Crammed Synchronized General Movements in Preterm Infants as an Early Marker for Cerebral Palsy

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Objective: To ascertain whether specific abnormalities (ie, cramped synchronized general movements [GMs]) can predict cerebral palsy and the severity of later motor impairment in preterm infants affected by brain lesions.

Design: Traditional neurological examination was performed, and GMs were serially videotaped and blindly observed for 84 preterm infants with ultrasound abnormalities from birth until 56 to 60 weeks' postmenstrual age. The developmental course of GM abnormalities was compared with brain ultrasound findings alone and with findings from neurological examination, in relation to the patient's outcome at age 2 to 3 years.

Results: Infants with consistent or predominant (33 cases) cramped synchronized GMs developed cerebral palsy. The earlier cramped synchronized GMs were observed, the worse was the neurological outcome. Transient cramped synchronized character GMs (8 cases) were followed by mild cerebral palsy (fidgety movements were absent) or normal development (fidgety movements were present). Consistently normal GMs (13 cases) and poor repertoire GMs (30 cases) either lead to normal outcomes (84%) or cerebral palsy with mild motor impairment (16%). Observation of GMs was 100% sensitive, and the specificity of the cramped synchronized GMs was 92.5% to 100% throughout the age range, which is much higher than the specificity of neurological examination.

Conclusions: Consistent and predominant cramped synchronized GMs specifically predict cerebral palsy. The earlier this characteristic appears, the worse is the later impairment.

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In the past 20 years, there has been a dramatic reduction in neonatal mortality of low-birth-weight and very low-birth-weight infants but a relative increase in the incidence of cerebral palsy among children with low birth weight and short gestation. An increased survival rate is associated with an increased proportion of infants with cerebral palsy, and it has been suggested that the reduction in neonatal mortality and the concomitant relative increase in cerebral palsy might be associated because the prevalence of cerebral palsy rises sharply the lower the weight of the infant at birth. Cerebral palsy occurs in 8% to 10% of very preterm babies, and approximately 40% of all children with cerebral palsy were born preterm.

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An early prediction of cerebral palsy will lead to earlier enrollment in rehabilitation programs. Unfortunately, reliable identification of cerebral palsy in very young infants is extremely difficult. It is generally reported that cerebral palsy cannot be diagnosed before several months after birth or even before the age of 2 years. A so-called silent period, lasting 4 to 5 months or more, and a period of uncertainty until the turning point at 8 months of corrected age have also been identified. The neurological symptoms observed in the first few months after birth in preterm infants who will develop cerebral palsy are neither sensitive nor specific enough to ensure reliable progress. Irritability, abnormal finger posture, spontaneous Babinski reflex, weakness of the lower limbs, transient abnormality of tone, and delay in achieving motor milestones are some of the neurological signs that have been described in these high-risk preterm in-

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SUBJECTS AND METHODS

High-risk preterm infants were enrolled at the University of Modena and the University of Pisa (Italy) for a prospective, collaborative study of GM observation. The scientific Research Committee of the Italian Ministry of Health, Rome, approved the study. Infants who fulfilled the following criteria—mother’s last menstrual date reliably known, gestational age less than 37 completed weeks, ultrasound abnormalities highly suggestive of brain parenchymal insult, repeated GM assessment and neurological examination until about 36 to 60 weeks’ postmenstrual age, and neurological follow-up until 2 to 3 years’ corrected age—were included in the study. We excluded infants with chromosomal defects or major malformations of the brain or other organs. All infants with GM observation or neurological examination missing at more than 1 key age were also excluded. We enrolled 93 infants, but 9 were omitted because of missing data. Eighty-four infants were included in the final sample. The clinical data of the study group are listed in Table 1. Some infants had taken part in previous studies,29-34 and all parents gave their informed consent.

ULTRASOUND SCANS

On the basis of serial ultrasound scans, performed with 5- to 7.5-MHz heads, we included infants with cystic (34 cases) or noncystic (34 cases) abnormalities of the white matter. Cystic lesions were categorized as small and localized, extensive periventricular, and/or subcortical cysts. Nocystic lesions consisted of increased periventricular echogenicity, characterized by globular, blotchy, coarse hyperechoic ultrasound images localized in the periventricular region that were seen both in coronal and parasagittal views, persisted for 2 weeks or longer, and resolved without subsequent development of cysts or enlargement of the lateral ventricles (adapted from Dammann and Leviton25). Sixteen infants with intraventricular hemorrhage grades 3 and 3+, according to Volpe,42 were also included. Ultrasound abnormalities were reviewed blindly by an expert in ultrasounds (A.B.) who was unaware of the clinical history and development of the infants.

OBSERVATION OF GMs

Videotape recordings were usually made at 3-week to 5-week intervals from birth until the preterm infants were discharged from the hospital. During the study period, each infant was recorded 5 to 10 times. Serial assessments of GM quality were displayed on a time axis to trace individual developmental trajectories.27 Because the functional repertoire changes at various ages, we divided our longitudinal data into 4 “key age” periods: preterm (up to 37 weeks’ postmenstrual age), term age (38-42 weeks’ postmenstrual age), 43 to 46 weeks’ postmenstrual age, and 47 to 60 weeks’ postmenstrual age. The quality of the GMs of infants recorded in Modena was assessed in Pisa (G.C.), and infants recorded in Pisa were assessed in Modena (F.F.). In addition, one of us (H.F.R.F.), who was unaware of the infants’ clinical histories and ultrasound results, reassessed the quality of GMs. Interobserver agreement in the judgment of the quality of GMs was 90.2%. If investigators disagreed, an agreement was reached after reassessment and discussion. From birth until the end of the second month postterm, GMs were scored as normal, poor repertoire, or cramped synchronized. From 47 to 60 weeks’ postmenstrual age, GMs of a fidgety character were scored as present (normal or abnormal) or absent. When more than 1 judgment per age period was available for a single subject, the first observation for this age period was used. In addition, GMs of a cramped synchronized character could be scored until 60 weeks’ postmenstrual age (Figure 1).

DEFINITIONS

General movements are gross movements that involve the whole body; they may last from a few seconds to several minutes. They appear early in gestation (9-10 weeks’ postmenstrual age) and are the most complex of the whole repertoire of endogenously generated distinct movements. What is particular about normal GMs is the variable sequence of arm, neck, and trunk movements. They wax and wane in intensity, force, and speed, and they have a gradual beginning and end. The majority of the sequence of extension and flexion movements of arms and legs is complex, with superimposed rotations and, often, slight changes in the direction of the movement. These additional components make the movement fluent and elegant and create

Continued on next page
the impression of complexity and variability. Despite this variability, GMs must be considered as a distinct coordinated pattern that is easy to recognize each time it occurs.

In poor repertoire GMs, the sequence of the components of the successive movements is monotonous, and the movements of the different body parts do not occur in the complex way seen in normal GMs.

Cramped synchronized GMs appear rigid and lack the normal smooth and fluent character. All limb and trunk muscles contract and relax almost simultaneously.

Fidgety movements are an ongoing stream of small, circular, and elegant movements of the neck, trunk, and limbs; they emerge at 6 to 9 weeks' and disappear around 15 to 20 weeks' postterm age. Abnormal fidgety movements look like normal fidgety movements, but their amplitude, speed, and jerkiness are moderately or greatly exaggerated.

Abnormal GM quality could persist throughout the entire period of observation or just part of it. We called an individual developmental trajectory with the same GM abnormality throughout the study period consistent. When GM abnormality was observed transiently during preterm and/or term age only, we used the term transient. When cramped synchronized GMs (preceded by poor repertoire GMs) were present for even longer and did not disappear until 60 weeks' postmenstrual age, the term predominant was used.

NEUROLOGICAL EXAMINATION AND FOLLOW-UP

During the preterm and term periods, neurological examination was carried out in accordance with the Dubowitz and Dubowitz and Prechtl protocols, respectively. During the first 5 months' postterm and afterward, videotapes of spontaneous motility and clinical checks were accompanied by a standardized neurological examination, based on items from Touwen. The neurological assessment was also videotaped. Any abnormal signs in the neurological examinations were noted. During the preterm period, we looked for the following abnormalities from the Dubowitz protocol: abnormal posture, generalized or segmental hypotonia or hypertonia, hypokinesia, abnormal head control, frequent tremors or startles, absent or abnormal responses or reflexes, hyporeactivity to stimulation, and irritability. The results of the Prechtl examination, performed at term, were classified according to the syndromes indicated in the summary form. The neurological examination was scored as abnormal when at least 1 of the abnormalities mentioned above was present. Additionally, at the age of 2 to 3 years, a developmental test according to the Griffiths Developmental Scales was performed. At this age, the outcome was classified as "normal" (no neurological signs) or "cerebral palsy." Cerebral palsy was defined as "a chronic disability characterized by aberrant control of movement or posture, appearing early in life and not the result of recognized progressive disease." At 2 to 3 years of age, the severity of motor disability was scored in accordance with the classification system for gross motor function in children with cerebral palsy recently proposed by Palisano et al. We distinguished mild (grade 1) and moderate to severe motor impairment (grades 2-5). In addition, we defined minor neurological deficits: mild sensory deficits, strabismus, severe postural delay without corticospinal tract dysfunction, and/or a score between 50 and 84 on the Griffiths Developmental Scales.

INTEROBSERVER RELIABILITY

The neurological examinations in Modena and in Pisa were performed by two of us (F.F. and G.C., respectively). To assess functional impairment in cerebral palsy, the same authors reviewed the neurodevelopmental records and videotapes of the infants at the time of the last clinical check. Preterm infants from Pisa were scored by one of us (F.F.), and while another of us (G.C.) scored infants from Modena; these scores were compared with the original scores given by local physical therapists and pediatric neurologists. In case of disagreement, an agreement was reached after reassessment and discussion.

STATISTICAL ANALYSIS

The receiver operating characteristic curve analysis was used to compare the power of ultrasounds and GMs to predict cerebral palsy. Receiver operating characteristic curve analysis provides a powerful means of assessing a test's ability to discriminate between 2 groups of patients, with the advantage that the analysis does not depend on the threshold value selected. To test the correlation between the time of appearance of the cramped synchronized GMs and the severity of motor impairment in children with cerebral palsy, a Yates test (2-tailed) was used. This test estimates the trend in data with consistent signs and is more appropriate and sensitive than a $\chi^2$ test for $P \times Q$ contingency tables. A $P$ value of $<.05$ was considered statistically significant. A standard formula was used to calculate the likelihood ratio of GMs, the cramped synchronized character of GMs, and findings from neurological examination.
Severe ultrasound abnormalities (ie, extensive cysts and germinal matrix–intraventricular hemorrhage grade 3+) were present in 31 infants and, with 1 exception, led to cerebral palsy. Minor ultrasound abnormalities (persisting increased echogenicity, small and localized cysts, and germinal matrix–intraventricular hemorrhage grade 3) were present in 33 infants. The majority of cases (39 infants) had a normal outcome; cerebral palsy with mild (7 infants) or moderate to severe (7 infants) impairment was also observed (Table 2).

Developmental Trajectories

The time course of GM quality in relation to the neurological outcome is provided in Table 3 and Figure 2.

The duration and consistency of GM quality determined to a high degree the normality or severity of the abnormal outcome. All 33 preterm infants who displayed predominant (19 cases) or consistent (14 cases) cramped synchronized character GMs throughout the study period developed cerebral palsy. None of them displayed fidgety movements between 47 to 60 weeks' postmenstrual age. By contrast, 13 infants with consistent normal GMs, 4 infants with transient poor repertoire GMs, 19 infants with consistent poor repertoire GMs, and 4 infants with transient cramped synchronized GMs had a normal outcome. Despite the different patterns of developmental trajectory, these infants had fidgety movements in common (3 showed abnormal fidgety movements). The only exception was 1 infant with no fidgety movements who showed a prolonged postural delay that disappeared at 3 years of age and was classified as normal (Table 4). Of the preterm infants with consistent poor repertoire GMs (7 cases) and transient cramped synchronized GMs (4 cases) who later developed cerebral palsy, 10 had no fidgety movements, and 1 had exaggerated fidgety movements. The relationship between the age of appearance of predominant or consistent cramped synchronized GMs and the severity of the neurological impairment demonstrates that the earlier the cramped synchronized quality GMs appear, the worse is the outcome. The Yates trend test (T, 3.207; P < .005) proved the statistical significance of this statement.

**Table 1. Clinical Characteristics of 84 High-Risk Preterm Infants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenstrual age at birth, mean ± SD, wk</td>
<td>30.2 ± 2.7</td>
</tr>
<tr>
<td>Birth weight, mean ± SD, g</td>
<td>1410.14 ± 456.71</td>
</tr>
<tr>
<td>Outborn</td>
<td>14</td>
</tr>
<tr>
<td>Inborn</td>
<td>86</td>
</tr>
<tr>
<td>Boys</td>
<td>50</td>
</tr>
<tr>
<td>Girls</td>
<td>50</td>
</tr>
<tr>
<td>Preeclamptic toxemia</td>
<td>7</td>
</tr>
<tr>
<td>Multiple pregnancies</td>
<td>6</td>
</tr>
<tr>
<td>Acute fetal distress†</td>
<td>13</td>
</tr>
<tr>
<td>Appropriate size for gestational age</td>
<td>76</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>24</td>
</tr>
<tr>
<td>Severe respiratory distress syndrome‡</td>
<td>42</td>
</tr>
<tr>
<td>Severe infection§</td>
<td>33</td>
</tr>
<tr>
<td>Seizures</td>
<td>17</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>30</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>13</td>
</tr>
<tr>
<td>Retinopathy of prematurity (grades 2-5)</td>
<td>17</td>
</tr>
</tbody>
</table>

*Data are given as percentage of subjects unless otherwise indicated.
†Acute fetal distress was indicated by late fetal heart deceleration.
‡Severe respiratory distress syndrome was indicated by more than 3 days of mechanical ventilation.
§Severe infections include positive blood culture; positive immature–total granulocyte ratio and reactive C protein; and 1 or more clinical signs of infection (respiratory distress, hypotension, metabolic acidosis, temperature instability, gastrointestinal symptoms, diminished activity or lethargy, and seizures).

**RESULTS**

**NEUROLOGICAL OUTCOME**

At 2 to 3 years of age, 40 infants were healthy, and 44 had spastic-type cerebral palsy (22 subjects had diplegia, 14 had tetraplegia, and 8 had hemiplegia). Fifteen infants showed grade 1 motor impairment, according to Palisano et al.49 5 infants had grade 2, 5 had grade 3, 9 had grade 4, and 10 had grade 5. With the exception of 1 infant with a mild hearing defect, no case of minor neurological disorder was observed.

**Ultrasound Findings**

Severe ultrasound abnormalities (ie, extensive cysts and germinal matrix–intraventricular hemorrhage grade 3+) were present in 31 infants and, with 1 exception, led to cerebral palsy. Minor ultrasound abnormalities (persisting increased echogenicity, small and localized cysts, and germinal matrix–intraventricular hemorrhage grade 3) were present in 33 infants. The majority of cases (39 infants) had a normal outcome; cerebral palsy with mild (7 infants) or moderate to severe (7 infants) impairment was also observed (Table 2).

**Developmental Trajectories**

The time course of GM quality in relation to the neurological outcome is provided in Table 3 and Figure 2.

**Figure 1. Types of normal (N) and abnormal (A) general movements (GMs) in 84 high-risk preterm infants during preterm, term, and the first 5 months of postterm age. F indicates fidgety; PR, poor repertoire; CS, cramped synchronized; and CH, chaotic.**
LIKELIHOOD RATIO AND ACCURACY OF GMs AND NEUROLOGICAL EXAMINATION IN PREDICTING CEREBRAL PALSY

The positive likelihood ratio of cramped synchronized GMs for predicting cerebral palsy is much higher than that of neurological examination throughout the age range. The negative likelihood ratio for predicting cerebral palsy based on GM quality was also much higher than that for neurological examination during the study period.

The GM observation was 100% sensitive throughout the age range; neurological examination was less sensitive during the study period. The sensitivity of cramped synchronized GMs was low (46.5%) in the preterm period because of those infants with cramped synchronized GMs preceded by poor repertoire GMs. Sensitivity rose to 65%, 78.7%, and 77.2% at term, early postterm...
The severity and prognostic value of the cramped synchronized character of GMs were known from previous investigations. Normal fidgety movements follow transient abnormalities of GM quality point to a normal outcome, absence of fidgety movements suggests a neurological deficiency, and GMs are a more powerful prognostic tool than traditional neurological examination and ultrasound scan.

The severity and prognostic value of the cramped synchronized character of GMs were known from previous studies. However, the finding that this motor abnormality is a specific marker of later cerebral palsy is new. A detailed analysis of the developmental trajectories of GMs in a large group of preterm infants affected by major or minor abnormalities detected by ultrasound demonstrates that the consistent or predominant cramped synchronized character of GMs, irrespective of the severity of the ultrasound abnormalities, is always followed by cerebral palsy.

The study has practical and obvious implications. It offers clues about the selection criteria for a strict neurological follow-up. Preterm infants who are waiting for a definite diagnosis of brain integrity are usually enrolled in prospective neurological follow-up programs based on their clinical history and the ultrasound findings rather than a functional assessment, which involves the evaluation of mental and motor performance. Recent studies have shown that mental retardation and learning deficiencies are common among preterm infants tested at school age. We are not sure whether normal, or only mildly abnormal, GMs at these early ages exclude these minor deficiencies at a later age. This study stresses the importance of functional assessment based on early observations of spontaneous motor behavior. The normal quality of GMs identifies those infants who are not affected by brain dysfunction and who will develop normally; they do not need strict neurological surveillance. In contrast, prolonged cramped synchronized character GMs identify infants who are most likely to develop cerebral palsy. They are the ones who need and can possibly benefit from early intervention.

The first videotape should be recorded as soon as possible after birth, when the effects of analgesia and/or

| Table 5. Age Period–Related Likelihood Ratios (LRs) and Accuracy for General Movement (GM) Observation, Cramped Synchronized Character, and Neurological Examination With Respect to Cerebral Palsy* |
|-----------------|-----------------|-----------------|-----------------|
|                  | Preterm          | Term Age         | Postterm         | Fidgety         |
| **Age Period**   | 28-37            | 38-42            | 43-46            | 47-60           |
| No. of infants†  | 83               | 79               | 70               | 84              |
| GM assessment    |                  |                  |                  |                 |
| LR+ (95% CI)     | 1.5 (1.19-1.99)  | 1.52 (1.20-1.93) | 2.11 (1.48-3.0)  | 7.8 (3.44-17.78) |
| LR− (95% CI)     | <0.07 (0.01-0.48) | <0.07 (0.01-0.50) | <0.06 (0.01-0.39) | <0.02 (0.04-0.18) |
| Sensitivity, %   | 100              | 100              | 100              | 100             |
| Specificity, %   | 38               | 41               | 53               | 82              |
| Positive predictive value, % | 63               | 63               | 55               | 86              |
| Negative predictive value, % | 100              | 100              | 100              | 100             |
| Cramped synchronized character    |                  |                  |                  |                 |
| LR+ (95% CI)     | 4.97 (1.57-17.5) | 22.4 (3.18-158)  | 28 (4.02-195.6)  | 30 (4.3-209)    |
| LR− (95% CI)     | 0.68 (0.53-0.87) | 0.44 (0.30-0.63) | 0.25 (0.13-0.46) | 0.26 (0.15-0.43) |
| Sensitivity, %   | 46               | 65               | 79               | 77              |
| Specificity, %   | 92               | 97               | 100              | 100             |
| Positive predictive value, % | 87               | 96               | 100              | 100             |
| Negative predictive value, % | 62               | 73               | 84               | 80              |
| Neurological examination results |                  |                  |                  |                 |
| LR+ (95% CI)     | 1.06 (0.81-1.39) | 1.71 (1.11-2.61) | 1.82 (1.29-2.57) | 1.66 (1.26-2.18) |
| LR− (95% CI)     | 0.85 (0.42-1.71) | 0.51 (0.30-0.87) | 0.18 (0.06-0.54) | 0.11 (0.03-0.43) |
| Sensitivity, %   | 58               | 68               | 89               | 85              |
| Specificity, %   | 54               | 63               | 52               | 70              |
| Positive predictive value, % | 54               | 66               | 67               | 77              |
| Negative predictive value, % | 48               | 65               | 84               | 93              |

*CI indicates confidence interval.
†The total number of infants ranges from 70 through 84 for the different observation periods because GM observation or neurological examination for 1 of the age periods was missing for some infants.

Two major findings emerge from this study. First, the cramped synchronized character of GMs, if consistent in time or predominant from preterm birth to 5 months’ postterm age, specifically predicts later cerebral palsy. Second, the time of appearance of cramped synchronized GMs predicts the degree of later functional impairment caused by cerebral palsy: the earlier the appearance, the more severe the functional impairment.

Our study also confirmed observations from previous investigations. Normal fidgety movements following transient abnormalities of GM quality point to a normal outcome, absence of fidgety movements suggests a neurological deficiency, and GMs are a more powerful prognostic tool than traditional neurological examination and ultrasound scan.
Cerebral palsy occurs in 8% to 10% of very preterm infants, whereas approximately 40% of all children with cerebral palsy are born preterm. An early prediction of cerebral palsy will lead to earlier rehabilitation programs. Unfortunately, reliable identification of cerebral palsy in very young infants is extremely difficult.19,20 It is generally reported that cerebral palsy cannot be diagnosed before several months after birth21-25 or even before the age of 2 years. In addition, traditional neurological examination fails to predict the development and severity of cerebral palsy.

Our study demonstrates that the cramped synchronized character of GMs, if consistent in time or predominant from preterm birth to 5 months’ post-term age, specifically predicts later cerebral palsy. Second, the time of appearance of cramped synchronized GMs predicts the degree of later functional impairment of cerebral palsy: the earlier the appearance, the more severe is the functional impairment.

The study has practical and obvious implications. It offers clues about the selection criteria for a strict neurological follow-up and helps the physician involved in the follow-up recognize the early signs of cerebral palsy and, consequently, begin early rehabilitation programs.

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