

Aetiological profile of global developmental delay in children under 5 years of age: experience from a tertiary referral centre

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Abstract

Introduction: Global developmental delay (GDD) is a common paediatric condition with an estimated prevalence of 1-3%. Aetiological diagnosis assists in preventive strategies, prognosis, assessing recurrent risk and treatment.

Objectives: To describe the aetiological profile of GDD, to identify preventable causes and to determine the percentage of undetermined aetiology.

Method: A descriptive study was conducted over a period of 5 months in a paediatric neurology clinic at a tertiary referral centre which included children with GDD below the age of 5 years. Interviewer administered standardised questionnaire was used to collect demographic data, while clinical data, examination and investigation results were extracted from the neonatal and neurology clinic records.

Results: A total of 185 patients met the inclusion criteria (female: male ratio 1:1.4). Mean age at recognition of GDD was 15.2 ± 1.99 months. An aetiological diagnosis was determined in 108 (58.4%), which was categorized under hypoxic ischaemic encephalopathy (HIE) (n=51, 27.6%), structural brain abnormalities (n=28, 15.1%), post infectious (n=13, 7.0%), genetic/chromosomal (n=7, 3.8%), embryo-fetopathy (n=5, 2.7%) and hypothyroidism (n=3, 1.6%). Aetiology was undetermined with the available clinical details and investigation results in 62 (33.5%). A possible diagnosis of genetic/chromosomal origin was suspected in 11 (5.9%) and a possible diagnosis of an inborn error of metabolism was suspected in 4 (2.2%) from historical and examination findings.

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Conclusions: In the paediatric neurology clinic at the tertiary referral centre, HIE, structural brain abnormalities, post infectious, genetic/chromosomal, embryo-fetopathy and hypothyroidism were the identified causes of GDD. Aetiology was undetermined with the available clinical details and investigation results in 33.5%.

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(Key words: Global developmental delay, paediatrics, paediatric neurology, aetiological profile, aetiological yield, Sri Lanka)

Introduction

Global developmental delay (GDD) is a relatively common paediatric condition and its prevalence is estimated to be 1-3%¹. GDD is defined as significant delay (2 SD below the age appropriate mean) in 2 or more developmental domains including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living in children younger than 5 years of age². The presence of GDD is thought to predict a future diagnosis of intellectual disability³, which is defined as an intelligence quotient (IQ) of below 70 at the age of 5 years or older⁴. In 2011, the World Health Organisation (WHO) International Classification of Diseases (ICD) Working Group on the Classification of Intellectual Disabilities proposed the term intellectual developmental disorders (IDD) to include a group of developmental conditions characterized by significant impairment of cognitive functions associated with limitation of learning, adaptive behaviour and life skills⁵. IDD comprises both intellectual disability and GDD in the respective age groups and is associated with the highest lifetime health care and economic costs of any disease, nearly equalling the economic impact of stroke, heart disease and cancer combined⁶.

Aetiologies of GDD includes genetic, metabolic, structural abnormalities of the brain, infections, complicated birth history (maternal pre-eclampsia, infectious embryo-fetopathy, prematurity, birth asphyxia, low birth weight, neonatal sepsis, kernicterus), endocrine disorders and exposure to environmental toxins^{3,7-12} to name a few. Arriving at an aetiological diagnosis would assist in predicting the prognosis, assessing the recurrence risk in future pregnancies, provision of refined

treatment options, avoiding unnecessary investigations, surveillance of known complications, parental counselling and overall improvement in the psycho-social outcome of both affected children and their families¹. A Sri Lankan study by Perera H, in 2005 to assess the developmental readiness for school entry at 5 years, detected a delayed cognitive development in 17.8%¹³. This highlights the importance of early detection and intervention, aiming at improving the neuro-developmental outcome. Currently, there is a paucity of published data on prevalence of aetiologies of developmental delay in Sri Lanka.

Objectives

The main objective of the study was to evaluate the aetiological profile of GDD in children under the age of 5 years presenting to a tertiary care referral centre. Further objectives included determining the percentage of children with GDD of ‘undetermined aetiology’ after the clinical evaluation and available investigations and describing GDD in relation to maternal, post-natal and early childhood causative factors.

Method

A descriptive study was conducted at the Paediatric Neurology Clinic at the Sirimavo Bandaranayake Specialised Children’s Hospital, Peradeniya to describe the aetiological profile of GDD in children under five years of age. All children with GDD who were under the age of 5 years at the time of diagnosis and attending the clinic between 1st of March 2019 and 30th of August 2019 were included in the study. The sample included children registered in the clinic from July 2013 to 30th of August 2019. Children who were above the age of 5 years at the time of diagnosis of GDD, children diagnosed with isolated developmental disorders such as Autistic Spectrum Disorders, attention deficit hyperactivity disorder (ADHD), children with isolated speech delay and children with isolated neuromuscular disorders were excluded. All patients attending the paediatric neurology clinic have been evaluated, including developmental assessment by the Consultant Paediatric Neurologist. A diagnosis of GDD was made when a significant delay in 2 or more developmental domains was detected in a child under the age of 5 years.

In this clinic setting, neuroimaging, either computed tomography (CT) or magnetic resonance imaging (MRI) of brain, depending on the clinical indication and availability, is performed as a routine test in children with GDD to support the aetiological diagnosis. Electroencephalography (EEG) is performed in patients with clinical features of epilepsy and epilepsy syndromes as per recommendations of the American Academy of

Neurology³ and also in GDD of undetermined aetiology. Karyotyping and some genetic studies are performed in patients with suspected genetic syndromes. Metabolic screening is offered to those who have compatible history. Patients with unexplained GDD or having CT evidence of congenital infections undergo TORCH screening.

An interviewer administered standardised questionnaire was used to obtain demographic data from the parent/guardian. The demographic data included the age, gender, geographical region (district lived during pregnancy and district lived during the first 2 years of life), parents’ occupation and level of education and maternal habits (alcohol, tobacco and substance abuse). Parents’ occupation was categorized into occupation groups as per guidelines published in the Labour Demand Survey¹⁴. Consanguinity and family history of developmental delay were also obtained during the interview. The rest of the clinical data, examination and investigation results were extracted from the patient’s neonatal records and neurology clinic records. The data obtained from the medical records included, the age of onset of developmental delay, presence of dysmorphic features, antenatal history (TORCHS, maternal pre-eclampsia, antepartum haemorrhage, maternal exposure to drugs, alcohol, smoking), perinatal history (birth asphyxia, Apgar score, prematurity, intrauterine growth retardation, birth trauma), postnatal (kernicterus, seizures, hypoglycaemia, meningitis, sepsis) and results of the investigations performed for diagnosis such as CT/MRI/EEG/ karyotyping/ genetic studies/ metabolic screening and TORCH screening.

The aetiological diagnosis was categorized under the following:

1. Diagnosis confirmed – Embryo-fetopathy, hypoxic ischaemic encephalopathy (HIE), post infectious (encephalitis/ meningitis), genetic or chromosomal defects, hypothyroidism, kernicterus, inborn errors of metabolism (IEM), structural brain abnormalities
2. Possible genetic aetiology
3. Possible metabolic aetiology
4. Undetermined

The diagnosis of HIE was based on the diagnosis given in the neonatal records (supported by Apgar score when available) or based on the clinical history of birth asphyxia and evidence from changes in CT/MRI brain supporting a diagnosis of HIE.

Results

Age at recognition of GDD and socio-demographic profile of the study population

The sample consisted of 185 subjects who met the inclusion and exclusion criteria. The mean age at the time of the study was 73.8 ± 6.1 months (age range 8 months to 15 years). Seventy seven (41.6%) were female while 108 (58.4%) were male, giving a sex ratio of 1:1.4.

Age at recognition of GDD ranged from birth to 56 months, with a mean age of 15.2 ± 1.99 months. Highest frequency of age at recognition of GDD in the study group was below 3 months of age ($n=27$, 14.6%), of which 17 (9.1% of total sample) were noted to have GDD since birth. (Figure 1)

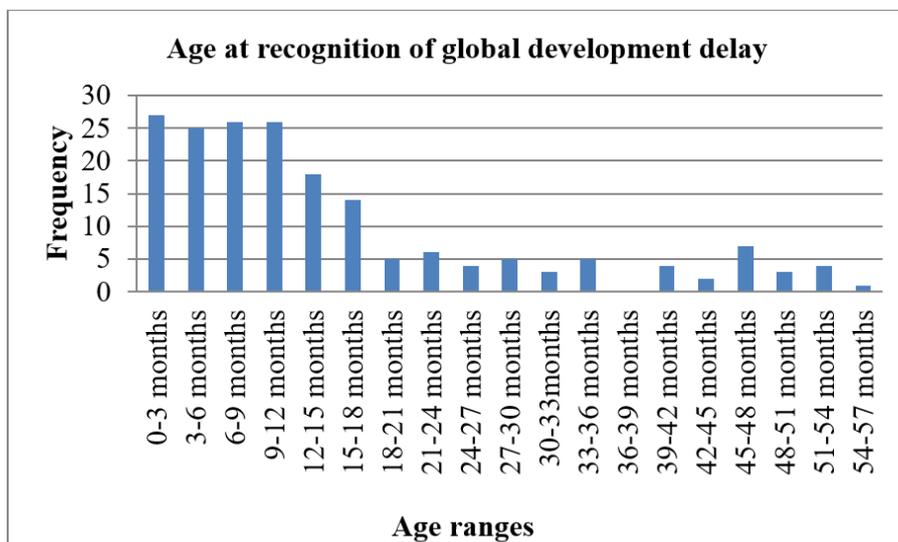


Figure 1: Age at recognition of global developmental delay

Majority (36.8%, $n=68$) of patients had lived in Kandy district during pregnancy. Majority (95.7%) had remained in the same district during the first 2 years after birth, of whom 61% were from the Central Province, 12.4% from Sabaragamuwa Province, 11.4% from Uva Province, 6.4% from North Western Province and 3.7% from North Central Province. The remainder were from

Western (2.1%), Eastern (2.2%) and Southern Provinces (0.5%).

Most mothers had Ordinary Level qualifications (40%, $n=74$), and 8.1% ($n=15$) had completed tertiary level. The most common level of education among fathers was Ordinary Level (38.4%, $n=71$) while 4.3% ($n=8$) had completed tertiary level (Figure 2).

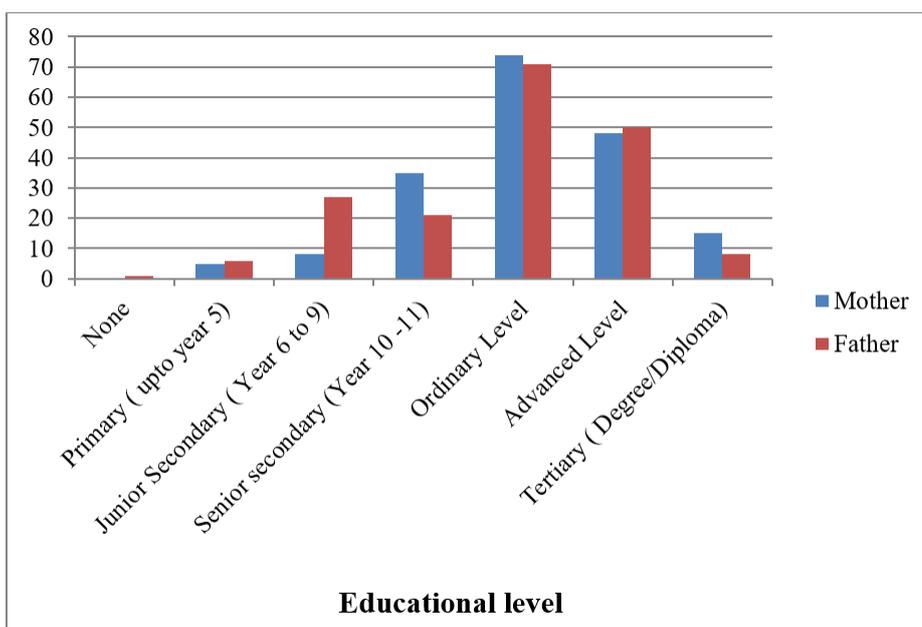


Figure 2: Educational level of parents

Most common occupational category among mothers was Service and Sales worker (87%, n=161), which included the position of housewife (85.4%, n=158), while 9 (4.7%) were employed as professionals. Sixty (32.4%) fathers were employed as Service and Sales workers, while 3 (1.6%) were professionals and 3 (1.6%) were unemployed.

Predisposing factors for GDD

Almost all mothers (n=184, 99.5%) denied using alcohol, tobacco or recreational drugs during pregnancy. Maternal habits were unknown in one subject who was adopted. History of consanguinity was present in 18 (9.7%) and 10 (5.4%) had a family history of developmental delay. History of consanguinity and family history of developmental delay was unknown in one patient who was adopted. An antenatal history of TORCHS infection was present in 1.1% (n=2). In this study group 37 (20%) had a maternal history of miscarriage in a previous pregnancy and 4 (2.2%) had an antenatal history of threatened miscarriage. A total of 32 (17.3%) patients had a history of birth asphyxia and 32 (17.3%) were premature at birth. Out of the premature babies only 9 (4.9%) had a history of birth asphyxia. Fifty six (30.2%) had a history of neonatal seizures. During the neonatal period, 52 (28.1%) were treated for suspected sepsis. The results of blood cultures were not available in the clinic records to further analyse the significance of this finding. Only one patient had a history of kernicterus. Three patients had history of late onset meningitis, age of onset at 5 months, 6 months and 2 years respectively (Table 1).

Investigations performed to diagnose aetiology of GDD

Majority of patients (n=156, 84.3%) had undergone EEG, while 94.6% (n=175) had undergone either CT or MRI. CT of the brain was performed in 129 (69.7%) and MRI was performed in 92 (49.7%). Twenty patients (10.8%) have had TORCHS screening performed postnatally. The decision to screen for congenital infection was based on the clinical features and CT/MRI findings. Two patients were screened postnatally purely due to a positive maternal TORCHS screening. (Table 2)

Sixteen (8.6%) patients had undergone metabolic screening which included thyroid function tests, serum lactate level, urine organic acids, urine mucopolysaccharide levels, amino acid profile and cerebrospinal fluid (CSF) glucose levels.

Table 1
Predisposing factors for global developmental delay

Predisposing factor	Frequency (%)
Antenatal	
Maternal use of alcohol/ tobacco or recreational drugs	0 (0)
TORCHS infection	02 (01.1)
Pre-eclampsia	04 (02.2)
Antepartum haemorrhage	08 (04.3)
Perinatal	
History of birth asphyxia	32 (17.3)
Prematurity	32 (17.3)
Intrauterine growth retardation	15 (08.1)
Risk factors for birth trauma	06 (03.2)
Cord prolapse	01 (0.5)
Obstructed labour	03 (01.6)
Cord round neck	01 (0.5)
Unspecified	01 (0.5)
Postnatal	
Kernicterus	01 (0.5)
Neonatal seizures	56 (30.3)
Neonatal hypoglycaemia	19 (10.3)
Neonatal meningitis	10 (05.4)
Treated for suspected sepsis	52 (28.1)
Meningitis - late onset	03 (01.6)

Table 2
Investigations performed for diagnosis of aetiology of global development delay

Investigation	Frequency (%)
Computed tomography of brain	129 (69.7)
Magnetic resonance imaging of brain	92 (49.7)
Electroencephalography	156 (84.3)
Karyotyping	13 (07.0)
Genetic testing	07 (03.8)
Metabolic screening	16 (08.6)
TORCH screening (Post-natal)	20 (10.8)

Diagnostic yield and aetiological diagnosis

A definitive aetiological diagnosis was determined in 58.4% (n=108). The commonest cause for GDD in this study group was HIE (n=51, 27.6%) followed by structural brain abnormalities (N=28, 15.1%), post infectious (n=13, 7.0%), genetic/chromosomal (n= 7, 3.8%), embryo-fetopathy (n=5, 2.7%) and hypothyroidism (n=3, 1.6%). Among the 32 preterm deliveries 20 (62% of all preterm) were diagnosed with HIE.

Aetiology was undetermined with the available clinical details and investigation results in 33.5% (n=62). A possible diagnosis of genetic/chromosomal origin was suspected in 5.9% (n=11) from historical and examination findings and were awaiting genetic studies for confirmation. Historical and physical examination findings were suggestive of a possible diagnosis of an inborn error of metabolism (IEM) in 2.2% (n=4) out of which 3 were awaiting metabolic screening and one subject had inconclusive results following full screening. (Table 3). Aetiological yield from history and examination alone was 25.4% (n=47). CT/MRI imaging alone provided a definitive diagnosis in 28(15.1%) and provided supportive evidence in arriving at a diagnosis in 88(47.6%) where a diagnosis was suspected from history, physical examination and other investigations.

Table 3
Aetiological diagnosis of global development delay (n=185)

Diagnosis	Frequency (%)
Embryo-fetopathy	05 (02.7)
Hypoxic ischaemic encephalopathy	51 (27.6)
Post Infectious (total)	13 (07.0)
Neonatal meningitis	10
Late onset meningitis	03
Genetic/ chromosomal	07(03.8)
Hypothyroidism	03 (01.6)
Kernicterus	01 (0.5)
Structural brain abnormalities	28 (15.1)
Possible inborn errors of metabolism	04 (02.2)
Possible genetic	11 (05.9)
Undetermined	62 (33.5)

Table 4
Distribution of genetic causes for global development delay based on clinical findings and/or investigations

Genetic causes	Frequency
Batten disease	1
Tuberous sclerosis	2
47,XY+mar1	1
Fragile X	1
Heterozygous variation in exon 4 TUBB2D gene	1
Translocation between chromosome 3 & 18, paternal inheritance	1

Table 5
Distribution of structural brain abnormalities as a cause for global development delay

Structural changes	Frequency
Lissencephaly	2
Low grade glioma	1
polymicrogyria/polygyric changes	2
Mega cisterna magna	1
Cortical malformations	1
Occipital gliosis	1
Colpocephaly	1
Holoprocencephaly	2
Hippocampal sclerosis	4
Schizencephaly	3
Agenesis of corpus callosum	3
hydrocephalus	3
Hemimegalencephaly	1
Delayed myelination	2
Cerebral infarction	1

Table 6
Possible genetic causes for global development delay

Possible genetic causes	Frequency
Rett syndrome	2
Fahr's syndrome	1
Angelman syndrome	1
Sturge weber syndrome	1
Cornelia de Lange	1
Pierre Robin sequence	1
Dysmorphism (unclassified)	1
History of consanguinity	2
Mitochondrial disease	1

Discussion

The aetiological yield of this study (58.4%) is lower but closer to the findings from a North American study and a Turkish study which reported aetiological yields of 63.3%¹⁵ and 64%¹⁶ respectively. Koul *et al.* reported a higher yield of 71.8% in Oman where metabolic screening was the second highest investigation requested, with a positive result of 12.5%¹⁸. This may have added to the higher aetiological yield in comparison to our resource limited setting. The percentage of undetermined aetiology (33.5%) was less than the study by Ozmen *et al* (36%)¹⁶, as we had further categorized into possible genetic and possible IEM disease. Finding of HIE, structural brain abnormalities, genetic/chromosomal, endocrine and

embryo-fetopathy as the common aetiologies of GDD was consistent with other studies^{15,17,18}. Percentage of HIE (27.6%) was similar in comparison to 2 previous studies in Turkey and Oman, 21%¹⁶ and 26%¹⁸ respectively and higher than reported by Majnemer *et al* (10%)¹⁵, and Tikaria *et al* (15%)¹⁷. The third common aetiology was neonatal meningitis and late onset meningitis (n=13, 7.0%) which was higher than reported by Koul *et al* in a study which included a sample size of 110 patients (n=1, 3%)¹⁸. Thus there is definite room for improvement in terms of antenatal and perinatal care in preventing perinatal asphyxia and neonatal meningitis.

The purpose of evaluating the district during pregnancy and during the first 2 years of age was to gain a basic understanding of the level of routine antenatal and paediatric care available for patients. Although our sample is not representative of the entire province, it is worthwhile looking into processes of improving perinatal care in the region in order to minimise perinatal asphyxia and infection. The aetiological yield from history and examination alone in this centre was 25.4% and when combined with neuroimaging, EEG and genetic studies, the aetiological yield rose to 50.8% (n=94). The majority of patients in this centre have undergone neuroimaging keeping in line with international guidelines³. The aetiological yield would further improve with the availability of genetic (Array CGH) and metabolic testing, which has become challenging in our resource limited setting.

The demographic data show that the majority of patients, as expected, were from the Kandy district in the central province due to the proximity to the tertiary centre. A small number presented from distant provinces. Since this tertiary referral centre in the central province is catering to patients from 8 out of 9 provinces in Sri Lanka, service improvement would benefit a widespread population in the country.

The study had some limitations. Since this was a retrospective study where history and examination was extracted from the clinic records, we encountered a limitation in grading of global developmental delay to mild, moderate and severe due to insufficient data. This study population, being the referrals in a tertiary care centre, might not represent the general population. Nevertheless, identifying preventable causes of GDD would be helpful to design neonatal screening programme for congenital infections, treatable metabolic disorders, for parent counselling. Exposure to environmental toxins has been linked to GDD in children^{3,7-12}. However, this study did not focus on the exposure to environmental toxins (lead, mercury and

pesticides) as aetiology. Nevertheless, the effect of environmental toxins on developmental delay in Sri Lankan children remains an important area for research.

This study was not aimed at identifying the prevalence of GDD. Therefore we propose a multicentre prospective study for a longer period of time, which would assist to determine the severity and the prevalence of GDD in the country. This will be useful for allocation of funds and other resources to improve rehabilitation care and to establish support groups for affected families. It may pave the way for establishment of a 'Global developmental delay registry' in Sri Lanka.

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Conclusions

In the paediatric neurology clinic at the tertiary referral centre, HIE, structural brain abnormalities, post infectious, genetic/chromosomal, embryo-fetopathy and hypothyroidism were the identified causes of GDD. Aetiology was undetermined with the available clinical details and investigation results in 33.5%.

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