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Early neurologic assessment in preterm-infants: Integration of traditional neurologic examination and observation of general movements

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ABSTRACT

Objective: To evaluate the possible additional benefit in terms of prognostic accuracy of an integrated application of a traditional scorable method of neurologic examination and the Prechtl's method of qualitative assessment of general movements (GMs) in a large population of 903 consecutive preterm infants.

Study design: Infants were enrolled from the Intensive Care Unit of the University of Catania. Inclusion criteria were a gestational age below 37 weeks and the absence of genetic disorders. All infants underwent serial ultrasound and at 3 months performed both the GMs assessment and the Hammersmith Infant Neurologic Examination (HINE). Outcome was assessed at 2 years by the Touwen neurologic examination and the Clinical Adaptive Test/Clinical, Linguistic and Auditory Milestone Scale.

Results: The integration of the two methods was shown to be more effective than the single assessments in predicting neurologic outcome. The additional benefit of combining the two approaches was particularly clear for the discrimination between unilateral and bilateral cerebral palsy.

Conclusions: The integrated use of a scorable neurological examination and Prechtl's assessment of GMs can improve early prediction of neurodevelopmental outcome in preterm infants and should complement other clinical and instrumental exams in follow-up programs.

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Abbreviations: GMs; general movements; HINE; Hammersmith Infant Neurologic Examination; CP; cerebral palsy; MD; mild disability; CAT/CLAMS; Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale; PTA; post-term age; FMs; fidgety movements; US; ultrasounds

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1. Introduction

In industrialised countries, preterm birth is responsible for 75% of neonatal morbidity and contributes to long-term neurodevelopmental problems, including neuromotor disorders, visual abnormalities and mental retardation.[1–3] Prediction of outcome in preterm infants requires a comprehensive clinical approach based on the use of instrumental tools implemented with neonatal indicators and serial clinical evaluations.[4] As the availability of such an organised multimodal follow-up program is often hampered by limited resources, neurologic examination necessarily plays a foremost role among the clinical tools, for its low-cost and high transferability.

Most of the studies assessing early neurologic function in preterm infants have either dealt with small groups of mainly high-risk newborns, or have used qualitative and non-standardised measures of neurologic development.[5–10] An overall good prognostic value of the different types of traditional neurologic assessment has been usually shown in these studies, however the number of false responses limits the application of infant traditional neuroexam as a tool for outcome prediction, especially when used in large follow-up and screening projects. [11,12]

A new approach to early neurologic assessment was developed in the last two decades, based on the qualitative assessment of videotaped spontaneous motility.[13] A wide agreement on the clinical value of this tool was shown, in particular concerning the quality of general movements (GMs) which is highly correlated to short and long-term neurologic outcome.[14] The highest predictive value of this tool is reached at around 3 months post-term age (PTA), both in full-term and preterm infants, when the so-called *fidgety* pattern should be present. A comparison of this method with more traditional neurologic examinations showed a similar, although generally higher, predictive power in preterm infants.[15–17]

In accordance with the outcome model of the National Advisory Board of Medical Rehabilitation Research,[18] a complementary role of the traditional neuroexam and the assessment of GMs in early outcome prediction was recently proposed, with the first one mainly representing a measure of *impairment* and the second one a measure of *function*.[4] As a consequence, a combined use of these methods in serial follow-up examinations was recommended. So far, however, only one study explored the additional benefit of integrating the two approaches, confirming a better prediction as to later outcome in a small population of infants at neurological risk.[19]

In the present study we report the results of the use of two concomitant neurologic assessments at 3 months PTA in a consecutive cohort of 903 preterm infants, the first one based on traditional neuroexam and the second on the observation of spontaneous motility, present from birth to about 20 weeks PTA. This specific time window for the examination was chosen as it was shown to be the time of early infancy when both approaches are more powerful.[13,20] Our aim was twofold: to compare the predictive power of each technique in relation to the 2 year neurodevelopmental outcome, and to explore the possible benefit in terms of prognostic accuracy, of an integrated use of the two methods.

2. Subjects and methods

This work is part of an ongoing prospective study performed from January 2000 to June 2005 and involving all the infants admitted to the Neonatal Intensive Care Unit of the University of Catania. As part of the follow-up program, neurologic development is systematically followed from birth to two years of age with (i) the Prechtl's method of qualitative assessment of GMs[13] from birth to 5 months of PTA, (ii) the Hammersmith Infant Neurologic Examination (HINE)[21] from 3 to 12 months PTA and (iii) the Touwen neurologic examination[22] and the Clinical Adaptive Test/Clinical, Linguistic and Auditory Milestone Scale (CAT-CLAMS)[23] at 24 months. For the purpose of the present study, the results of the 3 month assessments of GMs and HINE, and the 24 month assessments of Touwen neurologic examination and CAT-CLAMS scores were used.

All infants with a gestational age below 37 weeks, born between January 2000 and March 2004 were included in the present study. As we were interested in the early assessment of preterm infants at risk for brain damage, all infants with major congenital malformations or genetic disorders were excluded from the study. Cranial ultrasound (US) was generally obtained within the 6th day and then at least weekly up to infant discharge, and always around term age. The study protocol was approved by the Ethics Committee of our Institution and a signed informed consent was obtained from the parents in all cases.

2.1. *Assessment of GMs*

As part of the follow-up program, 15 min video recordings are performed during the hospitalisation and every 3–4 weeks in the outpatient clinic in all subjects. The video-camera was positioned approximately 1 m above the infant, at an angle of 45°. The subjects were recorded during inter-feeding time, in supine position, naked or in a nappy. At least one recording was performed during the *fidgety* period (12 weeks' PTA $\pm$ 3 weeks); when more than one assessment was available, the one closest to 12 weeks' PTA was selected. The quality of *fidgety* movements (FMs) was assessed according to the standard methodological principles of the Prechtl's method on the qualitative assessment of GMs[13] by certified evaluators (DR; AG).

Normal FMs are defined as circular movements of small amplitude, moderate speed and variable acceleration of neck, trunk and limbs, in all directions. Abnormal GMs at *fidgety* age are classified as follows: absent FMs were scored when normal FMs were never observed from age 6 to 20 weeks' PTA; abnormal FMs were scored when FMs could be detected but their amplitude, speed and jerkiness were moderately or greatly exaggerated (see Einspieler et al.[13] for review).

2.2. The HINE

All infants included in the study performed the HINE at 3, 6, 9 and 12 months' PTA. As the aim of the present work was to compare HINE and quality of GMs, only the assessment performed at 3 months was considered for the study. The HINE is a simple and structured method for neurological assessment of infants after the neonatal period between 2 and 24 months of age[21,24]. It includes 26 items assessing cranial nerve function, posture, movements, tone and reflexes. Table 1 shows a list of the items. The score may range between zero and 78.

2.3. Outcome measures

At two years of age all infants were assessed blindly to the early assessments by means of a neurologic examination according to Touwen,[22] and by means of the CAT-CLAMS developmental test.[23] The CAT-CLAMS is used to assess infants' development from 1 to 36 months; the CLAMS items measure receptive and expressive language development while the CAT items measure visual-motor problem-solving skills. This test was shown to highly correlate with the Bayley Scales of Infant Development.[25,26] As the test takes only 10–15 min to administer, it was preferred in this large follow-up program to other developmental scales.

According to the results on the above tests, children were classified in three categories: *normal*, for the children without neurologic abnormalities and with a CAT-CLAMS quotient above 70; *mild disability* (MD), for the children with mild neurologic signs and/or with a CAT-CLAMS quotient below 70, but no cerebral palsy; *cerebral palsy* (CP), for the children with a diagnosis of CP according to the criteria proposed by Hagberg et al.[27]

2.4. Statistical analysis

Spearman rank correlation was used to test correlations of the quality of GMs, HINE, cranial US and other clinical data with neurological outcome. Differences with a p value <0.05 were considered to be statistically significant.

Table 1 – Items included in the Hammersmith Infant Neurologic Examination

Neurologic examination
Assessment of cranial nerve function
Facial appearance, eye appearance, auditory response and visual response, sucking/swallowing
Posture
Head, trunk, arms, hands, legs, feet
Movements
Quantity/quality
Tone
Scarf sign, passive shoulder elevation, pronation/supination, adductors, popliteal angle, ankle dorsiflexion, pulled to sit, ventral suspension
Reflexes and reactions
Tendon reflexes, arm protection, vertical suspension, lateral tilting, forward parachute

3. Results

A total of 925 infants were eligible for the study, but 22 did not complete the two year assessment and were discarded. In all the remaining infants both three month examinations were available. The final population thus consisted of 903 infants, whose characteristics are reported in Table 2. US pictures were ranked as follows: (i) no abnormal signal or transient flare (periventricular echodensity lasting less than 14 days) or isolated intraventricular haemorrhage grade I according to Volpe[28] ($n = 509$); (ii) persistent flare (bilateral periventricular echodensity persisting more than 14 days) without haemorrhage ($n = 147$); (iii) isolated ventricular dilation ($n = 174$); (iv) intraventricular haemorrhage grade II or III according to Volpe[28] ($n = 21$); v) cystic periventricular leukomalacia with or without haemorrhage ($n = 23$) or unilateral intraparenchymal echodensity ($n = 29$).

At two years, 692 children (77%) were normal, 154 (17%) showed an MD and 57 (6%) showed a CP. The CP group was represented by 13 children with hemiplegia (23%), 25 with diplegia (44%) and 18 with tetraplegia (32%); only one infant showed a dyskinetic CP and was therefore not included in the correlation analyses.

One-hundred and forty-five infants were independently examined by two observers, both directly with the HINE and on video-recordings with the GMs evaluation method; inter-observer correlation coefficients were 0.90 and 0.89, respectively (Cohen's Kappa).[29]

3.1. Correlation between birth weight, gestational age and cranial US with outcome

A significant correlation ($p<0.001$) was found between outcome and birth weight (r_s 0.19), gestational age (r_s 0.33) and cranial US (r_s 0.39).

3.2. Correlation between GMs and outcome

A significant correlation ($p<0.001$) was found between GMs and outcome (r_s 0.70). Of the 799 infants with normal fidgety, 692 (87%) showed a normal outcome, 106 (13%) showed an MD and only one showed a CP (0.1%). Of the 49 infants with abnormal fidgety, 43 (88%) showed a MD and 6 (12%) showed a CP; none of them showed a normal development. Of the 55 infants with absent fidgety, five showed (9%) an MD and 50 (91%) showed a CP; none showed a normal development (Table 3).

On the whole, the 3 month GMs assessment, when considering normal fidgety vs abnormal/absent fidgety, showed a sensitivity of 98% and a specificity of 94% for the development of CP.

3.3. Correlation between HINE and outcome

A significant correlation ($p<0.001$) was found between the score at the HINE and outcome (r_s 0.47). Children with normal

Table 2 – Clinical characteristic of the population

	Below 28 weeks $n = 27$ (3%)	28–32 weeks $n = 119$ (13.5%)	33–36 weeks $n = 757$ (83.5%)	Total $n = 903$ (100%)
Birth				
Sex (M/F)	15/12	65/54	416/341	496/407
Gestational age	26.3±0.7	30.9±1.3	35.4±0.8	34.5±2.3
Birth weight	1131±379	1576±426	2320±449	2184±543
US				
Normal	12	21	476	509
Peristent flare	6	34	107	147
Cystic PVL	0	6	17	23
IVH	5	8	8	21
UIPE	4	14	11	29
Ventricular dilation	0	36	138	174
Outcome				
Normal	13	54	625	692
Mild disability	11	36	107	154
Cerebral palsy	3	32	22	57

M = male; F = female; PVL = periventricular leukomalacia; IVH = intra-ventricular haemorrhage; UIPE = unilateral intraparenchymal echodensity.

Table 3 – Distribution of the outcomes in relation to GMs assessment with the group of infants with absent fidgety subdivided according to HINE score cut-off at 50.

	Nor	MD	Hemi	Di	Tetra
Nor F	692	106	1	0	0
Abn F	0	43	1	5	0
F-HINE > 50	0	4	10	2	0
F-HINE < 50	0	1	1	18	18

Nor = normal, MD = mild disability, Hemi = hemiplegia, Di = diplegia.

outcome showed HINE scores ranging from 48 to 70 (median 62); children with MD showed scores ranging from 40 to 65 (median 58); children with CP showed scores between 24 and 61 (median 36). When subdividing subjects with CP according to the subtype, higher scores were found in children with hemiplegia (range 49–61; median 55) compared to those with diplegia (range 24–56; median 35) and those with tetraplegia (range 28–42; median 30.5) (Fig. 1).

On the whole, the 3 month HINE assessment, when using a cut-off score of 57, showed a sensitivity of 96% and a specificity of 87% for the development of CP.

3.4. *Integration of GMs and HINE and correlation with outcome*

A significant correlation ($p < 0.001$) was found between GMs and HINE (r_s −0.49). To examine the contribution of the two methods of neurologic evaluation, we grouped all infants in three categories: (i) presence of FM (normal or abnormal); (ii) absence of FMs with HINE score above 50 and (iii) absence of FMs with an HINE score below 50. A Spearman Rank order Correlation test was then performed, which indicated the integration of the two methods to be more effective than the single assessments in determining neurologic outcome (Table 4). The value of an integration of traditional neuroexam and GMs assessment was also clear when grouping infants with absent fidgety according to their HINE score, with a cut-off of 50 (Fig. 2). In fact, all infants with absent fidgety falling below 50 on the HINE developed a CP, that was bilateral (diplegia or tetraplegia) in all cases but one (hemiplegia); there was only one exception of a child showing a MD at 24 months. Conversely, of the 16 infants with absent fidgety falling above 50 on the HINE, most of them showed a CP (75%) that was a hemiplegia in 10 cases and a diplegia in two.

4. Discussion

This is the first study concurrently analysing at 3 months GMs assessment and a scorable traditional neuroexam in a large cohort of preterm infants. In general, our results confirm the high predictive power of these two methods of neurologic assessment, in infants born preterm. On the whole, the three month HINE showed a sensitivity and a specificity slightly below those found for the GMs assessment, as to the development of CP. This was also the outcome of a previous study which systematically compared neurologic examination and GMs assessment in preterm infants.[15] The authors showed an even higher gap between the predictive power of the neurologic examination and the GMs assessment, as a likely consequence of the different types of methods used in the two studies. In another recent study, GMs assessment and the Amiel-Tison neurologic examination were compared in 45 preterm infants with different degrees of neurologic risk, showing a similar and very high sensitivity and negative predictive value, but lower specificity and positive predictive

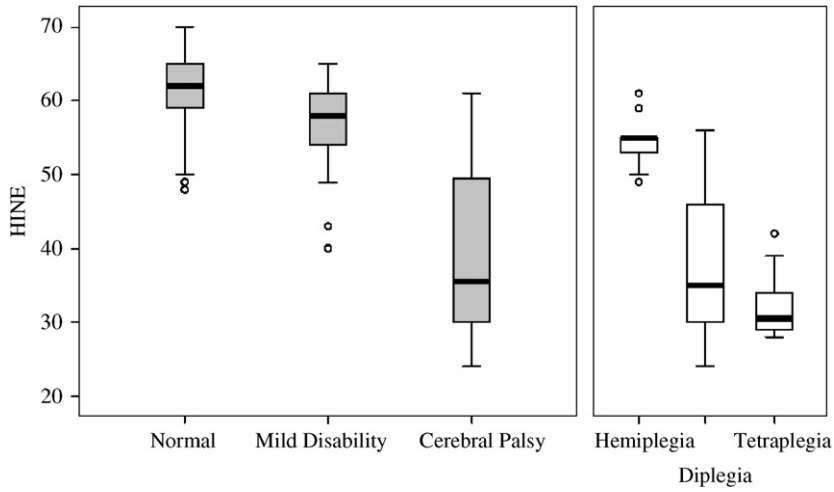

Fig. 1 – Correlation between HINE scores and outcome. On the right, infants with CP grouped according to the subtype. Median, quartiles and extreme values within each category are shown.

Table 4 – Correlation between outcome and HINE, GMs assessment and US category (*Spearman's rho*)

	Neurological outcome (no CP/CP)
Gms assessment	0.73
HINE	0.39
US	0.29
GMs+HINE	0.89

CP = cerebral palsy.

values, especially for the GMs assessment.[16] In that study, however, the outcome was only assessed before 15 months, when the identification of an abnormal outcome, especially for children who do not develop a CP, might be not reliable.

The absence of FMs was confirmed in our population to be a very specific marker of CP as only five infants among the 55 not showing the fidgety pattern at 3 months did not develop a CP (positive predictive value of 91%). The largest study so far, in which 130 infants participated, already emphasised the importance of showing FMs at 3 months.[14] In that study, 98% of the infants with an absent fidgety pattern later developed a CP. The observation of similar figures in a seven times larger population with different neurologic risk is of great relevance to confirm the clinical value of this method.

The quality of FMs at 3 months, despite being a very specific marker of CP, is not able to predict the subtype of CP nor its severity.[33,34] In this respect, Prechtl's method may provide useful indications only by means of longitudinal evaluations throughout the first months of life, exploring several other aspects of spontaneous motility, such as the presence of more segmental movements.[13] However, longitudinal examinations are not always possible, especially in low-risk preterm infants, and the level of additional expertise needed to correctly interpret these other aspects of spontaneous behaviour is still poorly known. Our results suggest that more traditional neurologic examinations, providing quantitative measures of neurologic development, might be of help in differentiating infants at risk for different types of CP, and in particular in the identification of those who will develop a bilateral spastic CP. All 31 infants with HINE scores below 40 and only two of those with a score above 50, developed a bilateral spastic CP. These observations are in line with previous studies reporting how low HINE scores after 6 months of age are associated with severe limitations in self-abilities at 2 and 4 years of age, often related to a bilateral CP.[30–32]

Among the subtypes of CP, the one requiring the highest efforts in terms of early identification is unquestionably hemiplegia. This disorder is in fact frequently diagnosed after the first year of life, due to a supposed delayed onset of clear clinical signs.[33,34] In this respect, the integration of two different approaches of neurologic assessment appeared to be particularly useful. As far as the traditional neuroexam is concerned, our results confirm the great difficulty of early identification of hemiplegia, as infants who later developed this type of CP, with only one exception, always showed HINE scores above or equal to 50, indistinguishable from many normal or mildly delayed children. Conversely, assessment of GMs in all cases but two (85%) showed an absence of FMs, highly suggestive of some type of CP. This is especially remarkable in consideration of the fact that 69% of our hemiplegic children only showed a persistent flare on US, with no signs of unilateral damage, thus not pointing to a significant risk for hemiplegia or any other form of CP. It might be concluded that the concurrent finding at 3 months of an absent fidgety associated to a HINE score above 50 is highly suggestive of an abnormal development towards a hemiplegic form of CP.

Another interesting outcome of our study concerns the definition of the predictive value of abnormal FMs. Interestingly, almost 90% of the infants with abnormal fidgety at 3 months showed an MD at 24 months. In the remainders, a CP was always present with no one developing a normal outcome. These findings are not in full agreement with previous studies reporting a less consistent association

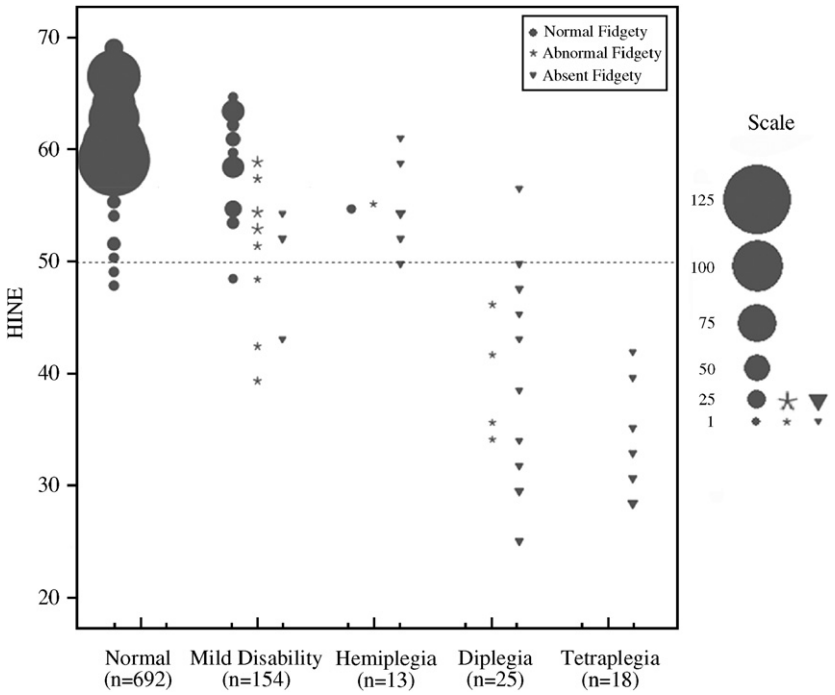

Fig. 2 – Correlation between GMs assessment, HINE scores and outcome. Symbol size corresponds to the number of subjects according to the scale on the right. The table summarizes the distribution of the outcomes in relation to GMs assessment with the group of infants with absent fidgety subdivided according to HINE score cut-off at 50. Nor = normal, MD = mild disability, Hemi = hemiplegia, Di = diplegia.

between abnormal fidgety and MD.[14,19,35,36] Important differences in group selection and outcome measures may partially account for the discrepancies found. It is of interest, however, that in 4–9 year old children, development of behavioural disorders, such as attention deficit hyperactivity disorder, aggressive behaviour or minor neurologic dysfunctions, was recently found to be significantly associated to mild GMs abnormalities at fidgety age.[19] We believe that the presence of an abnormal fidgety, even in a large follow-up program that includes infants at relatively low risk, strongly indicates the need for a very detailed assessment of all aspects of development, also in the absence of clear neurologic signs. The integration with a more traditional neuroexam providing more quantitative information might possibly contribute to the differentiation of the various degrees of minor disabilities. To prove it, however, further studies with long-term outcomes are needed, at a time when the presence of minor neurologic dysfunctions is more clearly defined.[37]

This is the first study clearly indicating that the integration of two complementary neurologic tools, such as the HINE and the GMs assessment, may provide an additional benefit for the early prediction of later neurodevelopmental outcome in pre term infants. The early recognition of a specific type of CP, and in particular the discrimination between unilateral and bilateral CP, can be favoured by this approach. In our population, GMs were able to consistently identify all infants at risk for CP, but provided limited information on its subtype, whereas the HINE correctly identified bilateral CP, but missed all the unilateral ones. All infants with absent fidgety and with HINE score below 50 developed a bilateral CP, with the exception of two infants (one with a hemiplegia and one with an MD). Infants with absent fidgety with HINE score above 50 showed a CP in 96% of the cases, mostly hemiplegia, and an MD in the remaining 4%. The same additional benefit was not reached combining anyone of the two examinations with other clinical data, including birth weight, gestational age or cranial US. It is conceivable that the integrated application of a scorable neurological examination and the assessment of GMs, supplemented by serial neuroimaging and electrophysiological findings, could improve prognostic accuracy in infants at neurodevelopmental risk.

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