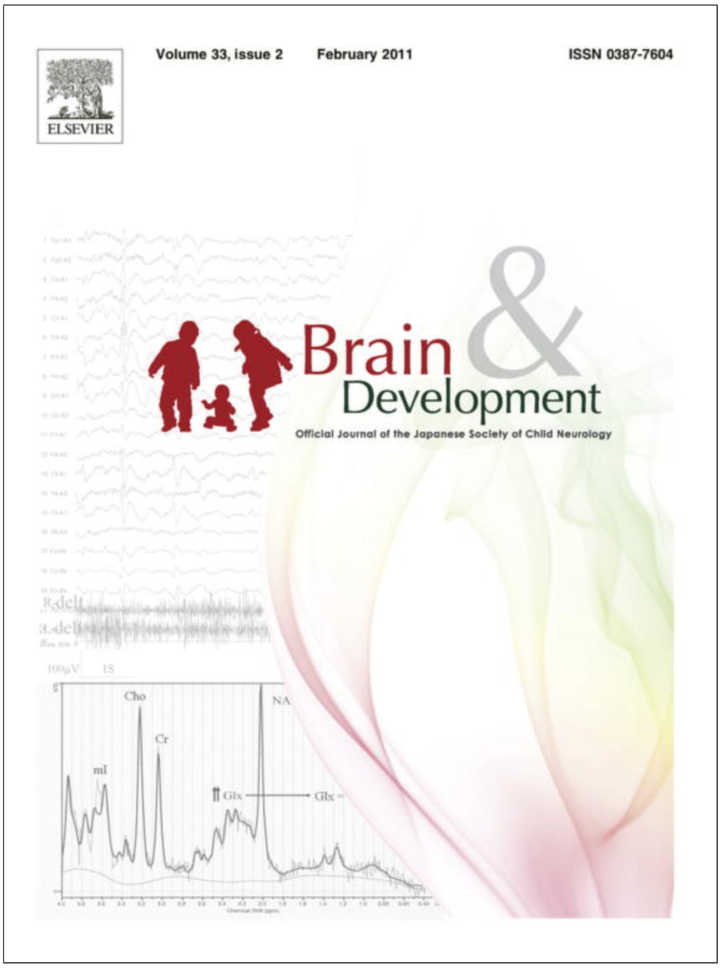
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Review article

Neurodevelopmental assessment of the newborn: An opportunity for prediction of outcome

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Abstract

Over the decades, the evolution of neonatology has been a continuum. After intense focus on cardiac and respiratory support, now more time, effort and research are concerned about brain development of the term and preterm infants. There is no single standardized neurodevelopmental assessment tool that can be advocated for infants in the neonatal intensive care unit. The tools that are currently available vary in their physiological bases, pre requisite training and expertise, time allotted to perform and score, and clinical utility and validity. In this communication, we describe the neurobehavioral and sensory capabilities of the neonate. We then compare the commonly used neurobehavioral examinations with an emphasis on premature infants. We envision this effort as an essential step before the development of a universal and comprehensive assessment tool.

Keywords: Neurobehavioral; Preterm; Clinical examination

1. Introduction

The history of neonatal neurobehavioral assessment began at the start of the last century. Before that time, a newborn was considered as being unstructured, and deficient in sensory and motor abilities. Over the years, scientists and clinicians have explored the different capacities of a newborn and have developed different tools to assess them. Though built on strong physiological basis and demonstrated to have good reliability, these tests are variable in their pre requisite training and expertise, time allotted to perform and score and their application in literature. When it comes to prediction of outcome, some of these tools are strong predictors, while others are either not as strong or have not been used for this purpose. In this review article we explore the most commonly used methods of assessing neurobehavior in the newborn infant and compare their usefulness as predictors of outcome, with special attention to premature infants.

2. Exploring the newborn neurobehavior

Over the years, the work of Sarnat [1], Amiel-Tison [2], and Dubowitz et al. [3] described and defined neurological assessment in the newborn via examination of tone and reflexes. The work of Prechtl and Beintema introduced the concept of state in the neurological exam [4]. They characterized different states of sleep and wakefulness and showed that the organization of the newborn is dependent on which state he is in during the assessment.

Others have described, the progression of central nervous system (CNS) organization and neonatal capabili-

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ties including their sensory function. The development of sensory function has been described to follow the sequence of tactile, vestibular, gustatory–olfactory, auditory then visual [6]. Most of the body is sensitive to touch by 15 weeks. However the response to touch varies between a diffuse behavioral response and habituation depending on the gestational age (GA). Non-nutritive sucking can be observed by 28 weeks GA and could act as a behavioral organizer and facilitator. Taste receptors are functional before birth and infants are able to discriminate different tastes even by 28 weeks GA [7]. The majority of preterm infants show behavioral response to smell by 28–32 weeks GA and at term olfactory functions include behavioral discrimination, preference, and conditioning. A classic example is that infants younger than 1 week of age will reliably prefer the odor of their mother's breast pad to the breast pad of another mother [7,8]. Though anatomically major auditory structures are in place by 25 weeks GA, functional maturation is characterized by an increase in spectral sensitivity at lower and higher frequencies and a decrease in auditory threshold. At term, infants have low threshold for sounds in the speech frequency, and respond differently to speech and non-speech stimuli [9]. They demonstrate preference to familiar sound even if they are exposed to in utero [10,11]. The visual system maturation is a more complex one that also starts in utero. The old concepts that an infant has little or no pattern vision in the early weeks of life changed after the work of Dr. Robert Fantz in the 1960s [12]. Though physiological and functional visual responses start at 24 weeks GA, functional maturation increases markedly at 32 weeks GA, when infants can briefly fixate. At 36 weeks GA, infants show spontaneous orientation, can track an object vertically and horizontally and prefer a patterned surface. A term infant can fixate to a high-contrast shape (1/16 inch wide line at a distance of one foot) and show preference for more complex shapes and for a human face [7].

After it became more and more obvious that a newborn can regulate his behavior, Brazelton developed the Neonatal Behavioral Assessment Scale (NBAS), the first truly standardized, comprehensive assessment of newborn neurobehavior [13]. It is considered the basis of more recent exams such as Assessment of the Preterm Infant's Behavior (APIB) [14] and the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) [15].

3. Neonatal neurobehavioral assessments

In Table 1 we compare the basic principles of the major exams discussed in this review and compare their utility in predicting the outcome in premature infants. These exams are further discussed in detail in the following section.

3.1. The Dubowitz neurological examination of the full-term newborn

3.1.1. Background and physiological basis for exam development

The Dubowitz neurological examination of the full-term newborn (sometimes referred to as Hammersmith Neonatal Neurologic Examination) covers different aspects of the neurobehavioral function. It has the advantage of being quick, practical, easy to perform and easy to record even by non experts using a recording sheet (proforma) that includes diagrams and definitions. It is applicable in the first few days of life even to preterm infants in an incubator [3]. It was initially developed in 1981 and revised in 1999 [16].

3.1.2. Administration, training, and reliability

The examination and recording are designed to take about 10–15 min. The examination is composed of 34 items clustered into six categories (tone, tone patterns, reflexes, movements, abnormal signs, and behavior) [3]. An optimality score has been developed by the authors in 1998 [17]. Each individual item gets a score of 0, 0.5, or 1. A compound score is calculated for each category and for the whole examination, by simple summation of the optimality scores of individual items. A total score less than 30.5 is considered as abnormal [17]. No formal training is required, and detailed instructions are available in the manual [16]. Inter-rater reliability reported is above 96% [3].

3.1.3. Applications and prediction of outcome

When used in a cohort of 380 low-risk preterm infants at term equivalent, the Dubowitz exam demonstrated that premature infants had less flexor limb tone, less head control, but better visual tracking than full-term infants [18]. The exam has also been used to differentiate infants with lesions in the central and peripheral nervous systems seen on neuroimaging [3]. Term infants with hypoxic ischemic encephalopathy (HIE), who have normal MRI or minimal changes tend to show only minor tone abnormalities. Infants with basal ganglia lesions show persistent and diffuse neurological abnormalities. Infants with white matter changes but intact basal ganglia had improved sucking reflex and behavior and less severe tone abnormalities [19]. In premature infants with intraventricular hemorrhage (IVH), the Dubowitz exam has been used to characterize three distinct clinical stages: proceeding, established, and recovery stages of IVH determined by head ultrasound (HUS) [20]. In patients with Cystic leukomalacia seen on late HUS, abnormal signs could be detected in the first weeks of life. If the causative insult occurred during the perinatal or neonatal period, signs were more severe and consisted of marked hypotonia and lethargy. In contrast, if the insult occurred some weeks before deliv-

Table 1
Comparison between basic principals of common neurobehavioral exams and their predictive value in premature infants.

Test	Physiological basis	Training	Examination time	Prediction of outcome of premature infants
The Dubowitz exam	A general neurodevelopmental exam	None	10–15 min	– Sensitivity of 50% to detect poor neurological outcome at 12 month [23]
ATNAT	Examination with emphasis the definitions of passive and active tone	None	5 min	– Poor prediction unless combined with HUS findings [28]
GMs	Depends on visual observation of video tapes of non-stimulated infants to characterize their movement patterns	Standardized training courses, lasting 4–5 days	30–60 min of videotaping, and 1–3 min to evaluate each GM	– At 37–46 weeks PMA cramped-synchronized GMs are highly predictive of CP (sensitivity of 65–79% and specificity 96–100%) [39] – At 3 months, absence of fidgety movements is highly predictive of CP (PPV: 89% NPV: 84%) – Abnormal in those who developed hemiplegia [40]
NBAS	A comprehensive examination of neonatal behavior	Requires a formal training program provided by the Brazelton Institute	No time limit (usually about 30 min)	– Predictive of normal outcome or major disabilities at 5 years of age [55] – At 40–44 weeks PMA, it predicts behavioral problems in childhood (sensitivity 75% and specificity 95–98%) [57]
NAPI	Measures the progression of neurobehavioral performance of preterm infants	Limited training to achieve reliability in exam and scoring	30 min	– Highly correlates with Bayley infant neurodevelopmental screener (BINS) at 12 months and BSID, at 18 and 30 months [68] – When combined with MRI, improved sensitivity (80%) and specificity (81%) [69]
APIB	Assesses the mutually interacting behavioral subsystems in the newborn and simultaneous interaction with the environment	Needs baseline experience and a training process that typically takes 1 year	No time limit (1 h to perform, 30–45 min to score, 3 h to write a report)	– N/A
NNNS	A comprehensive neurobehavioral exam and stress assessment targeted towards term infants at risk and preterm infants	Certification is needed. Training duration depends on previous experience	Less than 30 min. More time is needed for scoring	– At 44 weeks PMA was predictive of motor outcome at 12–36 months of age: ○ CP was associated with low quality of movement (OR: 1.95 (1.24–3.06) and high lethargy (OR: 1.67 (1.01–2.76) ○ Low PDI was associated with low quality of movement (OR: 2.16 (1.38–3.38), hypotonia (OR: 1.63 (1.14–2.32) and low handling (OR:1.83 (1.12–2.99)

ATNAT, Amiel-Tison neurological assessment at term; HUS, Head ultrasound; GMs, general movements; NBAS, the neonatal behavioral assessment scale; NAPI, neurobehavioral assessment of the preterm infants; APIB, the assessment of preterm infant's behavior; NNNS, the neonatal intensive care unit network neurobehavioral scale; BSID, Bayley scales of infant development.

ery, the infant showed only mild hypotonia and lethargy at birth that improved for a period of 4–6 weeks before gradually becoming progressively more abnormal [21]. In a cohort of 66 preterm infants examined at term equivalent, 60% scored in the suboptimal range relative to infants born full-term. MRI abnormalities were associated with lower mean tone and tone pattern scores. Infants with white matter abnormalities had a tendency toward lower mean reflex scores while those with gray matter abnormalities had a tendency toward lower spontaneous movements. The examination was found to have relatively good sensitivity (88%); but poor specificity (46%) for identifying infants with significant MRI abnormalities [22]. The Dubowitz neurological exam was recently studied in 102 very low birth weight (VLBW) preterm infants, as a predictor of adverse neurological outcome at 12 months corrected age (CA), defined as abnormal scores on the Hammersmith infant neurological examination [23]. When compared to published data for healthy infants born at term [17], suboptimal scores were detected in 76.5% and could predict adverse outcome with a sensitivity of 19% and specificity of 89%. When compared to normative published data for low-risk preterm infants at term equivalent [18] only 13.7% were assigned as suboptimal, but the sensitivity to predict adverse outcome increased to 50% [23].

3.2. The Amiel-Tison neurological assessment at term (ATNAT)

3.2.1. Background and physiological basis for exam development

The updated Amiel-Tison neurological assessment at term (ATNAT) [2] is an extension of the French method of infant neurological evaluation which is valid for both term and preterm (at term equivalent) infants [24]. It depends on the individual development of an upper and lower motor control systems. The lower system (the brainstem and cerebellum), matures early in an ascending pattern to maintain posture against gravity and flexor tone in the limb. The upper system (cerebral hemispheres and basal ganglia) matures later in a descending pattern to control the lower system, with relaxation of the limb, and finally allowing for fine motor skills, erect posture, and walking. The rationale for the distinction between upper and lower systems is based on the knowledge that brain injury in the neonate most commonly affects the upper system. Therefore, the best predictors of injury should be found in responses that depend on the upper control system, and not in the responses that depend mainly on brainstem activity [24].

3.2.2. Administration, training, and reliability

The assessment usually takes about 5 min to complete. It proceeds from observation to manipulation, with no specific order required. Full-term infants are to be assessed in the first week of life. Preterm infants can be examined at 40 ± 2 weeks. The ATNAT includes 35 items clustered into 10 domains: cranial assessment, neurosensory function and spontaneous motor activity, passive muscle tone, axial motor activity (active tone), primitive reflexes, palate and tongue, adaptation to manipulation, feeding autonomy, medical status, and unfavorable circumstances at the time of exam [2]. The scoring system for each item involves a non quantitative three-point scale (0, 1, and 2). An *optimal status* is defined by the absence of neurological signs. The *non-optimal status* for full-term infants can be graded into mild (abnormalities of tone and excitability), moderate (abnormalities of tone with signs of CNS depression, or up to two isolated seizures) and severe (repeated seizures, lasting more than 30 min, associated with overt CNS depression from lethargy to coma). For preterm infants for whom it may be more difficult to distinguish between mild and moderate degrees of impairment, only two categories are used [24].

No specific certification is required to perform the ATNAT. The transmission of manual skills has been facilitated by pictures and drawings accompanying precise descriptions [25] and a videotape. Interobserver reliability was assessed in 35 infants. Sixteen items had an excellent reliability, 11 items had a fair to good reliability, while two items had weak reliability. The final synthesis, yielded a good reliability with a kappa coefficient of 0.76 [26].

3.2.3. Applications and prediction of outcome

The original version of the ATNAT was evaluated as a predictor of neurodevelopmental outcome in full-term and preterm infants. In 28 full-term infants with presumed HIE, early (<48 h after insult) examination predicted adverse outcome (death or impairment with disability at 1 year of age) with a sensitivity of 100% and specificity of 31% while late neurological examinations (>7 days after insult) predicted adverse outcome with a sensitivity of 91% and specificity of 71%. Although the late exam was overall more predictive of outcome, an early normal examination was invariably associated with favorable outcome [27]. Moreover, in preterm infants born before 33 weeks' GA, none of the infants who had a normal HUS and a normal ATNAT had a major developmental disorder and only 2% had minor developmental abnormalities [28].

Moreover, the predictive validity of the updated ATNAT has been also reported and it correlated well with Bayley Scales of Infant Development-II at 1 year of age, as well as Griffiths Mental Scales at a mean age of about 3.5 years [24].

3.3. Pretchl's assessment of general movements (GMs)

3.3.1. Background and physiological basis for exam development

The premature nervous system generates a variety of endogenous motor patterns. In the human fetus and newborn, specific patterns have been identified such as startles, general movements (GMs), isolated limb movements, twitches, stretches, yawning, and breathing movements. Of these patterns, GMs are considered the most reliable for functional assessment of the neonatal nervous system [29]. The history of this technique dates back to the early 1980s with Heinz Prechtl's studies, when he used his unaided eye to observe non-stimulated preterm infants and documented what they do if left alone [30]. By this approach, he recognized certain movement patterns that he could apply in the fetus using video ultrasound recordings [31]. GMs are complex, frequent and last long enough to be observed properly. They have a variable sequence of arm, leg, neck, and trunk movements. They are variable in intensity and speed, and have a gradual beginning and end which gives an impression of complexity and variability [32]. Prior to term, GMs are referred to as fetal or preterm GMs. Between term and 6–9 weeks CA, they have the same characteristics but are called writhing movements. At 6–9 weeks CA, fidgety GMs (characterized by small amplitude, moderate speed, and variable acceleration of neck, trunk, and limbs) gradually appear [33] and persist until 6 months CA when intentional and antigravity movements start to dominate [29].

3.3.2. Administration, training, and reliability

The examination is composed of 30–60 min of videotaping. A comfortably dressed infant, preferably with arms and legs uncovered, is videotaped whether awake or asleep. The GMs are then copied to an assessment tape that is reviewed by an expert (actual assessment of each GM may take only 1–3 min). Spontaneous generalized movement could be defined as normal or abnormal. The normal GM varies by age [29] while abnormal GMs are classified into several categories:

- Poor-repertoire: the sequence of the successive movement components is monotonous,
- Cramped-synchronized: rigid movements with contraction and relaxation occurring simultaneously,
- Chaotic GMs: large amplitude movements occurring in a chaotic order without any fluency.

Fidgety movement can be either normal, abnormal (with exaggerated amplitude, speed, and jerkiness) or totally absent.

Standardized basic and advanced training courses, lasting 4–5 days, are provided by the general movements trust (http://www.general-movementstrust.info). A manual, including a CD-ROM and a demonstration video, is available in different languages. The advanced course increased the percentage of correct assessments from 83% to 88% and the ability to differentiate normal from abnormal GMs from 92% to 94%. The overall agreement between observers ranged between 89% and 93%. The average kappa in other studies was 0.88 [29]. When repeated on archived videotapes after a time-interval of 2 years, trained examiners demonstrated a 100% test–retest reliability for global judgment and an 85% reliability for a detailed analysis [34].

3.3.3. Applications and prediction of outcome

GMs have been extensively described as a predictor of poor outcome in the form of cerebral palsy (CP) or developmental retardation [5,35–37]. Prediction may even be possible by observing fetal movements [35]. Abnormalities at early age (mainly poor repertoire) can normalize before or during the fidgety movement period and end with normal outcome. This explains the lower specificity of early age assessment (46–93%) when compared to assessment at older ages (82–100%) [29]. Furthermore, the ability of specific GMs to predict specific types of neurodevelopmental impairments has been investigated. In a large longitudinal study of 130 preterm and term infants with wide range of normal to abnormal HUS findings, 96% of infants with normal fidgety movements had a normal neurological outcome. Abnormal quality or total absence of fidgety movements was followed by neurological abnormalities in 95% of infants. Specificity and sensitivity of fidgety movement assessment were higher (96% and 95%, respectively) than of HUS (83% and 80%, respectively). Additionally, all children who at repeated assessments showed consistently cramped-synchronized GMs, later developed severe spastic CP [38]. In a more a recent study of 84 preterm infants, transient cramped-synchronized character GMs were followed by either mild cerebral palsy when fidgety movements were absent, or normal development when fidgety movements were present [39]. In two studies, infants with subsequent hemiplegia had an absence of fidgety movements after bilateral cramped-synchronized or poor repertoire GM [40,41]. In infants that later became dyskinetic, poor repertoire of general movements, finger spreading and lack of arm and leg movements towards the midline, and absence of fidgety movements were observed [42]. On long term follow up, mildly abnormal GMs between 2 and 4 CA were associated with minor neurological dysfunction, attention-deficit-hyperactivity disorder, and aggressive behavior at 4–9 years of age [43]. A 15-years of age, children with a history of abnormal fidgety movements had lower Griffiths scores at 2 years and lower scores in the test of motor proficiency, particularly in fine motor performance [29]. When compared to ATNAT in VLBW infants at term, assessment of GMs had a positive predictive value of 89% and negative predictive value of 84% while ATNAT had a positive predictive value of 33% and negative predictive value of 88% for motor outcome at 1 year [44].

3.4. The neonatal behavioral assessment scale (NBAS)

3.4.1. Background and physiological basis for exam development

The NBAS is an assessment for neonatal behavior from birth to 2 months of age. It has been used as a reliable research tool to identify individual differences in newborn behavior [13,45,46]. Dr. T. Berry Brazelton et al. developed the NBAS in 1973. It is based on the assumptions that "newborns are highly capable of controlling their behavior in order to respond to their new environment, that they communicate through their behavior and, with their own unique qualities, are ready to shape as well as be shaped by the care-giving environment".

3.4.2. Administration, training, and reliability

NBAS examiners attempt to get the best performance from the infant, even at the expense of the length of the exam (though it commonly takes about 30 min). The scale was built on 28 behavioral and 18 reflex items that assess different developmental areas: autonomic, motor, state and social-interactive systems. It describes their integration in adaptation to the surrounding environment without yielding a single score.

The NBAS requires a formal training program provided by the Brazelton Institute: http://www.brazelton-institute.com/train.html. Inter-rater agreement reported by the Brazelton group is $\geqslant$90% [47]. However, when studied in 120 term infants, low estimates of test–retest reliability were obtained for many items. Items assessing orientation capacity and regulation of state showed better test–retest stability when the predominate states were identical [48].

3.4.3. Applications and prediction of outcome

The NBAS provides a behavioral "portrait" of the infant that can be shared with parents. NBAS has also been used in different research studies to examine the effects of prenatal and perinatal risk factors [49,50], maternal substance abuse [51], obstetric medication [52], and mode of delivery [53] on neonatal behavior. The NBAS has also been used as a teaching tool in early intervention [54], and to examine the relationship between neonatal behavior and parent–child interactions.

The usefulness of the NBAS as a tool to assess the risk of later developmental disabilities was studied in 209 low birth weight and/or premature infants. The NBAS was repeated at 36–38, 40–42, and 44–46 weeks PMA, and developmental outcome was measured at the age of 5 years. In outcome prediction, 94–97% of the subjects in the normal group, 50–78% in the mild disability group and 71–85% in the severe disability group were correctly classified [55]. When used in preterm infants with cystic leukomalacia, those who developed later CP demonstrated poorer motor control, less responsiveness to environmental stimuli, less regulatory capacity, and more abnormal reflexes [56]. The NBAS was also tested as a predictor for later behavioral problems in VLBW preterm infants. Risk factors for behavioral problems in childhood included poor motor performance, poor state regulation, and poor interaction ability [57]. In full-term infants, the ability of various NBAS clusters to predict behavior problems in later childhood was variable based on timing of examination (at 3 days versus 4 weeks of life). For example, higher orientation scores at 3 days was the best predictor of later psychological problems while habituation scores were the most predictive in the 4 week exam [58].

3.5. Neurobehavioral assessment of the preterm infants (NAPI)

3.5.1. Background and physiological basis for exam development

The neurobehavioral assessment of the preterm infant (the NAPI) measures the differential maturity and the progression of neurobehavioral performance of preterm infants between 32 weeks PMA and term. It was developed at Stanford University with large samples of premature infants in three phases that included a pilot study, an exploratory study and a validation study [59].

3.5.2. Administration, training, and reliability

The administration of the exam takes about 30 min. It is a relatively brief and gentle instrument consisting of seven clusters and 41 single-items. These clusters are: motor development and vigor, scarf sign, popliteal angle, alertness and orientation, irritability, quality of crying, and percent sleep ratings. An invariant standard sequence is followed during administration. Additionally, the procedure includes 30 summary rating scales involving the quality of spontaneous movements, visual behavior, and crying. Each infant's response is scored on an ordinal scale. The infant's score is then converted to a standard metric score (0–100) and derived cluster score. Finally, a behavioral state rating is scored. Normative cluster scores have been published [60].

Potentially any professional caring for or studying preterm infants is eligible to become a NAPI examiner. The training aims to achieve reliability in administration of the examination and scoring. A training video tape along with a manual of instructions is available at http://childdevelopmentmedia.com/infant-development-evaluation/70140psb.html. Multiple studies have established the NAPI's reliability, developmental, and clinical validity [61–63]. The items retained in the final version of the test had high test–retest reliability ($r = 0.41$–0.85) and inter-rater reliability ($r = 0.67$–0.97) [64].

3.5.3. Applications and prediction of outcome

NAPI can be used to screen preterm infants, monitor individual progress and to detect effects of NICU interventions [64]. It has been used to compare groups of preterm infants in the NOPAIN study receiving either morphine, versed or placebo [65]. It was also used to assess the effect of prenatal exposure of cocaine, alcohol, and tobacco on preterm infants [66]. When VLBW infants with IVH were compared to those without IVH, they were more hypertonic in the lower extremities and showed more alertness [67].

NAPI has been evaluated as a predictor of outcome in premature infants. When studied in 113 babies, extremely low birth weight infants (ELBW) infants (<1000 g) showed significantly lower NAPI scores compared with VLBW infants (1000–1499 g) at 36 weeks PMA. The pre-discharge NAPI scores (especially the orientation and attention cluster) correlated with Bayley Infant Neurodevelopmental Screener (BINS) at 12 months and the Bayley Scales of Infant Development at 18 and 30 months. All the infants that developed CP had significantly lower NAPI, BINS and Bayley scores [68]. When combined with MRI, it was recently shown to have high sensitivity (80%) in predicting the presence of CP at 18 months of age [69].

3.6. The assessment of preterm infants' behavior (APIB)

3.6.1. Background and physiological basis for exam development

The APIB is a newborn neurobehavioral assessment designed for preterm, at risk, and full-term newborns from birth to 1 month CA. It was inspired by the original work of Brazelton [70]. The main objective of the APIB is the assessment of infant individuality and competence, based on observation of the behavioral subsystems in interaction with each other and with the environment. The subsystems include the autonomic (respiration, digestion, and color), motor (tone, movement, and postures), state organization (range, robustness, and transition patterns), attention (robustness and transitions), and self-regulation (effort and success) systems as well as the degree of facilitation required. The environment is represented by a sequence of distal, proximal, tactile, and vestibular challenges derived from the NBAS.

3.6.2. Administration, training, and reliability

Like the NBAS, the goal is to define the best performance from the infant, even at the expense of the length of the exam. The examination of a preterm infant may take up to an hour, and scoring by a skilled examiner takes between 30 and 45 min. Finally, writing the clinical assessment report may take up to 3 h. The examination consists of six item packages: (1) sleep/distal stimuli; (2) uncover and supine positioning; (3) low tactile stimuli; (4) medium tactile and vestibular stimuli; (5) high tactile and vestibular stimuli; and (6) attention/interaction. The APIB yields six main system variables (the arithmetic means of the 81 scores of the six sets of system scores); and 26 additional variables. The six system scores range from 1 to 9. Low scores (1–3) denote degrees of well-modulated and well organized behavioral regulation, whereas high scores (7–9) denote easily disorganized, poorly modulated behavioral regulation with low thresholds of disorganization and stress [70].

APIB training is available from two national training centers. The use of the APIB requires extensive background and training in the understanding and interaction with preterm and full-term newborns to identify and modulate their integrative capacities. Typically the training process will need one full year. Inter-rater reliability between a trainer and examiner, as well as between two examiners, trained to reliability, is readily established when appropriate preparation and training conditions are met.

3.6.3. Applications and prediction of outcome

The APIB is used by the newborn individualized developmental care and assessment program (NIDCAP) to determine intervention needs and for guiding the therapy program. It is used to develop reports every 1–2 weeks describing each infant's strengths and weaknesses, with recommendations explaining the support needed by each infant to minimize stress and optimize performance. The NIDCAP program was developed under the hypothesis that avoidance of stresses in the environment provides physiological stability and minimizes interference with normal brain development. Using the APIB to facilitate minimizing infant stress, while at the same time providing adequate stimulation, provides a basis for improved long term neurodevelopmental outcome [71,72]. However the cost-benefit ratio and the actual effect on long term outcome has recently become questioned [73,74].

In spite of its extensive use, to our knowledge, the APIB has not been studied as a predictor for later neurodevelopmental outcomes.

3.7. The neonatal intensive care unit network neurobehavioral scale (NNNS)

3.7.1. Background and physiological basis for exam development

The NNNS is a comprehensive neurobehavioral exam that depends on the main principals of NBAS [13] with input from exams as the NAPI, the APIB and others [75,76]. The signs of stress and withdrawal were derived from the Neonatal Abstinence Score [77]. The NNNS was originally developed for the National Institutes of Health's "maternal lifestyle study" (MLS) [78]. The aim was to develop a standardized exam that can be used in either term or preterm infants, especially those with higher risk for developmental abnormalities. The two main differences between NNNS and NBAS are the target population and the structure. While the NBAS was developed to describe the behavior of normal, term, healthy infants, the NNNS added different items to assess infants at risk, with a focus on drug-exposed and preterm infants. While the NBAS was designed to elicit the best behavior that can be achieved at the expense of the structure of the exam and time taken, the NNNS is more structured, less dependent on examiner–infant interaction, and takes less time to administer. NNNS assesses the infant's full range neurobehavioral organization, which also includes neurologic reflexes, motor development, active, and passive tone. It also assesses infant stress, abstinence and withdrawal, and neurologic functioning.

3.7.2. Administration, training, and reliability

Less than 30 min is needed to complete the exam. The target population is medically stable infants $\geqslant$30 weeks' GA, up to 46–48 weeks PMA. During the exam, the state is scored using the traditional 1–6 criteria described by Prechtl [79]. The NNNS has 45 items administered in 12 packages. After attempting to elicit the habituation response, the infant's posture, skin color, texture, and movement are observed and scored. While the infant is an awake state, lower extremity reflexes, upper extremity reflexes, upright responses, and prone responses are administered including classic reflexes and measures of tone and angles. Then the baby is picked up and cuddled in the arm and shoulder, and then six orientation items are administered. After a final set of reflexes, the baby is observed for the post-examination period. Finally, the stress/abstinence scale including physiologic, autonomic, CNS, skin, visual, gastrointestinal, and state are scored [15]. One hundred and fifteen items are scored in the NNNS scoring form. These scores are computed and the output is clustered in 13 summary scores. Higher score indicates maturity in habituation, attention, regulation, and quality of movement. On the other hand, higher score indicates dysmaturity in arousal, excitability, lethargy, non-optimal reflexes, asymmetry, hypertonicity, hypo-tonicity, handling, and stress/abstinence.

Administering the NNNS requires formal training and certification. In a recent study, psychometric properties of the summary scores were evaluated with coefficient alphas ranging from 0.56 to 0.85 which indicates an acceptable to good reliability [80].

3.7.3. Applications and prediction of outcome

NNNS has been used in different studies to delineate the effect of perinatal exposures on neurobehavior. Infants exposed to cocaine and alcohol exposure were compared with infants exposed to alcohol alone and those without prenatal drug exposure [81]. When used in a sample of 1400 one-month-old infants, prenatal cocaine exposure was associated with less arousal, poorer quality of movement and self-regulation, and more excitability, hypertonia, and non-optimal reflexes [78]. In neonates with opiate withdrawal syndrome, those treated with diluted tincture of opium combined with phenobarbital were more interactive, had smoother movements, were easier to handle, and less stressed than those treated with diluted tincture of opium alone [82]. When studied to document the effect of cigarette smoking during pregnancy, tobacco-exposed infants were more excitable, hypertonic, required more handling, and showed more stress/abstinence signs. Maternal salivary cotinine (metabolite of nicotine) and the number of cigarettes per day correlated with the number of stress/abstinence signs in exposed infants [83].

NNNS has also been used to evaluate 168 premature infants (<30 weeks GA or <1250 g) at term equivalent. Preterm infants performed poorly on 8 (of 11) NNNS summary scores. A longer duration of assisted ventilation was associated with increased non-optimal reflexes and hypo-tonicity. Grade III/IV IVH was associated with worse attention scores and more non-optimal reflexes. Maternal antenatal steroid was related to better scores on non-optimal reflexes. Receiving any amount of breast milk on discharge was related to better self-regulation capacities. Finally, girls had a better quality of movement when compared to boys [84].

Although, normative data for the NNNS have been published since 2004 [85], there is limited data on its role as a predictor of outcome. Recently, when data collected for 395 preterm infants (<36 weeks GA) enrolled in the MLS study were analyzed, NNNS at 44 weeks PMA was predictive of motor outcome at 12–36 months of age. CP was associated with low quality of movement and high lethargy; while low Bayley's psychomotor index (PDI) was associated with low quality of movement, hypotonia and, surprisingly, low handling [80]. Two other publications further explored data from the MLS study. The first study used the NNNS to define five discrete behavioral profiles amongst the total 1248 infants (subjects and controls) enrolled in the study. An extreme negative profile was present in 5.8% of infants. This profile was associated with prenatal drug exposure, low GA and birth weight, HUS abnormalities, and neurologic and brain disease. It was also correlated with abnormal behavior problems, school readiness, and IQ at 4.5 years of age [86]. In the second study, the NNNS was used as part of a developmental model of neurobehavioral dysregulation that could relate prenatal substance exposure to behavioral problems at age 7 years [87].

4. Can we predict the outcome of premature infants by neurobehavioral examination?

Prediction of neurodevelopmental outcome of premature infants has been and still is the focus of many clinical researchers. Premature birth is a major cause of neurodevelopmental impairments, disabilities, and socioeconomic burden. Early prediction can help in counseling parents and directing early intervention services. However, developmental outcome is very complex and is influenced by gross and microscopic brain injury, abnormal environmental exposure and socioeconomic status. Though recent neuroimaging advances have helped us delineate anatomical changes in the brain, it does not give us a complete picture of cerebral function. Likewise, though several neurobehavioral examinations have shown promise with regard to their ability to predict later outcome, none have been demonstrated to do so with adequate accuracy. Most likely a combination of tools including neurobehavioral exam, neuroimaging, and neurophysiological studies will be needed to most accurately and reliably predict long term outcome in at risk newborns.

5. Conclusion

Newborn neurobehavior is much more complex than previously believed. Newborn infants have higher cerebral functions that influence their tone, movements, and behavior. The ability to evaluate a newborn effectively requires deep understanding of different aspects of development. The available standardized examinations are variable in the training required, time of administration, and scoring systems, which all affect the ability to use them in clinical practice or in research. Until the time we are able to develop a universal, comprehensive and practical tool to be used in all neonates, clinicians/researchers have to carefully formulate the question they want to answer and choose the most appropriate assessment tool to evaluate the different aspects of neurobehavior in the newborn.

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