


Developmental profile at initial presentation in children with infantile spasms

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ABBREVIATION

HIE Hypoxic ischaemic encephalopathy

AIM To describe the baseline developmental profile and influence of clinical and demographic factors on the developmental skills of infants diagnosed with infantile spasms.

METHOD Ninety-five infants (55 males, 40 females) newly diagnosed with infantile spasms were recruited for a cross-sectional, longitudinal study. All infants underwent Bayley Scales of Infant and Toddler Development assessments in the cognitive, receptive communication, expressive communication, and fine and gross motor developmental domains; they also underwent visual, auditory, and social behaviour assessments. Infants were categorized as 'early' (<6mo) or 'late' (≥6mo) presenters; if presented within 28 days, this was considered as 'early presentation', whereas a delay greater than 28 days was considered as a 'delay in presentation'. Antenatal, perinatal, and postnatal risk factors were identified.

RESULTS Over 90% of infants showed impairment in all domains, with the majority having severe delay; 99% showed cognitive impairment. Delayed presentation was significantly associated with receptive communication delay (odds ratio [OR]=5.35; 95% confidence interval [CI]=1.05–27.32). Onset at 6 months or less influenced auditory (OR=2.8; 95% CI=1.16–6.8) and visual (OR=3.03; 95% CI=1.22–7.57) behaviours. Neonatal infections impacted both receptive (OR=1.12; 95% CI=1.04–1.2) and expressive communication (OR=1.08; 95% CI=1.02–1.14) delay. Neonatal seizures significantly influenced visual, auditory, and social impairments. Expressive communication and gross motor development shared common perinatal risk factors.

INTERPRETATION Adverse developmental status at presentation, associated with delayed presentation and neonatal risk factors should alert clinicians to the surveillance of at-risk infants and seek out timely interventions.

Developmental manifestation is a frequent but not essential clinical feature in infantile spasms.^{1–3} Epileptic spasms and hypsarrhythmia on the electroencephalogram (EEG) are the most consistent features of infantile spasms. Infantile spasms are the most common epileptic encephalopathy presenting during early infancy, coinciding with the most rapid phase of early neural circuit formation in the brain.^{4–6}

Developmental impairment or regression may precede infantile spasms, accompany them, or become a long-term manifestation. A systematic review by Widjaja et al.⁷ reported a significant impact of infantile spasms on long-term neurodevelopmental outcomes, with cognitive impairment reported to be as high as 80% to 90% in several other longitudinal studies.^{7–10} Intellectual disabilities and autism spectrum disorder are reported as long-term adversities of infantile spasms.^{2,4,11} Hypotonia and abnormal visual and auditory behaviours, including abnormal

electrophysiology, have been described at presentation.^{10–13} The presence of visual and auditory abnormalities even before the onset of clinically apparent spasms may contribute to poor cognitive skills even during the presentation of infantile spasms.^{5,10–13}

Many factors contribute to the developmental manifestations of infantile spasms. The age at onset of seizures, aetiology, and abnormal electrical activity may influence developmental attainment.^{8–10,14,15} The majority of the literature has discussed the impact of aetiology, delayed presentation, age at onset of seizures, and sex on the long-term developmental outcomes.^{9,11,15–18}

Furthermore, several cohort studies demonstrated deterioration of development despite spasm control, emphasizing the need to understand how spasms are generated as well as the neurodevelopmental decline that accompanies them.^{7,19} Despite this understanding of the importance of development as an outcome parameter, most studies of

infantile spasms concentrate predominantly on how to manage them.^{20,21} Moreover, there is a scarcity of detailed evidence on the developmental profiles of infants with infantile spasms at presentation and the factors that influence developmental delay at such an early developmental stage. Availability of such evidence will encourage clinicians to seek out timely interventions.

This article aims to describe the baseline developmental profiles in the domains of cognitive, language (receptive and expressive), and motor (fine and gross) development, as well as early behavioural patterns in infants with infantile spasms. It also attempts to assess how several demographic and clinical factors may contribute to the developmental profile at presentation.

METHOD

Ninety-five infants with newly diagnosed infantile spasms were recruited for the study. This cross-sectional study was part of a randomized controlled trial conducted to assess the efficacy of two types of hormonal therapies in controlling spasms and manage developmental outcomes in infants with infantile spasms. Details of the setting, study population, sample size, and recruitment process are published elsewhere.²² In summary, eligible infants (whose parents consented to participate in the study) with previously untreated infantile spasms were recruited from the Lady Ridgeway Hospital for Children, Colombo, the premier children's hospital in Sri Lanka. The diagnosis of infantile spasms was confirmed by a paediatric neurologist (JW) by direct observation of the spasms, examination of videos provided by the parents, or using video telemetry. Thereafter, only those infants with hypsarrhythmia on the EEG were included in the study because this is mandatory for the classification of infantile spasms. Infants with spasms but no hypsarrhythmia demonstrate different developmental progression patterns and were likely to bias the developmental attainment results.²³ Children younger than 2 months or older than 3 years 6 months, with a diagnosis of tuberous sclerosis or any contraindications for the use of hormonal therapies, were excluded from the study. Children with tuberous sclerosis were excluded because they have more complex developmental progression and require different treatment regimes.²⁴ Infants whose parents could not manage to monitor the response to therapy, as judged by the recruiting investigator, were also excluded. Previous prescription of anticonvulsants for any other type of seizure was permitted.

Ethical clearance was obtained from the ethics review committee of the Faculty of Medicine, University of Colombo, Sri Lanka. Parents of eligible infants were told about the study in detail and were invited to participate. After attaining written informed consent by the parents, infants were recruited for the study. For this article, only baseline developmental and related demographic and clinical data obtained at initial presentation are considered. This baseline assessment was conducted within 48 hours of confirmation of diagnosis.

What this paper adds

- Ninety per cent of infants showed impaired cognitive, communication, and motor skills at presentation.
- Visual, auditory, and social behaviour impairments were significantly associated with perinatal risks.
- Visual, auditory, and social behaviour impairments were significantly associated with neonatal seizures.

Clinical and imaging data at presentation

On recruitment, infants underwent an evaluation with detailed history and comprehensive examination. The age at onset of infantile spasms was determined to the nearest month and was categorized as 'early' (≤ 6 mo of age) and 'late' (> 6 mo of age) for the purpose of developmental data analysis. The duration from onset to presentation for treatment (lag period) was calculated in days from the onset of spasms to the presentation of the infant to the hospital. If presented within 28 days, this was considered as 'early presentation'; a delay greater than 28 days was considered as 'delayed presentation'.

The majority of infants underwent an array of investigations to arrive at an aetiological diagnosis. All infants had neuroimaging (computed tomography or magnetic resonance imaging). Most of the infants with a negative history/examination and/or neuroimaging underwent relevant genetic and/or biochemical investigations. However, because Sri Lanka is an under-resourced country, these investigations were not completed before the first developmental assessment or commencement of treatment.

The underlying aetiology was categorized according to the presence of an antenatal, perinatal, or neonatal risk factor, as indicated by the history, examination, and investigations including imaging of the infant. All infants were categorized as having 'preterm birth-related complications' (gestational maturity < 36 wks combined with any one of several factors, such as a birthweight < 2500 g, hypoglycaemia, jaundice, or periventricular haemorrhage) or not. Furthermore, irrespective of maturity, infants with sepsis (due to any reason), neonatal seizures, and hypoxic ischaemic encephalopathy (HIE) (based on Apgar scores or other clinical events) were identified. Details about seizure semiology during the infantile spasms and any EEG findings represent inclusion criteria but have not been used for the analysis and discussion in this article.

Developmental assessment at presentation

All infants underwent detailed developmental assessment before treatment was started. The assessment included developmental assessment using the Bayley Scales of Infant and Toddler Development and a clinical assessment of visual, auditory, and social behaviours.²⁵ Formal assessment included cognitive, language (receptive and expressive communication subsets), and motor (fine and gross motor subsets) domains according to the Bayley Scales of Infant and Toddler Development. Raw scores were calculated and converted to scaled scores (range 1–19: cognitive, receptive, and expressive communication, fine and gross motor domains) and composite scores (range 1–166: cognitive,

language, and motor domains). A scaled score of 8 or more was considered as no delay. Scaled scores of 6 and 7 were categorized as mild delay, scaled scores of 4 and 5 as moderate delay, and scaled scores of 1, 2, and 3 as severe delay. Infants with mild, moderate, and severe delay were grouped together to form the 'with-delay' group for the purpose of data analysis. A composite score of 90 or above was considered average or better. Therefore, any infant with a composite score of less than 90 in two or more domains was considered as having 'global developmental delay'.

Furthermore, each infant was assessed for early visual, auditory, and social behaviours. Visual attention was assessed by their response to a bright object, black and white pattern, and human face; the presence of visual tracking was assessed by their response to a moving human figure and a dangling red ball. Auditory attention was assessed by their response to a human voice and the sound of a rattle. Social responsiveness was assessed by an awareness of the surroundings, social smile, and attention to the caregiver. Absence of any single component within any single area of behaviour was considered as impairment in that respective area.

Data analysis

Data were analysed with SPSS version 21 (IBM Corp., Armonk, NY, USA). Descriptive statistics included the mean, SD, and 95% confidence interval (CI) for numerical data, and percentages for categorical data. The associations between potential risk factors and developmental delay were assessed using prevalence odds ratios (ORs) and 5% CIs. Risk factors were not adjusted for confounders and interactions using logistic regression analysis because the sample was smaller in some categories of the variables.

RESULTS

The baseline clinical and developmental characteristics of the 95 infants who were eligible for developmental follow-up are presented here.

Infant demographic and clinical characteristics

Table I shows the demographic and clinical characteristics of the infants at presentation. The majority were male (58%), term-born infants (88%), with an adequate birthweight of 2500g or more (65%). Mean age at onset of seizures was 5.99 months (SD=5.27), ranging from 0.03 months to 34 months. Mean age at presentation to the hospital was 8.75 months (SD=6.37), ranging from 1.46 months to 34.4 months. The average birthweight was 2.61kg (SD=0.52), ranging from 0.74 to 3.75kg.

Of the infants, 24% had experienced neonatal seizures before experiencing infantile spasms.

Development at presentation

Figure 1 illustrates the scaled scores of each developmental domain. More than 90% of the infants recruited showed

Table I: Demographic and clinical characteristics of infants with infantile spasms (*n*=95)

Descriptive characteristics	<i>n</i> (%)	Median (IQR)
Sex		
Male	55 (58)	NA
Female	40 (42)	
Age at onset of seizures		
<6mo	62 (65)	5.0 (4.0)
≥6mo	33 (35)	
Delay in presentation		
<1mo (early)	41 (43)	1.4 (3.5)
≥1mo (late)	54 (57)	
Presence of neonatal/perinatal risk factors		
Yes	24 (26)	NA
No	71 (74)	
Gestational age at birth		
Preterm (<36wks)	11 (12)	NA
Term (≥36wks)	84 (88)	
Birthweight		
<2.5kg	33 (35)	2.6 (0.7)
≥2.5kg	62 (65)	
Preterm birth-related complications		
Yes	8 (8)	NA
No	87 (92)	
Presence of neonatal seizures		
Yes	23 (24)	NA
No	72 (76)	
Presence of neonatal infections		
Yes	11 (12)	NA
No	84 (88)	
Presence of HIE		
Yes	13 (14)	NA
No	82 (86)	
Presence of abnormal imaging		
Yes	22 (23)	NA
No	73 (77)	

IQR, interquartile range; NA, not applicable; HIE, hypoxic ischaemic encephalopathy.

developmental delay in several domains at presentation. The most affected domain was cognitive development (99%); the least affected was receptive communication (91%; Table II). Only one infant had developmental scores within the average scores in all domains at presentation.

Auditory behaviour was affected in 64.2% of infants, while 50.5% showed evidence of lack of social responsiveness at presentation. Infants with impaired visual behaviour showed a 12-fold risk of developing a poor social smile (OR=11.84; 95% CI=4.43–31.64).

Factors associated with developmental delay

The developmental delay for each domain at initial presentation was compared with several epidemiological and clinical features (Table SI, online supporting information).

Delay in receptive communication was significantly associated with delay in treatment for infantile spasms (OR=5.35; 95% CI=1.05–27.32) and neonatal infections (OR=1.12; 95% CI=1.04–1.2). Furthermore, delay in expressive communication was significantly associated with low birthweight (OR=1.1; 95% CI=1.02–1.2), presence of HIE (OR=1.08; 95% CI=1.02–1.15), preterm birth-associated complications (OR=1.07; 95% CI=1.01–1.14), and neonatal infections (OR=1.08; 95% CI=1.02–1.14). A delay

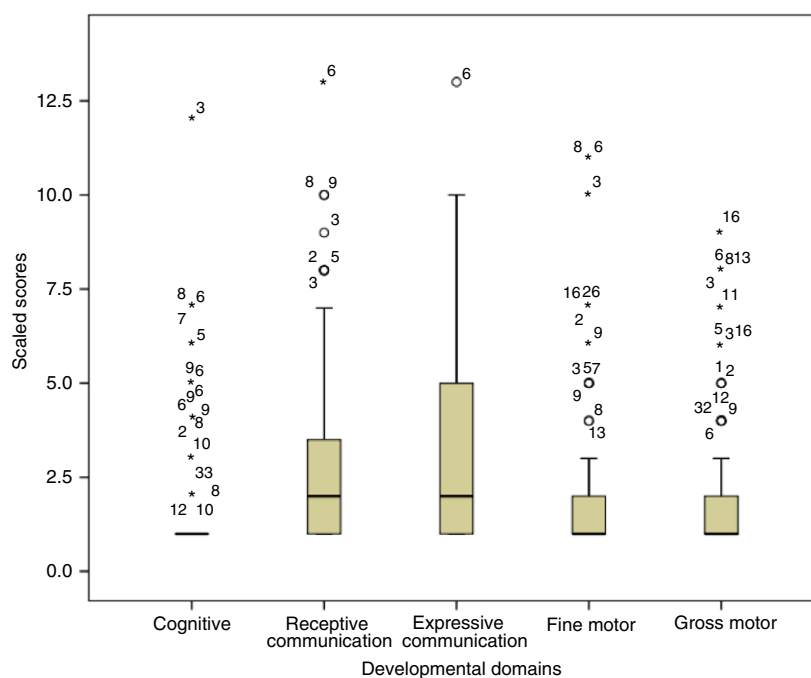


Figure 1: Developmental attainment at initial presentation (based on scaled scores). The boxplot shows the median (bold line), interquartile range (box), outliers as circles (individuals with values between 1.5 and 3 box lengths from the upper or lower edge of the box), and extreme cases as asterisks (cases with values more than 3 box lengths from the upper or lower edge of the box) of individual variables; extreme cases are labelled according to their age at presentation (months) to the hospital. [Colour figure can be viewed at wileyonlinelibrary.com]

Table II: Scaled scores and percentage of infants with delay in each developmental domain and visual, auditory, and social behaviour impairment ($n=95$)

Profile Developmental domain	Scaled scores		<i>n</i> (%)			
	Mean (SD)	Median (IQR)	No delay	Mild delay	Moderate delay	Severe delay
Cognitive	1.9 (1.9)	1.0 (0.0)	1 (1)	5 (5)	10 (11)	79 (83)
Receptive communication	2.7 (2.6)	2.0 (3.0)	9 (9)	4 (4)	11 (12)	71 (75)
Expressive communication	3.0 (2.6)	2.0 (4.0)	6 (6)	11 (12)	15 (16)	63 (66)
Fine motor	2.0 (2.2)	1.0 (1.0)	3 (3)	5 (5)	6 (6)	81 (85)
Gross motor	2.1 (2.0)	1.0 (1.0)	5 (5)	4 (4)	9 (10)	77 (81)
Behaviour			Impairment			
Visual	NA	NA	42 (44)	NA	NA	NA
Auditory	NA	NA	61 (64)	NA	NA	NA
Social	NA	NA	48 (51)	NA	NA	NA

IQR, interquartile range; NA, not applicable.

in gross motor development was significantly associated with HIE (OR=1.07; 95% CI=1.01–1.13), preterm birth-associated complications (OR=1.06; 95% CI=1.01–1.12), and neonatal infections (OR=1.06; 95% CI=1.01–1.12). Cognitive, fine motor, and global delays were not associated with any factor.

The same epidemiological and clinical characteristics were compared with the visual, auditory, and social behaviours (Table III).

Neonatal seizures were significantly associated with impaired visual (OR=9.0; 95% CI=2.74–29.56), auditory (OR=4.52; 95% CI=1.23–16.67), and social (OR=9.43; 95% CI=2.54–34.48) behaviours. Early onset of infantile spasms was associated with impaired visual (OR=3.03; 95%

CI=1.22–7.57) and auditory (OR=2.8; 95% CI=1.16–6.8) behaviours. In contrast, global delay was associated with impaired visual (OR=1.82; 95% CI=1.52–2.19) and social (OR=2.07; 95% CI=1.68–2.55) behaviours.

DISCUSSION

The findings of this study show developmental delay in all three domains as well as impaired sensory and social behaviours in the majority of infants who presented with infantile spasms. Developmental impairment was significantly associated with a delay in presentation for treatment and some of the risk factors, namely a history of HIE, complications of preterm birth, and neonatal infections. Auditory and visual behaviours were impaired in infants with infantile spasms

Table III: Factors associated with sensory and social behaviour impairment at presentation

Factor	Impairment in behaviour, n (%)		
	Visual	Auditory	Social
Sex			
Male (n=55)	24 (45)	38 (69)	25 (46)
Female (n=40)	18 (45)	23 (58)	23 (58)
Age at onset			
≤6mo (n=62)	33 (53) ^a	45 (73) ^a	34 (55)
>6mo (n=33)	9 (27)	16 (49)	14 (42)
Delay in treatment for infantile spasms			
≥28d (n=54)	26 (48)	36 (67)	24 (44)
<28d (n=41)	16 (39)	25 (61)	24 (59)
Birthweight			
<2500g (n=33)	15 (46)	21 (64)	19 (58)
≥2500g (n=62)	27 (44)	40 (65)	29 (47)
Global delay			
Yes (n=93)	42 (45) ^a	60 (65)	48 (52) ^a
No (n=2)	0 (0)	1 (50)	0 (0)
HIE			
Present (n=13)	6 (46)	9 (69)	6 (46)
Absent (n=82)	36 (44)	52 (63.4)	42 (51)
Neonatal seizures			
Present (n=23)	18 (82) ^a	19 (86) ^a	19 (86) ^a
Absent (n=72)	24 (33)	42 (58)	29 (40)
Preterm birth complications			
Present (n=8)	3 (38)	6 (75)	4 (50)
Absent (n=87)	39 (45)	55 (63)	44 (51)
Neonatal infections			
Present (n=11)	5 (46)	7 (64)	5 (46)
Absent (n=84)	37 (44)	54 (64)	43 (51)
Abnormal imaging			
Present (n=22)	11 (50)	14 (64)	11 (50)
Absent (n=73)	31 (43)	47 (64)	37 (51)

^aSignificant associations (95% confidence interval of the prevalence odds ratio does not cross 1). HIE, hypoxic ischaemic encephalopathy.

who had spasm onset at less than 6 months of age. Infants with neonatal seizures showed impairment in all sensory and social behaviours at presentation.

Developmental profiles

The presence of developmental delay in all domains in more than 90% of participants at presentation confirms the severe neurodevelopmental adversities during early infancy.

In contrast to our findings, several previous studies reported a lower frequency (50–70%) of developmental delay at time of first presentation.^{7,8,11} Matsumoto et al.¹¹ assessed the motor and cognitive abilities at initial presentation only using clinical observations, while the methodology used to assess development at baseline is inadequately explained in some studies.^{8,11} Yet, the study by Vendrame et al.⁸ described 57% of infants with developmental delay.⁸ None of these studies conducted detailed developmental assessment in all infants at initial presentation. Widjaja et al.⁷ described this heterogeneity in developmental assessment as a major setback in using neurodevelopmental outcome data to explain any possible discrepancies.⁷ However, it is possible that our group of patients had different and more severe pathologies.

Similar to the findings in the present study, a few studies also described that most adversities assessed at the time of

initial presentation are related to cognitive skills.^{8–11} In a small prospective study conducted in Italy, Guzzetta et al.¹⁰ described in detail the impact of infantile spasms on cognitive impairment at presentation. They showed that early impairments in auditory and visual behaviours significantly impacted cognitive skills at presentation. However, unlike the Italian study, this study did not identify any factor as significantly influencing cognitive skills. This discrepancy in findings may be due to the rigorous, standardized, multi-step assessments used by Guzzetta et al.¹⁰ to evaluate visual and auditory behaviours; in contrast, only clinical observations were used in the present study. The large proportion of infants with impaired visual, auditory, and social behaviours and the similarly large proportion of infants with delay in all developmental skills observed in this study population may reflect a reciprocal influence between behaviours and attainments, although this was not statistically significant. The association between early impaired visual and social behaviours with global developmental delay reflects the significance of these inputs on the attainment of developmental skills.

Factors associated with impaired developmental skills at presentation

Analysis of previously published data mainly discusses the impact of associated factors on the long-term neurodevelopmental outcome in children with infantile spasms.^{7–9,11,15,18} This study tried to associate those previously identified factors with developmental skills at presentation.

Sex

No significant impact of sex on development at presentation was found, although a possible significance of sex on long-term developmental outcome has been discussed previously.^{11,21} However, a 2016 UK and USA update on infantile spasms³ did not identify sex as a significant factor affecting developmental outcome at 4 years; several other publications report sex as a non-significant factor when forecasting developmental outcomes.²⁰

Age at onset of seizures

Younger age at onset of seizures significantly impacted longer-term developmental and seizure outcomes in several studies.^{9,21} This study did not find age at onset of seizures to be significantly associated with developmental delay in the main subsets. However, auditory, visual, and social behaviour impairments were significantly associated with younger age at onset of infantile spasms (6mo). These precursor behaviours are essential for later developmental milestones.^{5,6}

Presence of neonatal seizures

Neonatal seizures were significantly associated with impaired visual, auditory, and social behaviours. The effect of early abnormal electrical discharges on these key developmental skills possibly highlight the significant implications of these chaotic discharges on early neural circuit

formation. Several studies have described the influence of previous seizures on the long-term neurodevelopmental outcome in infantile spasms, but the impact of neonatal seizures is less described.

Age at presentation

Several previous studies described younger age at presentation as a significant risk factor for a poorer long-term developmental outcome; however, in this study age at presentation was not significantly associated with developmental skills at presentation.⁹ Similarly, some of the larger prospective studies looking at long-term developmental outcomes have not reported an association with age at presentation.¹⁶

Treatment lag

In previous studies, delayed diagnosis due to late presentation or misdiagnosis has been considered a significant risk factor for long-term neurodevelopmental delay. O'Callaghan et al.¹⁶ described how an increment in lead time impacted adversely on developmental outcomes at 2 years. The prolonged impact of seizures on developing neural circuits is a possible explanation for this significant association. Our study showed a significant impact of this factor on the development of receptive communication, even at the time of presentation.

Aetiologies

The definitive genetic, metabolic, or radiological diagnoses were not considered separately because of the small sample size and the uncertainty in accuracy due to limited resources in Sri Lanka for technologically superior investigations. The significant association of a perinatal/neonatal risk factors such as HIE, preterm birth-associated complications, sepsis, and neonatal seizures with the impairment of several developmental domains and skills at a very early presentation is noteworthy. A known aetiology that includes hypoxia and infections has been identified as a strong predictor of unfavourable long-term neurodevelopmental outcomes in several studies in the past.^{9,12,14,18}

Furthermore, the strong association between neonatal seizures and impaired sensory and social behaviours also possibly predicts a negative impact on later cognitive skills, as described previously.⁹ Since our study highlights the impact of several risk factors on specific developmental domains and behaviours at an early stage of infantile spasms, it possibly confirms the initiation of a triad of events proposed by Lux and Osborne:¹⁷ the insult, infantile spasms, and neurodevelopment.

CONCLUSIONS

Significant developmental adversities were seen in the majority of infants, even at initial presentation of infantile spasms. The statistically significant association between early infant behaviours and neonatal seizures illustrates the close relationship between seizures and developmental attainment. The significant association between neonatal complications such as HIE, preterm birth, neonatal infections, and neonatal seizures and developmental impairments emphasizes the need for close developmental surveillance of these infants; clinicians should look out for any early and subtle features of infantile spasms.

The results of this study also demonstrate a heterogeneity in the factors contributing to developmental adversities at the time of presentation of infantile spasms. Therefore, longitudinal follow-up and more detailed analysis of developmental signs and symptoms are essential to further understand the pathology of infantile spasms and the associated developmental manifestations.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Factors associated with developmental delay

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