor repertoire	Poor repertoire	Normal or sporadic fidgety movements with monotonous, jerky, or stiff character and/or lack of various finger postures	Cognitive dysfunctions[3,7,20-26]

Abbreviations: GMs, general movements; NICU, neonatal intensive care unit.

Another report describes a child with DiGeorge syndrome (22q11.2 deletion) who had normal fidgety movements, as well as an infant later diagnosed with Smith-Magenis syndrome who had absent fidgety movements.[14] Infants with trisomy 21 are more likely to have an abnormal quality of general movements during the term period,[15] and many go on to develop abnormal fidgety movements[14,15] and a suboptimal motor repertoire.[16]

Seventeen infants later diagnosed with Rett syndrome were retrospectively analyzed with the GMA. None of these infants had a normal general movement trajectory, and during the fidgety period most had abnormal fidgety movements or absent fidgety movements.[17] The early motor abnormality seen in the general movements was surprising, given that typical Rett syndrome was originally thought to have a silent period during infancy and early childhood. Similarly, 68% of infants studied (17 of 25) who were subsequently diagnosed with autism spectrum disorder had abnormal general movements in their first months of life.[18] During the fidgety movement period in 32 infants later diagnosed with autism, 11 children had normal fidgety movements, 17 had abnormal fidgety movements, and 4 children had absent fidgety movements.[18,19]

GENERAL MOVEMENTS AND COGNITIVE DEVELOPMENT

Cognitive impairments can be seen in 25% to 50% of infants born preterm, especially if they are born prior to 32 weeks gestational age.[20] However, many of these deficits only become evident at school-age when the children face higher cognitive demands. The GMA is most often noted for predicting motor disorders, mainly cerebral palsy. However, researchers are now studying the association between general movements and cognitive and language development in infants born preterm. During the preterm period, poor repertoire general movements are commonly seen in preterm infants. Whereas some infant general movements normalize within a few weeks, others do not normalize until term-equivalent age or later. Preterm infants whose movements normalized at or before term-equivalent age were more likely to have an IQ score 5 to 13 points higher than infants who had abnormal general movements beyond term age.[21] In infants born with very low birth weight (<1,500 g), those with aberrant fidgety movements (absent, sporadic, and abnormal) were more likely to have worse cognitive, language, and

motor outcomes at both age 2[22,23] and 4 years.[23] It should be noted that most of the preterm infants (96%) included in the study did not have an eventual diagnosis of cerebral palsy.

A detailed analysis of the quality of movements at 3 to 5 months post-term age has been predictive of intelligence at age 7 to 10 years in preterm infants.[24-26] The number of normal postural patterns observed in preterm infants between 11 and 16 weeks post-term age was a significant predictor of verbal IQ at age 7 to 11 years.[26] The overall movement character (smooth and fluent versus monotonous, jerky, and/or stiff) predicted the IQ of children born with very low birth weight (<1,500g) without cerebral palsy at age 10 years with a sensitivity of 90% and a specificity of 58%.[24] Similarly, in a group of children with history of extremely low birth weight (<1,000 g) who did not develop cerebral palsy, an abnormal motor repertoire at age 3 to 5 months was associated with decreased working memory and processing speed, inattention, and hyperactivity at age 10 years.[25] These findings indicate that abnormalities in spontaneous motor behavior in the young infant may presage later cognitive dysfunction in children without cerebral palsy but who were still at high risk due to preterm birth. Alternatively, a history of normal general movements with a normal motor repertoire during the first months of life is a behavioral biomarker for normal cognitive development until at least age 10 years.

GENERAL MOVEMENTS AND RELATIONSHIP TO NEUROIMAGING

General movements are thought to be an age-specific expression of the functioning nervous system during infancy; therefore, several investigators have studied how the general movements relate to brain structure as measured by cerebral magnetic resonance imaging (MRI). Abnormal general movements seen during the preterm age, term age, and 3 months post-term age were associated with brain abnormalities on (term equivalent age) MRI in infants born preterm with very low birthweight.[22,27-29] Infants having abnormal general movements prior to 34 weeks gestation had greater cortical grey matter abnormalities.[27] Preterm infants who had abnormal general movements at term age had more global brain abnormalities in addition to higher cortical grey matter abnormalities and a smaller transcerebellar diameter.[27] In a separate cohort, white matter abnormality (seen at term MRI) was associated with infants having consistently abnormal general movement trajectories both at 1 and 3 months post-term age.[28] All infants in this study with consistently normal general movement trajectories had either no or mild white matter abnormalities.[28] Similar findings were noted in a separate group of preterm infants wherein white matter abnormality at term-age MRI was associated with abnormal general movements at age 3 months.[29] A more sophisticated MRI technique identified specific white matter tract damage in the corpus callosum, inferior longitudinal and front-occipital fasciculi, internal capsule, and optic radiations of infants with abnormal general movements at age 3 months post-term in a very low birth weight cohort, suggesting that fidgety movements may arise from connectivity among multiple brain regions.[22]

MRI patterns and general movements were also compared in term-age infants who had hypoxic ischemic encephalopathy. In these infants, the general movements at age 1 and 3 months were significantly associated with lesion patterns and severity of damage to the basal ganglia and thalami, posterior limb of the internal capsule, white matter, and cortex.[30] The correlation was greatest between the basal ganglia and thalami score and general movements at 3 months.[30] Importantly, the best predictors of motor outcome (defined as normal, mild motor impairment, or cerebral palsy) were the combination of MRI scores together with general movements at age 3 months.[30] However, if the infant had an abnormal MRI but normal fidgety movements at age 3 months, then the chances of normal outcome or mild motor impairment were fair.[30]

HOW CAN I USE THE GENERAL MOVEMENT ASSESSMENT IN CLINIC?

The GMA is based on visual gestalt perception, and assessors are required to participate in a 3.5-day training course provided by the General Movements Trust (http://www.general-movements-trust.info). The basic training course yields an 83% agreement with the gold standard, and this improves to 88% after an advanced training course.[3] In addition, discrimination between normal and abnormal general movements was significantly higher (basic 92%, advanced 94%).[3] Ideally, it is best to obtain a trajectory of infant movements, with 2 to 3 recordings in the preterm period, one recording at term age, and at least one recording between post-term ages 12 and 16 weeks.

The infants should be video-recorded in the supine position, dressed in a "onesie," and without a pacifier. In the preterm period, the infant should be filmed for 2 minutes while moving, and can be either asleep or awake but not crying. In the term period and the 3- to 4-month post-term period, the infant should be awake without fussiness or crying, and a video-recording of 2 to 3 minutes in length should be made. For optimal assessment, it is best to avoid a crowded

infant bed, colored blankets, or caregivers or siblings in the video frame, as this can negatively affect the gestalt perception of the rater.[3]

FUTURE USE OF THE GENERAL MOVEMENT ASSESSMENT

The current assessment is based on global gestalt perception, which is effective but vulnerable in that it depends on the both the availability and skill of the assessor. New attempts are being made for automated detection of general movement abnormalities using computer-based software and sensor technologies. However, at present the most well-established and widely used method is gestalt perception. A new smartphone technology is being developed to broadly implement the GMA in neurologically vulnerable infants around the world.[5]

CONCLUSION

The patients who are most often seen in a specialized NICU follow-up session can be grouped into the following three categories: (1) infants born preterm, (2) infants born at term age with an adverse event, and (3) infants with genetic syndromes or congenital anomalies. These children are at higher risk of developing motor and/or cognitive difficulties, but they can be difficult to identify at a young age, which is when intervention may be most beneficial. After more than 25 years since its original introduction, the GMA has now been established as a tool to identify neurologic impairment, and research has shown that in all three types of NICU graduates, early motor behavior can be linked with later outcome. The timing of general movement appearance and disappearance is age-specific and is related to the ongoing development of the brain. These early motor behaviors most likely represent the complex structural network that foreshadows executive function, and motor, language, and cognitive abilities. This early indicator can be used to refer children sooner for targeted intervention, during times of greater brain plasticity, when a greater impact of intervention may be seen. Conversely, we are also able to use this information to reassure the families of high-risk infants when consistently normal general movements are observed.

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