0031-3998/97/4205-0665$03.00/0
PEDIATRIC RESEARCH

Vol. 42, No. 5, 1997
Printed in U.S.A.

Diagnostic and Predictive Value of Auditory Evoked Responses in Preterm Infants: I. Patient Characteristics and Long-Term Neurodevelopmental Outcome

JACO W. PASMAN, JAN J. ROTTEVEEL, BEN MAASSEN, RUURD DE GRAAF, AND YVONNE VISCO

Department of Clinical Neurophysiology [J.W.P., Y.V.], Interdisciplinary Child Neurology Center [J.J.R., B.M.], Institute of Medical Psychology [B.M.], Department of Medical Statistics [R.d.G], University Hospital, Nijmegen, The Netherlands

ABSTRACT

The diagnostic and predictive value of brainstem, middle latency, and cortical auditory evoked responses, obtained in the neonatal period, in 81 preterm infants was assessed in relation to neurodevelopmental outcome. Eighteen healthy term infants served as a control group. In this report the patient characteristics and neurodevelopmental outcome are presented. The preterm infants were neonatally classified according to risk category and gestational age. At 5 y of age the neurodevelopmental outcome was assessed based on neurologic and neuropsychologic evaluations. The neuropsychologic test results showed the highest IQ scores in term infants, intermediate IQ scores in low risk preterm infants, and lowest IQ scores in high risk preterm infants. The intermediate IQ scores in the low risk preterm group were due to significantly lower test scores in a small subgroup of low risk preterm infants. In a *post hoc* analysis 12 low risk preterm infants with an unfavorable outcome could be identified. The neuropsychologic test results of the remaining low risk infants showed no clear differences compared with the term infants. The results suggest that the unfavorable outcome of the low risk preterm group as a whole is due to moderate to severe impairment of the few, rather than slight impairment of the majority. (***Pediatr Res* 42: 665–669, 1997**)

Abbreviations

ADIT, auditory discrimination test
BMC-AER, brainstem, middle latency, and cortical auditory evoked response
BWVK, Bourdon-Wiersma-Vos concentration test for infants
GA, gestational age
GAG, gestational age group
LDT, Leiden diagnostic test
NNI, neonatal neurologic inventory
SES, socioeconomic status
VMI, visual-motor integration test
WISC-r, Revised Wechsler Intelligence Scale for Children
TIQ, total intelligence quotient
VIQ, verbal intelligence quotient

Although the survival rate of preterm infants has gradually improved over the past 20 years, the rate of preterm infants with neurodevelopmental disabilities has remained stable. Consequently, an increasing number of surviving preterm infants will show major disabilities such as cerebral palsy, mental retardation, epilepsy, and visual and hearing impairments in early life. The relatively high short-term and long-term morbidity in preterm infants has encouraged many authors to focus on the determination of neonatal risk factors to improve the prediction of neurodevelopmental outcome (1–3). Several neonatal risk factors and risk scores have been put forward as predictors of neurodevelopmental outcome in preterm infants and/or infants with low birth weight (2, 4). However, these neonatal risk factors and risk scores are of limited clinical value, because a considerable number of preterm infants, predicted to be at low risk, develop neurodevelopmental impairments during infancy or childhood. Neurophysiologic methods such as EEG and evoked responses are useful noninvasive techniques for evaluating brain function at the bedside in newborn infants (5). Furthermore, some authors have stated that early physiologic indices can be used to predict long-term developmental trends (6, 7).

In this prospective study the diagnostic and predictive value of BMC-AERs, obtained in preterm infants in the neonatal period, is assessed in relation to the long-term neurodevelop-

Received July 12, 1996; accepted June 3, 1997.
Correspondence: Jaco W. Pasman, M.D., Ph.D., Department of Clinical Neurophysiology, Institute of Neurology, University Hospital, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
Supported by Grant 28-1940 from "Het Praeventiefonds," The Hague, the Netherlands.

mental outcome. In this report we present the patient characteristics and long-term neurodevelopmental outcome of the preterm infants involved in the study. In a companion study (24), we will report on the diagnostic and predictive value of BMC-AERs in relation to the long-term neurodevelopmental outcome in the same cohort of preterm infants.

METHODS

Patients. Eighty-one randomly selected preterm infants (GA 25–34 wk) were included in this prospective study. This group consisted of inborn and out born infants who were admitted to the Neonatal Intensive Care Unit of the University Hospital Nijmegen between 1983 and 1985. Infants with dysgenetic brain lesions, major congenital anomalies, or well defined clinical syndromes were excluded from the study. A group of 25 healthy, term infants (GA 38–42 wk) served as a control group.

In the neonatal period the infants were classified as high risk or low risk according to the semiquantitative NNI, which was performed in the first 2 wk after birth. The NNI is based on four items: *1*) clinical neurologic examination, *2*) echoencephalography, *3*) arterial or capillary blood pH, and *4*) Apgar score. The neurologic examination was performed according to Dubowitz *et al.* (8). Along with the items of the Dubowitz score the examination contained a qualitative analysis of spontaneous and evoked motility. A similar approach has recently been described by Albers and Jorch (9). Based on the clinical neurologic examination, infants with neonatal seizures, cranial nerve palsies, asymmetric neurologic syndromes, or echoencephalographically determined brain lesions were classified as high risk. The neurologic and echoencephalographic examinations were performed at least once biweekly until discharge. In case of hemorrhage the echoencephalographic studies were classified according to Papile *et al.* (10). Periventricular leukomalacia was assessed as present or absent. The NNI assessment was also based on blood pH and Apgar score. In low risk infants the blood pH had to be above 7.10 (arterial) or 7.00 (capillary), and the Apgar score had to be above 7 at 5 min. The low risk preterm infants were divided into two GAGs: the early low risk preterm group (25–30 wk GA) and the late low risk preterm group (31–34 wk GA). Based on the NNI, 65 of the 81 preterm infants were classified as low risk and 16 as high risk (*i.e.* having one or more of the four NNI high risk criteria). Five of the 65 low risk infants and seven of the 16 high risk infants died in the neonatal period. Forty-four of the surviving low risk infants (73%), 18 of the 25 term infants (72%), and all of the nine surviving high risk infants (100%) had a complete follow-up. The other infants were not available to follow-up because of migration or withdrawal by the parents. In Table 1 GA, birth weight, and head circumference at birth of the preterm subgroups are given.

Neurologic and neuropsychologic follow-up. At the age of 5–7 y, a follow-up investigation was performed consisting of a neurophysiologic, neurologic, and neuropsychologic evaluation. The clinical neurologic examination was carried out by an experienced child neurologist using standard pediatric neurologic examination methods. The neurologic abnormalities were classified, using the WHO classification of impairments, disabilities, and handicaps (11). Neurologic abnormalities were classified as minor if they did not result in disability and/or handicap, and they were classified as major if they did. Based on the neurologic examination, the infants were divided into two groups: *1*) the neurologically normal group, consisting of infants with no or minor neurologic abnormalities, and *2*) the neurologically abnormal group, consisting of infants with major neurologic abnormalities.

The parents received two questionnaires, one to be filled out by them, the other to be filled out by the child's teacher. These questionnaires were used to signal developmental and/or educational problems and to establish SES.

The neuropsychologic diagnostic work-up consisted of standardized tests: VMI, LDT or WISC-r, BWVK, and ADIT (12–16). Based on the neuropsychologic test results the infants were classified as poor performers or normal performers.

Based on the NNI and the neurologic evaluation at 5–7 y of age four preterm subgroups were determined: *1*) low risk preterm infants without major neurologic abnormalities at age 5–7 y, *2*) low risk infants with major neurologic abnormalities,

Table 1. *Patient characteristics*

	n		Age at birth (GA) mean ± SD (wk)		Birth weight mean ± SD (g)		Head circumference mean ± SD (cm)	
Infant	Neurol.*	Psychol.	Neurol.	Psychol.	Neurol.	Psychol.	Neurol.	Psychol.
Early preterm	28		29.1 ± 1.5		1113 ± 254		26.2 ± 2.2	
Low risk	21		28.9 ± 1.5		1071 ± 269		26.0 ± 2.4	
Normal	15	16	28.8 ± 1.6	28.9 ± 1.5	1025 ± 222	1059 ± 236	25.3 ± 1.8	25.7 ± 2.4
Abnormal	6	5	29.7 ± 1.4	29.2 ± 1.3	1185 ± 360	1110 ± 388	27.7 ± 3.2	26.8 ± 3.4
High risk	7		29.5 ± 1.2		1240 ± 159		26.9 ± 1.1	
Normal	1	2	27.3	28.1 ± 1.2	1230	1375 ± 205	27	28.0 ± 1.4
Abnormal	6	5	29.9 ± 0.8	30.1 ± 0.7	1242 ± 174	1186 ± 120	26.9 ± 1.3	26.4 ± 0.8
Late preterm	25		32.5 ± 1.0		1570 ± 359		29.5 ± 2.6	
Low risk	23		32.6 ± 1.0		1568 ± 351		29.6 ± 2.7	
Normal	21	18	32.6 ± 1.0	32.5 ± 1.0	1579 ± 343	1567 ± 342	29.7 ± 2.8	29.9 ± 2.9
Abnormal	2	5	32.6 ± 1.6	32.8 ± 1.2	1458 ± 576	1573 ± 425	28.4 ± 1.6	28.6 ± 1.1
High risk	2		32.0 ± 1.4		1585 ± 615		28.5 ± 2.1	
Normal	1	0	33	—	2020	—	30	—
Abnormal	1	2	31	32.0 ± 1.4	1150	1585 ± 615	27	28.5 ± 2.1

* Neurol., neurologic outcome at 5–7 y of age; Psychol., neuropsychologic outcome at 5–7 y of age.

3) high risk infants without major neurologic abnormalities, and *4*) high risk infants with major neurologic abnormalities. Based on the NNI and the neuropsychologic evaluation at 5–7 y of age the preterm infants were divided in four groups in an analogous way.

Statistics. The neuropsychologic tests (VMI, ADIT, BWVK, LDT) are standardized, and information on reliability and validity is available (12–16). For the VMI and LDT age norms are available, so performances on these tests could be transformed to standard scores. Because the standard scores of the BWVK and ADIT are expressed in steps of 1 SD, we decided to use more refined raw scores instead; this procedure is justified if age-matched groups are compared.

Based on the neuropsychologic test results, children who obtained a score in the lowest 10% range on the VMI (*i.e.* VMI < 7) and/or the intelligence test (*i.e.* TIQ < 80) were classified as poor performers. Also, children with a moderately poor VMI score of 7 combined with a below average score (*i.e.* TIQ < 100) on the intelligence test, were identified as poor performers. The significance of the difference between the poor performers and the remaining preterm born children was tested using a randomization test (17).

To test the significance of the differences in test scores between the term group and preterm groups, three separate analyses of variance were conducted. In the first analysis, the term group was compared with the early low risk and late low risk preterm groups. In the second analysis, the term group was compared with the early and late low risk preterm group with a normal outcome. In the third analysis, the term group was compared with the low risk preterm group with an unfavorable neurodevelopmental outcome, *i.e.* the low risk preterm infants with an abnormal neurologic and/or neuropsychologic development at 5 y of age. In the first two analyses of variance the factors in the analyses were: GAG, *i.e.* early preterm, late preterm, and term group, gender, and SES; in the third analysis the factors were: GAG, *i.e.* preterm (with unfavorable outcome) and term, gender, and SES. The statistical analyses were conducted with SPSS for Windows 6.0.

RESULTS

The distributions of neurologic and neuropsychologic abnormalities at age 5–7 y for the early/late and low risk/high risk preterm subgroups are given in Table 2. Eight of the 44 surviving low risk preterm infants (18%), seven of the nine surviving high risk infants (78%), and none of the term infants showed major neurologic abnormalities. The neurologic deficits in the preterm group consisted of mental retardation, epilepsy, infantile encephalopathy with diplegia, hemiplegia, quadriplegia or extrapyramidal movement disorders, and visual, auditory, or sensory disturbances (Table 3).

The VMI and TIQ criteria given in the "Methods" section were applied to identify neuropsychologic poor performers. According to these criteria 10 low risk preterm children were identified as neuropsychologically poor performers, nine exclusively based on a poor VMI score and one based on a moderately poor VMI combined with a below average TIQ. To validate the classification of these neuropsychologically poor performers, a randomization test was used (17). As a group, the 10 neuropsychologically poor performers had a composite *z*-score based on VMI, BWVK, and LDT, which was significantly different from the composite *z*-score of the remaining low risk preterm children ($p < 0.001$). A considerable overlap between neuropsychologically poor performers and infants with neurologic abnormalities at 5 y was found: six of the 10 neuropsychologically poor performers were also classified as neurologically abnormal, four born between 25 and 30 wk GA and two born between 31 and 34 wk GA. Two infants with neurologic abnormalities had normal neuropsychologic outcome. Thus, a total number of 12 low risk preterm infants emerge with an unfavorable outcome at age 5 y. The neuropsychologic test results are summarized in Table 4.

No differences for SES between groups ($F(2;55) = 0.34$, $p > 0.10$) were found. The results showed a trend for the IQ scores of the LDT (LDT-TIQ, LDT-PIQ, and LDT-VIQ) to be highest for the term group, intermediate for the low risk preterm groups, and lowest for the high risk preterm group. In the first analysis, the term group was compared with the early low risk and late low risk preterm groups. Significant differences were found for LDT-PIQ ($F(2;54) = 3.45$, $p < 0.05$), which was primarily due to the lower test scores in the early low risk preterm group. Furthermore, girls in the late low risk preterm group had higher VIQ scores than the girls in the term group, resulting in a similar TIQ score. For the VMI there was a trend toward decreasing scores with decreasing GA. On the ADIT, early low risk preterm infants had lower scores than late low risk preterm infants. Percentages of infants passing the BWVK dropped from 83% for the early preterm girls to 71% for the late preterm boys and 44% for the early preterm boys ($F(2;54) = 3.11$, $p = 0.05$). Girls generally performed better than boys. The differences with respect to the factor gender were significant for LDT-TIQ [$F(1;54) = 4.80$, $p < 0.05$], LDT-PIQ [$F(1;54) = 7.70$, $p < 0.01$], VMI [$F(1;54) = 9.84$, $p < 0.01$] and BWVK [$F(1;54) = 6.28$, $p < 0.05$].

Table 2. *Frequency distributions of long-term neurologic and neuropsychologic outcome for different preterm subgroups*

	Neurologic outcome			Neuropsychologic outcome		
Infant	Normal	Abnormal	Total	Normal	Abnormal	Total
Low risk preterm (25–30 wk GA)	15 (71%)	6 (29%)	21 (100%)	16 (76%)	5 (24%)	21 (100%)
Low risk preterm (31–34 wk GA)	21 (91%)	2 (9%)	23 (100%)	18 (78%)	5 (33%)	23 (100%)
High risk preterm (25–30 wk GA)	1 (14%)	6 (86%)	7 (100%)	2 (29%)	5 (71%)	7 (100%)
High risk preterm (31–34 wk GA)	1 (50%)	1 (50%)	2 (100%)	0 (0%)	2 (100%)	2 (100%)
Total preterm	38 (72%)	15 (28%)	53 (100%)	36 (68%)	17 (32%)	53 (100%)

Table 3. *Neurologic deficits in 15 preterm infants at age 5–7 y*

Infant	Deficit
Low risk	
25–30 wk CA*	1. Mental retardation, epilepsy, hemiplegia, vision loss
	2. Epilepsy, hemiplegia
	3. Mental retardation, epilepsy
	4. Hemiplegia, ataxic gait
	5. Mental retardation, quadriplegia, epilepsy
	6. Quadriplegia
31–34 wk CA	1. Mental retardation, dyspraxia
	2. Quadriplegia
High risk	
25–30 wk CA	1. Diplegia, vision loss
	2. Mental retardation, diplegia, attention deficit disorder
	3. Attention deficit disorder, diplegia, hearing loss
	4. Mental retardation, diplegia, hydrocephalus (VP-drain),† retinopathy
	5. Mental retardation, quadriplegia, epilepsy
	6. Mental retardation, quadriplegia, vision loss
31–34 wk CA	1. Mental retardation, quadriplegia, hydrocephalus (VP-drain), epilepsy

* CA, conceptional age.
† VP, ventriculoperitoneal.

In the second analysis the neuropsychologic test results of the term group were compared with the results of the early and late low risk preterm groups with a normal neurodevelopmental outcome at 5 y of age. In this analysis the factor gender reached significance for VMI [$F(1;44) = 7.81, p < 0.01$]. Girls performed better than boys, GAG was a significant factor for the ADIT [$F(2;44) = 3.67, p < 0.05$]. Early low risk preterm infants (25–30 wk GA) scored lower on the ADIT than late low risk preterm (31–34 wk GA) and term infants.

In the third analysis the term infants were compared with the low risk preterm infants with an unfavorable outcome. For the neuropsychologic test results, larger differences were found between term and low risk preterm infants with an unfavorable outcome than between term infants and late and early low risk preterm infants with a normal outcome. The difference between term infants and low risk preterm infants with unfavorable outcome was significant for LDT-TIQ [$F(1;24) = 5.49, p < 0.05$], LDT-PIQ [$F(1;24) = 9.27, p < 0.01$], VMI [$F(1;24) = 26.0, p < 0.001$], and BWVK [$F(1;24) = 5.71, p < 0.05$]. The term infants clearly performed better than the low risk preterm infants with an unfavorable outcome. Finally, in the high risk groups there were significantly more poor performers than in the low risk preterm groups (χ^2 test: $df = 1, p < 0.001$).

DISCUSSION

In this study, the incidence of major neurologic abnormalities established by clinical examination at age 5–7 y (*i.e.* abnormalities leading to disability and/or handicap), was higher in the high risk preterm group (78%) than in the low risk preterm group (18%). It has to be emphasized that six of the eight low risk infants and six of the seven high risk infants with major neurologic abnormalities were born between 25 and 30 wk GA. The percentage neurologic dysfunction is of the same magnitude as reported by other authors (18, 19).

The neuropsychologic test results showed the highest IQ scores in term infants, intermediate IQ scores in low risk preterm infants, and lowest IQ scores in high risk preterm infants. With respect to the neuropsychologic test results, the differences between term and low risk preterm infants can be the result of a few low risk preterm infants with a moderate to severe disability (low incidence-high morbidity) or by a majority of the low risk preterm infants with only slight impairment (high incidence-low morbidity). In a *post hoc* analysis of both the term and low risk preterm groups, 12 low risk infants with an unfavorable outcome at 5 y of age could be identified based on the neurologic examination and neuropsychologic tests, compared with none of the term infants. Six of these eight low risk preterm infants were not only neuropsychologically poor performers but also belonged to the low risk preterm infants with major neurologic abnormalities. A pronounced (overall) difference was found between the term group and these low risk preterm infants with an unfavorable outcome. These differences were significant for LDT-TIQ, LDT-PIQ, VMI, and BWVK. In contrast, in the comparison of the term group with the remaining infants of the early and late low risk preterm groups no significant differences were found due to GA. In other words, the majority of the low risk preterm infants showed no differences if compared with the term group; the difference between term and preterm infants—as a group—is caused by a minority of low risk infants showing moderate to severe neurologic and/or neuropsychologic abnormalities. Our findings are compatible with the results presented by some other authors (20, 21). In other reports, however, more evidence was found for the condition referred to as handicaps of "low severity-high incidence" or as "hidden handicap" (22, 23).

The classification of the preterm groups in normal performers and poor performers is used in a separate paper in which we

Table 4. *Test scores of 12 preterm infants with an unfavorable outcome at age 5 y compared with the mean test scores of the term infants, early and late preterm infants with a normal outcome at 5 y of age*

Group	GA	*n*	Neurologic ranking	VMI	VIQ	PIQ	TIQ	BWVK*	ADIT
Term	38–42	18	1–2	10.4	113	111	114	100%	28.1
Late low risk preterm with a normal outcome	31–34	18	1–2	9.6	117	108	116.3	83%	28.8
Early low risk preterm with a normal outcome	25–30	14	1–2	10.4	108	107	108.9	86%	27.4
Low risk preterm with an unfavourable outcome	27–33	12	1–3	6.1	99.2	94	96.4	50%	28
High risk preterm	25–34	9	1–3	8.6	79	81	78	33%	—†

* BWVK, percentage of infants passing the test.
† —, not tested.

report on the diagnostic and predictive value of auditory evoked responses in the same group of preterm infants.

Acknowledgments. The authors thank the infants and their parents participating in this study. We thank Bill Sloman for helping with the English version of this manuscript.

REFERENCES

1. Vohr BR, Garcia-Coll C, Oh W 1989 Language and neurodevelopmental outcome of low-birthweight infants at three years. Dev Med Child Neurol 31:582–590
2. Scheiner AP, Sexton ME 1991 Prediction of developmental outcome using a perinatal risk inventory. Pediatrics 88:1135–1143
3. Abel Smith AE, Knight-Jones EB 1990 The abilities of very low-birthweight children and their classroom controls. Dev Med Child Neurol 32:590–601
4. Brazy JE, Eckerman CO, Oehler JM, Goldstein RI, O'Rand AM 1991 Nursery neurobiologic risk score: important factors in predicting outcome in very low birthweight infants. J Pediatr 118:783–792
5. Watanabe K 1992 The neonatal electroencephalogram and sleep cycle patterns. In: Eyre JA (ed) The Neurophysiological Examination of the Newborn Infant. Mac Keith Press, London, pp 11–47
6. Karmel BZ, Gardner JM, Zappulla RA, Magnano CL, Brown EG 1988 Brain-stem auditory evoked responses as indicators of early brain insult. Electroencephalogr Clin Neurophysiol 71:429–442
7. Molfese DL 1989 The use of auditory evoked responses recorded from newborn infants to predict later language skills. Birth Defects 25:47–62
8. Dubowitz LM, Dubowitz V, Palmer P, Verghote MA 1980 New approach to the neurological assessment of the preterm and full-term infant. Brain Dev 2:3–1
9. Albers S, Jorch G 1994 Prognostic significance of spontaneous motility in very immature preterm infants under intensive care treatment. Biol Neonate 66:182–187
10. Papile L, Burstein J, Burstein R, Koffler H 1978 Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 92:529–534
11. World Health Organization 1980 International Classification of Impairments, Disabilities and Handicaps. World Health Organization, Geneva, pp 1–205
12. Schroots JJF, Alphen de Veer RJ van. 1976 Leidse Diagnostische Test. Swets & Zeitlinger BV, Lisse, the Netherlands, pp 16–141
13. Haassen PP van, Bruyn EEJ de, Pijll YJ et al 1974 Wechsler Intelligence Scale for Children-Revised: Scoring en normen. Swets & Zeitlinger BV, Lisse, the Netherlands, pp 1–167
14. Vos P 1988 Handleiding Bourdon-Vos Test. University of Nijmegen, Nijmegen, the Netherlands, pp 16–43
15. Crul Th AM, Peters HFM 1976 Auditieve Discriminatie Test. Swets & Zeitlinger B.V., Lisse, The Netherlands, pp 21–56
16. Beery KE 1989 The Developmental Test for Visual-Motor Integration. Modern Curriculum Press, Cleveland, pp 19–95
17. Edgington ES 1987 Randomization Tests, 2nd Ed. Marcel Dekker, New York, pp 179–196
18. Stewart AL, deL Costello AM, Hamilton PA, Baudin J, Townsend J, Bradford BC, Reynolds EOR 1989 Relationship between neurodevelopmental status of very preterm infants at one and four years. Dev Med Child Neurol 31:756–765
19. Kitchen WH, Ryan MM, Rickards A, McDougall AB, Billson FA, Keir EH, Naylor FD 1980 A longitudinal study of very low-birthweight infants. IV. An overview of performance at eight years of age. Dev Med Child Neurol 22:172–188
20. Smedler AC, Faxelius G, Bremme K, Lagerström M 1992 Psychological development in children born with very low birth weight after severe intrauterine growth retardation: a 10-year follow-up study. Acta Paediatr 81:197–203
21. Mutch L, Leyland A, McGee A 1993 Patterns of neuropsychological function in a low-birthweight population. Dev Med Child Neurol 35:943–956
22. Herrgard E, Luoma L, Tuppurainen K, Karjalainen S, Martikainen A 1993 Neurodevelopmental profile at five years of children born at ≤32 weeks gestation. Dev Med Child Neurol 35:1083–1096
23. Zubrick SR, Macartney H, Stanley FJ 1988 Hidden handicap in school-age children who received neonatal intensive care. Dev Med Child Neurol 30:145–152
24. Pasman JW, Rotteveel JJ, Maassen B, de Graaf R, Visco Y 1997 Diagnostic and predictive value of auditory evoked responses in preterm infants. II. Auditory evoked responses. Pediatr Res 42:670–677