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Neurological Examination at 6 to 9 Months in Infants with Cystic Periventricular Leukomalacia

Abstract

The Hammersmith Infant Neurological Examination was performed in 24 infants with cystic periventricular leukomalacia whose gestational age ranged between 26–38 weeks. The infants were examined between 6 and 9.5 months corrected age. The aim of the study was to establish the different patterns of neurological abnormality as well as the optimality scores that predict the severity of motor sequelae at 2 years. Increased neck and trunk extensor tone, and a posture of flexed arms and extended legs between 6 and 9 months were always associated with the inability to sit unsupported at 2 years, whilst truncal hypotonia and extended arms and legs were associated with unsupported sitting but not walking. Optimality scores between 41 and 60 were generally associated with sitting but not walking at 2 years whilst scores below 40 were always associated with the inability to sit independently at 2 years. All infants who did not develop cerebral palsy at 2 years had scores > 60. Our results suggest that the pattern of findings on neurological examination performed between 6 and 9 months as well as the calculated optimality score helps to predict motor impairment in infants with PVL.

Key words
PVL · neurological · outcome

Introduction

Cystic periventricular leukomalacia (PVL) is the most frequent cause of cerebral palsy in preterm infants [7,17]. Several studies have reported the value of cranial ultrasound in identifying the extent and the location of cystic lesions and in predicting cerebral palsy [1,6,18,20,22]. However, good early cranial ultrasound examinations are not always available and to date no MRI study in a large number of infants with PVL has been used to predict motor outcome. Frequently ex-preterm children are seen in clinic in the first year and found to have some neurological abnormality but from an unstructured examination it can be difficult to predict accurately later motor outcome. We have recently reported the application of a structured and scorable assessment, the *Hammersmith Infant Neurological examination* [9], in a cohort of preterm infants with and without brain lesions suggesting that the optimality scores can predict not only the presence of cerebral palsy but also the maximal motor functional activity achieved at 2 years [8]. In that study however only 2 infants with cystic PVL were included.

The aim of the present study was to use the *Hammersmith Infant Neurological examination* at 6–9 months corrected age in a cohort of infants with cystic PVL. More specifically we wished to evaluate: 1) whether there are specific patterns of clinical neurologic abnormalities and whether these, if present, are related to severity of motor sequelae at 2 years; 2) the range of the optimality scores and their correlation with early cranial ultrasound findings and outcome.

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Patients and Methods

Infants with cranial ultrasound evidence of periventricular cystic lesions (grade > II according to de Vries et al.) [2], born at or referred to the Hammersmith Hospital, London, UK, and to the Gemelli Hospital, Rome, Italy, between 1998 to 2002, were prospectively enrolled. Ethical permission was obtained from the Research Ethics Committee at each hospital and parental permission was given in each case. The patients were included if they had at least one infant neurological examination between 6 and 9 months corrected age and one at 2 years corrected age. The same observers examined the infants at 6 – 9 months and at 2 years (GB, VD, DR in Rome, FC, EM, LD in London).

Cranial ultrasound

Infants were scanned with an ATL Ultramark 4 mechanical sector scanner using a multifrequency transducer (5 – 7.5 – 10 MHz crystals). All infants except one were born preterm, admitted to the neonatal unit and scanned as part of their admission assessment and then at least weekly for 4 weeks, and every two weeks till discharge and at term equivalent age. Cystic PVL was classified according to the grading system of de Vries et al. [2]. Grade II PVL was defined as transient periventricular densities, evolving into small localised cystic lesions; grade III PVL was defined as areas of periventricular densities evolving into extensive periventricular cystic lesions; grade IV PVL was defined as cysts extending additionally into the deep or subcortical white matter.

We also classified the lesions according to the location of the cysts in the white matter on the parasagittal view (the frontoparietal region [A] or posterior to the trigone in the parieto-temporal-occipital region [B]) using the classification suggested by Rademaker et al. [19] for unilateral parenchymal lesions.

All the ultrasound scans were reviewed by two examiners (RL and FC) who were unaware of the clinical findings in the other centre and who had complete concordance in scoring the scans.

Neurological examination

The Hammersmith Infant Neurological Examination was used to assess neurological status [9,11]. The examination includes 26 items assessing cranial nerve function, posture, movements, tone and reflexes/saving reactions and behaviour. The findings of each item in this assessment are subdivided into four columns and the examiner marks each item by circling the relevant response. The subdivision was initially based on the frequency distribution at 12 and 18 months of age but a subsequent study [9] has reported that infants between 6 and 9 months have a similar distribution. Column 1, and in some cases column 2, include findings which occur in 90% of the normal population and were regarded as optimal. If the findings are in column 1, they are given a score of 3, if in column 2 a score of 2, in column three a score of 1 and in column 4 a score of 0. An optimality subscore can be given for each section and the overall global optimality score can be calculated by summing up all the 26 items, with a maximum global score of 78.

We also analyzed single items, such as arm protection and parachute reactions or combinations of items such as neck and trunk extensor and flexor tone that in the past have been found to be predictive of functional abilities. Arm protection in our examination is assessed by pulling the infant by one arm from the supine position noting the reaction of the opposite side [9].

Outcome

All infants were assessed with a structured examination. Cerebral palsy, if present, was classified according to the criteria proposed by Himmelmann et al. [12].

Maximal locomotor function at 2 years corrected age was graded according to the simplified version of the classification suggested by Palisano et al. [16]:

1. walks independently without restriction: can take more than ten steps without any help
2. sits independently: maintains floor sitting and may pull to stand and take steps holding on to furniture
3. cannot sit: able to maintain antigravity head and trunk control in prone and when held in a sitting position

Results

In the study period 24 infants fulfilled the inclusion criteria (Table **1**). All but 1 were preterm infants (range 26 – 35 gestational age, mean 30,6 weeks). One infant was born at 38 weeks gestational age and had cystic lesions, typical of PVL, present at birth.

Cranial ultrasound scan findings

Six infants had PVL grade II; of these four had lesions in the fronto-parietal region (A) and two in the posterior (B) region. Seventeen infants had PVL grade III of whom 10 had lesions in both fronto-parietal and posterior regions and 7 had lesions localised posteriorly. One infant had grade IV PVL with cysts in the frontoparietal region and posterior regions plus subcortical lesions. Details of the extent of the lesions are shown in Table **1**.

Neurological examination

All 24 infants had a neurological examination between 6 and 9.5 months (mean age 7.3 months). Five of the infants had a normal neurological examination, another one had mildly abnormal movements and one mild asymmetry of upper limb tone.

The remaining 17 infants all had abnormalities of tone, posture and movements.

Seven of these 17 had an abnormal pattern of axial tone with increased extensor tone of the neck and trunk and a posture characterised by flexion of the upper limbs and extension of the lower limbs.

The other 10 all had a degree of axial hypotonia affecting both flexor and extensor neck and trunk muscles and a posture characterised by a variable degree of extensor tone in the legs and of extensor tone and dystonia in the upper limbs (Table **1**).

Table **2** shows details of reflexes and reactions.

Optimality scores

The total scores ranged between 16 and 78 (mean 49.9, SD 17).

Table 1 Details about neurological examinations, ultrasound findings and outcome

			Neurological examination					Ultrasound findings		Outcome at 2 years				
	GA (w)	Age at first exam (m)	Posture	Neck and trunk tone	Vision	Movements	Total score	PVL class.*	Location of lesion**	Cerebral palsy	Functional ability	Seizures	Drugs	Micro-cephaly
1	27	6	normal	normal	normal	normal	67	III	B	no	walks	–	–	–
2	33	6	normal	normal	normal	jerky	64	II	B	no	walks	–	–	–
3	33	6	normal	normal	normal	normal	78	III	A + B	very mild diplegia	walks	–	–	–
4	29	6	normal	normal	normal	normal	69	II	B	no	walks	–	–	–
5	33	7	normal	normal	normal	normal	73	II	A	no	walks	–	–	–
6	34	6	normal	normal	normal	normal	74.5	II	A	no	walks	–	–	–
7	31	8	mild UL asymmetry	normal	normal	mild asymmetry UL	70	II	A	no	walks	–	–	–
8	31	7	extension LL	↓	squint	poor repertoire; dystonic	49	III	A + B	quadriplegia	sits	–	–	–
9	35	7	dystonia UL and LL	↓	squint	dystonic	44	III	A cystic + B non cystic	quadriplegia	sits	–	–	+
10	34,5	6	mild dystonia	mild ↓	normal	poor repertoire	57	III	A + B	diplegia	sits	infantile spasms	VPA, VGB	–
11	26	9	mild extension LL	↓	no fixation; squint	poor repertoire	48	III	A + B	quadriplegia	sits	–	–	+
12	32,2	8	extension LL	↓	squint	poor repertoire	44	III	B	diplegia	sits briefly	–	–	–
13	30,4	9.5	asymmetry	↓	normal	jerky	44.5	III	B	diplegia	sits	–	–	+
14	29,3	9.5	extension LL	↓; flexion > extension	normal	Abnormal cramped	42	III	B	diplegia	sits	–	–	–
15	38	7	mild extension LL	↓	normal	poor repertoire	44	III	B	diplegia	sits	–	–	–
16	35	9	mild asymmetry	↓	normal	poor repertoire	56.5	II	A	diplegia R > L	sits	–	–	–
17	27,2	9	mild asymmetry	↓	normal	Excessive	49	III	B	diplegia	no sitting	–	–	–
18	28	6.5	flexion UL; extension LL	↓; increased extension	normal	poor repertoire	42	III	A + B	quadriplegia	no sitting	–	–	–
19	30	8	flexion UL; extension LL	↓; increased extension	follows briefly; squint	poor repertoire, dystonic	36	IV	A + B + subcort.	quadriplegia	no sitting	–	–	+
20	29	6	flexion UL; extension LL	↓; increased extension	follows; squint	poor repertoire, dystonic	35.5	III	B	quadriplegia	no sitting	–	–	–
21	35	6	flexion UL; extension LL	↓; increased extension	Absent	dystonic	16	III	A + B	quadriplegia	no sitting	–	–	+

Table **1** Details about neurological examinations, ultrasound findings and outcome *(continued)*

			Neurological examination				*Ultrasound findings*		*Outcome at 2 years*				
	GA (w)	*Age at first exam (m)*	*Posture*	*Neck and trunk tone*	*Vision*	*Movements*	*Total score*	*PVL class.**	*Location of lesion***	*Cerebral palsy*	*Functional ability*	*seizures*	*drugs*	*Micro cephaly*
22	29	6	flexion UL; extension LL	↓; increased extension	squint; poor following	dystonic	36.5	III	A + B	quadriplegia	no sitting	–	–	–
23	28	7	flexion UL; extension LL	↓; increased extension	follows; squint	poor repertoire, dystonic	40	III	A + B	quadriplegia	no sitting	general-ised	PB	–
24	27	6	flexion UL; extension LL	↓; increased extension	squint; poor following;	dystonic	19	III	A + B	quadriplegia	no sitting	general-ised	PB, VPA	–

GA: gestational age; w: weeks; m: months; * according to de Vries classification; ** according to Rademaker classification A: lesions in the fronto-parietal region; B: lesions in the trigonal area; UL: upper limb; LL: lower limb; R: right; L: left; – no seizures or drugs or microcephaly; VPA: valproate; VGB: vigabatrin; PB: phenobarbitone; + head circumference less than 3rd centile

Motor outcome

Eighteen infants had neurologic signs consistent with a diagnosis of cerebral palsy: ten had spastic quadriplegia and 8 a spastic diplegic pattern. Six infants did not show any signs of cerebral palsy.

Eight of 24 infants were not able to sit independently at two years. Nine of 24 infants achieved independent sitting but not walking at two years. The remaining 7 were able to walk.

Cranial ultrasound scan findings and outcome

Of the 20 infants with lesions posterior to the trigone, three had a normal motor outcome and 17 developed cerebral palsy (1 able to walk, 8 able to sit and 8 unable to sit).

Of the four infants with lesions localised in the areas anterior to the trigone, 3 had a normal motor outcome and 1 developed cerebral palsy.

Neurological examination at 6 – 9 months and motor outcome at 2 years

Tables **1** and **2** show details of the correlation between the neurological findings and motor outcome. Items assessing posture and axial tone were the ones that were most consistently predictive of severity of outcome.

Five infants had a normal neurologic examination, and two had minimal abnormal signs (one had jerky movements and the other had minimal asymmetries of tone in the upper limbs). All 7 achieved independent ambulation by 2 years but one had a mild diplegia.

Ten infants had axial hypotonia, increased extensor tone in the legs and variable extensor tone and two dystonia in the upper limbs. All 10 had cerebral palsy, 7 a diplegia and 3 a quadriplegia. All but one were able to sit unsupported at 2 years but none walked independently at this time.

Seven infants had increased extensor axial tone and a posture characterised by flexion of the upper limbs and extension of the lower limbs; all had a quadriplegia and none achieved independent sitting by 2 years.

Optimality scores

Seven of the 24 infants had scores above 60: they were all able to walk independently at 2 years of age; only one of these children had a mild diplegic cerebral palsy.

Eleven infants had scores between 60 and 41: none of them was able to walk independently at 2 years; 9 of the 11 were able to sit. All 11 developed cerebral palsy: 4 had a quadriplegia and 7 had a diplegia.

Six infants had scores ≤ 40: none of them was able to sit independently at 2 years and all had quadriplegia.

Table **2** Relationship between axial tone, reflex responses and outcome

		Neurological examination at 6–9 months			
		Axial tone	***Arm protection***	***Forward parachute***	***Vertical suspension***
Outcome at 2 years	Able to walk	○○○○	○○○○	○●○○	○○○○
		○○○	○○○	○○○	○○○
	sits unable to walk	▼▼▼▼▼▼▼▼▼	○□●●○	□●●●●	□●□□●
			○□□□○	●●●●	●□□□
	Unable to walk	▼EEE	●●●●	●●●●	●●●●
		EEEE	●●●●	●●●●	●●●●

The table shows the relationship between gross motor function at 2 years and axial tone and reflex items at 6–9 months. ○ normal; ▼ decreased; □ partial; ● abnormal/absent; E extensor

Discussion

In this study we have identified different patterns of neurological abnormalities in preterm infants with cystic PVL and we have established that a structured and scorable neurological examination performed at 6–9 months of age can provide prognostic information on motor ability at 2 years.

We have previously reported on the reliability of the Hammersmith Infant Neurological optimality score in preterm infants at 9 and 18 months in predicting independent walking at 2 years [8]. In that study, however, only 2 infants with cystic PVL were included.

In the present study we applied the same scoring system to a cohort of 24 infants with cystic PVL detected in the neonatal period that were examined between 6 and 9 months corrected age. The magnitude of the scores was related to the severity of motor sequelae at 2 years. Scores below 40 were always associated with the inability to sit independently at 2 years while scores between 41 and 60 were associated with independent sitting but not with walking, except in two cases where sitting was not achieved. Scores above 60 were always associated with the ability to walk independently at 2 years. This data suggests that the optimality score obtained as early as 6 months corrected age can be used to predict the severity of motor impairment in this clinical grouping. These data confirm the prognostic value of the scores we have previously found for sitting and independent ambulation in preterm and full-term infants [8,10].

In addition to scoring the examination we wished to identify clinical patterns of neurological abnormality which relate to the severity of outcome. In the last few years there has been increasing evidence that evaluating combinations of items assessing specific aspects of tone may provide important information on abnormal distribution of tone [5]. In full term infants with neonatal encephalopathy, the persistence of increased neck and trunk extensor tone in the first year, assessed by comparing the items evaluating ventral suspension (extensor tone) and pulling to sit (flexor tone) was generally found in infants with the most severe motor outcome, unable to sit unsupported [5]. In the present study on infants mostly born preterm with cystic PVL we also found that between 6 and 9 months corrected age a similar abnormal distribution of tone, with increased neck and trunk extensor tone, and a posture of flexed arms and extended legs, was always associated with severe cerebral palsy and the inability to sit unsupported at 2 years. In contrast infants with axial hypotonia, with no or minimal difference between extensor and flexor tone, and with extended legs but not with flexed arms, also developed cerebral palsy but were able to sit independently.

We also looked at other individual items, such as some reflexes and reactions that in the past have been found to be predictive of age of walking [13–15]. Arm protection, a forward parachute reaction and kicking in vertical suspension were generally normal in the infants who achieved independent ambulation and abnormal in the infants who developed cerebral palsy and did not achieve independent sitting at 2 years but the results were more variable in the group of infants who were able to sit but not to walk. This variability may be partly explained by the fact that 65% of our infants had examinations performed between 6 and 7 months. Previous studies have reported that a parachute reaction is present in less than 10% of preterm infants at 6 months corrected age [15]. Although we cannot exclude that a proportion of the infants we examined at 6 months may have developed a parachute reaction by 9 months (data not available), 6 of the 7 children who achieved independent ambulation were assessed between 6 and 7 months and all had a parachute reaction.

We also examined the association between severity of outcome and site of the lesion.

In agreement with previous studies [19] reporting the association between extensive lesions posterior to the trigone and cerebral palsy we also found that, with 1 exception, all infants with cerebral palsy had cystic lesions in these areas. This however did not provide further information on the severity of motor impairment as lesions posterior to the trigone were found both in children who achieved and did not achieve independent sitting at 2 years. More extensive lesions involving anterior and posterior areas to the trigone were more often associated with the most severe motor outcome but this was not always the case.

In conclusion our results suggest that although it is well known that early prediction of cerebral palsy can be obtained by neonatal ultrasound and MRI scans [3,4,18,21,23], a clinical neurolog-

ical examination performed between 6 and 9 months corrected age is effective in predicting the severity of motor impairment in infants with PVL, not only by using the optimality scoring system but also by simple examination of the chart. Importantly, a normal examination at 6 to 9 months is associated with the ability to walk independently at 2 years. Bedside examination of differences in tone and posture appear to be the items that most reliably identify infants at risk of developing the most severe motor sequelae. Establishing the reliability of this clinical data is particularly important where imaging data is incomplete or not available. Further studies using longitudinal assessments at 6, 9 and 12 months will help to establish better the evolution of abnormal neurological signs and their prognostic value for gross motor skills at two years and also later in life; correlation of the neurological signs with lesion distribution as seen on MRI may help to understand better the relation between outcome and the extent and location of lesions.

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