Original Article

Communication Impairments in Children with Inborn Errors of Metabolism: A Preliminary Study

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ABSTRACT

Purpose: Inborn Errors of Metabolism (IEMs) are a group of complex genetic conditions, predominantly affecting the pediatric population. While the understanding and identification of various IEMs has significantly improved over recent times, not much is known about the communication disorders in this population. The present study focused on identification and profiling of communication impairments in children diagnosed with IEMs. **Methods:** Data was obtained retrospectively from medical records of children visiting a tertiary care hospital over a period of ten years (2005 – 2014). Selected data was reviewed to obtain demographic details, clinical signs/manifestations, laboratory findings, risk factors, developmental disorders and reported communication impairments. **Results:** The findings of the study showed a variety of clinical signs and laboratory findings in children with inborn errors of metabolism. A few of the risk factors observed in the group were consanguinity, sibling death and family history of other disorders. Many children with IEM displayed communication disorders, most common as the delay in speech and language development. **Conclusions:** The results of this study showed that various communication disorders were seen in almost half of the children with a diagnosis of IEM. Findings are discussed with implications for future research in this direction.

Key words: *Communication, inborn errors of metabolism, Indian, retrospective*

INTRODUCTION

Inborn errors of metabolism (IEM) are a heterogeneous group of genetic conditions mostly occurring in childhood. They are caused by single-gene defects resulting in the abnormalities in synthesis or catabolism of proteins, carbohydrates, or fats through defective enzymes or transport proteins, leading to a block of metabolic pathway. IEMs were first discovered by Sir Archibald Garrod in early 19th century.[1]

However, at present, more than 500 different IEMs have been described and most of them are rare conditions/diseases.[2,3] Metabolic disorders account for a substantial percentage of the morbidity and mortality directly attributable to genetic diseases. According to a recent survey, the estimated incidence of metabolic disorders is approximately 1 in every 2500 live births[4] or 10% of all monogenic conditions in children.

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A majority of the IEMs are inherited in an autosomal recessive fashion. In most of these cases, the disease can only manifest itself fully in homozygotes for the mutation. This is generally a rare occurrence, except in consanguineous families. However, some IEMs are caused by mutations in gene located on the X-chromosome, and the disease is then called "X-linked." The effect is 2-fold: First, the disease becomes dominant in male offspring inheriting the mutation; second, due to variable random X-chromosome inactivation in various tissues, the expression of the disease can be highly variable from one tissue to another and from one girl to another. Few IEMs are autosomal dominant. Finally, subsets of the respiratory chain genes that are encoded within the mitochondrial DNA are maternally inherited. Metabolic diseases can present with single or recurrent life-threatening events, such as coma due to hyperammonemia or hypoglycemia, or status epilepticus. In other diseases, the clinical picture is that of a chronic progressive process with epilepsy and mental regression and other organ involvement.

Most IEMs affect the nervous system. Still, the exact pathogenic mechanism of metabolic deficits causing central nervous system (CNS) anomalies is not clear. However, the possible explanation put forth is that energy deficiency or toxic effects from the storage of certain metabolites lead to neuronal death.[5] IEMs thus cause brain damage (sometimes irreversible) through metabolic intoxication or substrate depletion. Brain injury patterns for various IEMs may involve gray matter, white matter, or both, and subcortical or cortical gray matter nuclei.[6] As the CNS is frequently involved, children with IEM often present with disorders affecting motor and cognitive systems. Many children with IEM do present with epilepsy and psychomotor retardation. Consequently, children born with various types of IEM may present with an array of communication impairments ranging from mild developmental delay, cerebral palsy to mental retardation, and social-behavioral disorders such as autism. A couple of studies have documented motor impairments in children with IEM including ataxia, movement disorders, spasticity, peripheral neuropathy, and myopathies.[7,8] In a very recent study, a variety of movement disorders were reported in children with IEM, namely, dystonia, myoclonus, ataxia, tremor, orofacial dyskinesias, and hypokinesia, the first few being more common.[9] While motor disorders in children with IEM are well documented in literature, there are hardly any studies documenting the communication impairments found in this group.

IEM is lesser known in the Indian context. Although the general awareness about various IEMs has increased globally, including India, the metabolic testing is not yet included in the newborn screening, thereby resulting in many undiagnosed cases of IEM. Only a few studies have systematically investigated the incidence rates of IEM in India.[10,11] These studies report an overall incidence rate of IEM to be 1:540.[10] Some of the types of IEM estimated in these studies include disorders of amino acid, congenital hypothyroidism, congenital adrenal hyperplasia, galactosemia, glucose-6-phosphate dehydrogenase, and sickle cell anemia. While these data show lower incidence than those reported as a collective incidence based on data in various other countries and worldwide (1:1500),[12,13] it is largely because of the lack of widespread studies in the Indian context. Although the exact prevalence of IEM in not known in India, it is expected to be higher owing to its huge population and frequent consanguineous marriages in the region. While these handfuls of studies provide an estimate of incidence rates of a few types of IEMs in India, none of the studies discuss on the communication impairments found in this group.

In this context, the present study is a preliminary attempt that was aimed to profile various communication impairments and associated risk factors along with documented clinical signs in children diagnosed with IEM during the period of 10 years (2005–2014) in a tertiary care hospital (in Manipal, Karnataka, Southern India) using a retrospective study design.

METHODS

Before the commencement of the study, permission was obtained from both the Institutional Ethical Committee and the Medical Superintendent of the hospital to access the case files/records of all children with the diagnosis of IEM during a 10-year period between 2005 and 2014. Following this, all medical files/records of children with a diagnosis of IEM who visited in the Department of Pediatrics, Kasturba Hospital, Manipal, Karnataka, between 2005 and 2014 were retrospectively reviewed. All children were investigated by metabolic workup and received the diagnosis of IEM. We obtained a total of 392 cases, of which 25 cases were dead. Hence, only 367 case records were finally included in this study.

All the medical records/files of cases with IEM were reviewed retrospectively to collect the demographic and clinical data. The demographic data included age and gender. The clinical data consisted of clinical signs/manifestations, laboratory findings/results, risk factors, medical diagnosis, and developmental disorders reported in the cases with IEM. Further, we also investigated the type of communication disorders reported in children with IEM based on available medical records.

RESULTS

All medical records of cases who received a diagnosis of IEM (during 2005–2014) were retrospectively reviewed and the relevant details were recorded in the Excel spreadsheet. All the cases underwent metabolic workup on obtained random urine and blood samples to identify the presence of metabolites including proteins, glucose, ketone bodies, urobilinogen, bilirubin, and sulfite. Other metabolic tests were also performed to detect disorders such as phenylketonuria, homocystinuria, Maple Syrup Urine Disease (MSUD), tyrosinemia, tyrosine, and alkaptonuria. A few of the special tests administered were ammoniacal silver nitrate test, osazone test, Mucopolysaccharidosis (MPS) spot test, methylmalonic acid test, and porphobilinogen test.

Of the total 392 cases retrieved, 245 (62.5%) were male and 147 (37.5%) were female [Figure 1], indicating that more males than females were affected by this condition. Among the 392 cases identified with IEM, 4 (1%) were below 6 months of age, 76 (19.4%) were between 6 and 12 months of age, 217 (55.4%) were between 1 and 5 years of age, 78 (19.9%) were between 6 and 10 years, and 17 (4.3%) were above 10 years of age [Figure 2].

Table 1 below presents the results of laboratory tests on all cases with IEM. The laboratory results showed that 275 (70.2%) of the total cases with IEM had metabolic disorders, 108 (27.6%) were found to have respiratory chain defects, and 98 (25%) revealed lactic acidosis with increased Lactate to Pyruvate ratio (L/P) ratio. Further, 29 (7.4%) had metabolic acidosis, 23 (5.9%) had organic academia, 9 (2.3%) showed hyperammonemia, 9 (2.3%) showed hypoglycemia, 3 (0.8%) showed hyperglycemia, 2 (0.5%) showed lactose intolerance, 2 (0.5%) showed hypothyroidism, 1 (0.3%) each presented with hyperthyroidism, metabolic syndrome, hyperalueria, hyposapedemia, and tryosiuria, respectively. Children with IEM presented with a range of clinical signs as shown in Table 2. The most common clinical signs observed in children with IEM were respiratory infections (48.9%) and seizures (40.6%), followed by failure to thrive (12.5%), gastroenteritis (6.6%), iron deficiency anemia (6.4%), bronchopneumonia (5.9%), microcephaly (4.6%), and CNS infections (4.1%) such as meningitis and encephalitis. Children with IEM also presented with signs such as vomiting (2.3%), sepsis (2%), renal failure (1.5%), diarrhea (1.5%), and malnutrition (1.3%). A few of the children also presented with certain syndromes (1.3%), such as Reye syndrome, Down's syndrome, Lennox–Gastaut syndrome, and Bernard–Soulier syndrome. Few other children showed heart problems (1%), asphyxia (1%), muscle jerks (0.8%), muscle atrophy (0.8%), and optic atrophy (0.8%). The other less common signs included aspiration pneumonia, laryngomalacia, ataxia, hemiplegia, rickets, Wilson's disease, Moyamoya disease, cyanosis, megaloblastic anemia, lymphoblastic leukemia, hypertrophy, hepatosplenomegaly, Vitamin B12 deficiency, and chorea.

We further looked into the presence of certain risk factors for communication disorders in the sample of children with IEM. Table 3 presents the risk factors found in children with IEM. These children

Table 1: Laboratory findings of children with IEM

Finding (s)	Number (% of total)
Metabolic disorders	275 (70.2)
Respiratory chain defects	108 (27.6)
Lactic acidosis/increased l/p ratio	98 (25)
Metabolic acidosis	29 (7.4)
Organic academia	23 (5.9)
Hyperammonemia	9 (2.3)
Hypoglycemia	9 (2.3)
Hyperglycemia	3 (0.8)
Lactose intolerance	2 (0.5)
Hypothyroidism	2 (0.5)
Hyperthyroidism	1 (0.3)
Metabolic syndrome	1 (0.3)
Hyperalueria	1 (0.3)
Hyposapedemia	1 (0.3)
Tyrosinemia	1 (0.3)
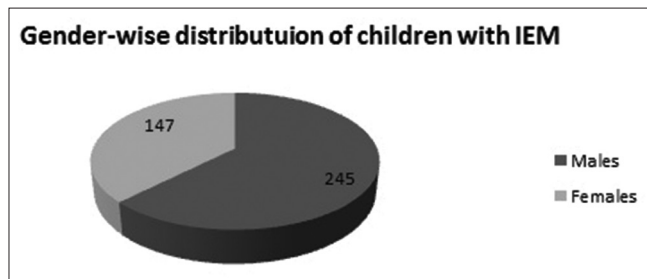
Figure 1: A pie chart showing gender-wise distribution of children with inborn errors of metabolism
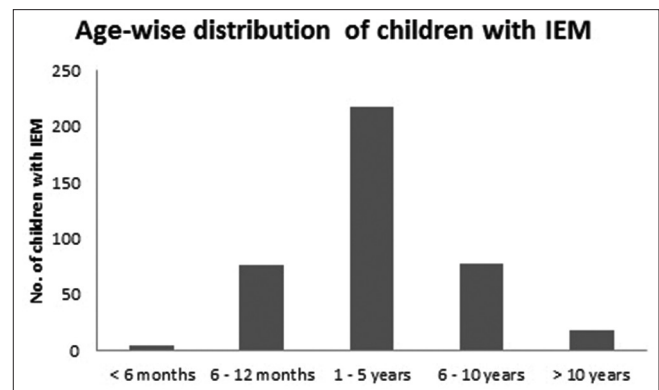
Figure 2: Bar diagram showing age-wise distribution of children with inborn errors of metabolism

presented with IEM presented with risk factors such as history of consanguinity (17.2%), history of sibling death (14.7%), family history of any other disorder (s) (14.2%), history of abortions (4.6%), family history of IEM (3.5%), and sibling (s) affected with communication delay/disorder (1.1%).

We also looked into the developmental profiles of children with IEM based on the reported findings in their medical files. Accordingly, 105 (26.8%) of the children showed global developmental delay, 50 (12.8%) showed developmental delay, and 13 (3.3%) of these children presented with neuroregression [Table 4].

Interestingly, children with IEM displayed a variety of communication disorders as shown in Table 5. The most common communication disorder observed in these children was the delayed speech and language (33.5%). Few children also presented with communication impairments such as delayed speech and language associated with cerebral palsy (3.8%), autism (2.4%), attention deficit hyperactivity disorder (1.6%), hearing loss (1.4%), and mental retardation (1.1%). Certain other children also presented with inadequate speech and language development (1.4%), misarticulation (0.5%), cleft lip and palate (0.5%), and fast rate of speech (0.3%). However, these statistics are derived only from children with IEM who underwent speech and language evaluation on referral from the Department of Pediatrics.

DISCUSSION

IEMs are a group of rare (yet, collectively common) single-gene defects that result from the abnormalities in either the synthesis or catabolism of proteins, carbohydrates, or fats by defective enzymes or transport proteins, leading to a block of the metabolic pathway. One of the common effects of IEM involves brain damage, which is more likely to result in a range of communication impairments in young children with IEM. Yet, the IEM literature is largely silent on communication impairment and related issues in this population. The present study was a preliminary step toward documenting the communication disorders in children diagnosed with IEM through a retrospective design, over a period of 10 years. We reviewed 392 case records retrospectively between the years 2005 and 2014. Of these identified children with IEM, 25 were dead, hence showing a mortality rate of 6.4%. Although the mortality rate in children with IEM is not reported in the Indian context, many studies predict a high or substantial mortality in children with IEM.[14,15] Further, our data showed that more male than female children were affected by various IEMs, with a ratio of approximately 1.6:1. This is closer to the ratio of 1.9:1 as reported in

earlier studies.[15] Another study in the Indian context reported the male to female ratio of 15:11,[14] supporting our finding where males are more affected than females. A higher male to female ratio may be because certain IEMs are transmitted by X-linked inheritance.

Table 2: Associated clinical signs in children with IEM

Clinical sign (s)	Number (% of total)
Respiratory infections	192 (48.9)
Seizures	159 (40.6)
Failure to thrive	49 (12.5)
Gastroenteritis	26 (6.6)
Iron deficiency anemia	25 (6.4)
Bronchopneumonia	23 (5.9)
Microcephaly	18 (4.6)
CNS infection (meningitis/encephalitis)	16 (4.1)
Vomiting	9 (2.3)
Sepsis	8 (2)
Renal failure	6 (1.5)
Diarrhea	6 (1.5)
Malnutrition	5 (1.3)
Syndromes	5 (1.3)
Heart problems	4 (1)
Asphyxia	4 (1)
Muscle jerks	3 (0.8)
Muscle atrophy	3 (0.8)
Optic Atrophy	3 (0.8)
Aspiration pneumonia	2 (0.5)
Laryngomalacia	2 (0.5)
Ataxia	2 (0.5)
Hemiplegia	2 (0.5)
Rickets	2 (0.5)
Wilsons disease	2 (0.5)
Moya-moya disease	2 (0.5)
Cyanosis	1 (0.3)
Megaloblastic anemia	1 (0.3)
Lymphoblastic leukemia	1 (0.3)
Hypertrophy	1 (0.3)
Hepatosplenomegaly	1 (0.3)
Vitamin B12 deficiency	1 (0.3)
Chorea	1 (0.3)

Table 3: Risk factors in children with IEM

Risk factor (s)	Number (% of total)
History of Consanguinity	63 (17.2)
History of sibling death	54 (14.7)
Family history of other disorder (s)	52 (14.2)
History of abortions	17 (4.6)
Family history of IEM	13 (3.5)
Sibling (s) affected with communication delay/disorder	4 (1.1)

Table 4: Developmental disorders in children with IEM

Developmental disorder (s)	Number (% of total)
Global Developmental Delay	105 (26.8)
Developmental Delay	50 (12.8)
Neuro-regression	13 (3.3)

Table 5: Communication disorders observed in children with IEM

Communication disorder (s)	Number (% of total)
Delayed Speech and Language	123 (33.5)
Delayed Speech and Language with Cerebral Palsy	14 (3.8)
Delayed Speech and Language with Autism	9 (2.4)
Delayed Speech and Language with Attention Deficit Hyperactivity Disorder	6 (1.6)
Delayed Speech and Language with Hearing Loss	5 (1.4)
Inadequate Speech and Language	5 (1.4)
Delayed Speech and Language with Mental Retardation	4 (1.1)
Misarticulation	2 (0.5)
Cleft lip and palate	2 (0.5)
Fast rate of speech	1 (0.3)

Children with IEM, in this study, ranged in ages between 1 month and 19 years. In addition, the majority of the children in our data belonged to the age range of 1–5 years (55.4%), followed by those in the age ranges of 6–12 months and 6–10 years, respectively. This finding is, however, quite distinct from the results of another[15] study, where they report a very early age of onset before 1 month of age. This disparity in findings could be due to the lack of metabolic screening for newborns in the Indian context, which would have resulted in late identification and diagnosis of children with IEMs.

The results of laboratory tests showed as many as 70% of the total cases with metabolic disorders, followed by respiratory chain defects (27.6%), lactic acidosis (25%), metabolic acidosis (7.4%), organic academia (5.9%), and others (hyperammonemia, hypoglycemia, hyperglycemia, lactose intolerance, hypothyroidism, hyperthyroidism, metabolic syndrome, hyperalueria, hyposapedemia, and tyrosinemia). Earlier studies' samples of IEM have reported similar results[11,12,16] though the distribution of the findings varies across the studies. The observed variations in the findings across the studies could probably be due to the inclusion of children with IEM from various age ranges. Besides laboratory findings, the results of the present study showed a range of clinical signs in children with IEM as respiratory infections (48.9%), seizures (40.6%), failure to thrive (12.5%), gastroenteritis (6.6%), iron deficiency anemia (6.4%), bronchopneumonia (5.9%), microcephaly (4.6%), and CNS infections (4.1%). The other less commonly reported clinical signs included vomiting, sepsis, renal failure, diarrhea, malnutrition, syndromes, heart problems, asphyxia, muscle jerks, muscle atrophy, optic atrophy, aspiration pneumonia, laryngomalacia, ataxia, hemiplegia, rickets, Wilsons disease, Moyamoya disease, cyanosis, megaloblastic anemia, lymphoblastic leukemia, hypertrophy,

hepatosplenomegaly, and Vitamin B12 deficiency. Most of these signs have also been reported by studies in the past.[8,11,12,16-18] The range of clinical findings and signs, in turn, indicate lack of energy and toxic effects of certain metabolites in the bodies of individuals with IEM.

In our data, we also looked for the presence of risk factors in children with IEM. Some of the risk factors observed in the data included history of consanguinity (17.2%), history of sibling death (14.7%), family history of other disorders (14.2%), history of abortions (4.6%), family history of IEM (3.5%), and siblings affected with communication delay/disorder (1.1%). Few of the previous studies have reported certain risk factors in children with IEM, such as parental consanguinity, sibling death, and positive family history.[11,16,18] A few studies have also reported that a history of regression in milestones and developmental delay are crucial in the identification of IEM in children.[16,18] A few children with IEM in our data too presented with regression and developmental delay as reported in the section of clinical signs in results. Taken together, the observed and reported risk factors indicate genetic causation in IEM. Furthermore, we found a few developmental disorders in our data, such as global developmental delay (26.8%), developmental delay (12.8%), and neuroregression (3.3%). In addition to these disorders, few children with IEM also showed developmental disorders such as ataxia, muscle atrophy, muscle jerks, and hemiplegia [Table 2: clinical signs], suggesting damage/insult to developing brains of children with IEM. Available literature on IEM documents developmental disorders include global developmental delay,[18] developmental delay,[8,11,12,16] developmental regression,[11,16] and various movement disorders such as ataxia, chorea, and muscle weakness.[9,11,16] These developmental disorders, therefore, reveal the nature and extent of brain damage in children with IEM.

Communication impairments were observed in many children with IEM in our data, namely, delayed speech and language (33.5%), inadequate speech and language (1.4%), and delayed speech and language followed by cerebral palsy (3.8%), autism (2.4%), attention deficit hyperactivity disorder (1.6%), hearing loss (1.4%), and mental retardation (1.1%). A few children with IEM in our data also presented with misarticulation (0.5%), cleft lip/palate (0.5%), and fast rate of speech (0.3%). Certain studies highlighting IEM symptomatology have reported a few communication disorders such as mental retardation,[8,11,12,16] and more often autism[16] as part of the general clinical presentation in children with IEM. There is increasing literature indicating associations between autism and a variety of IEMs.[19,20] However, none of the studies have investigated

and/or documented the range of communication impairments in this group. In addition to this, a good number of children with IEM presented with global developmental delay when they received the diagnosis of IEM, who are quite likely to present a profile with delayed speech-language skills if they are reviewed/followed up in the future. An important limitation of this study is that not all children with IEM were screened/assessed for communication delay or disorder. However, based on routine examination of these children, few of them were referred for detailed speech and language evaluation whenever speech delay was reported or suspected. Yet, it is possible that many parents do not bring their children for the same, or it is also possible that communication disorder may be missed by the physicians during a routine examination. It, therefore, indicates that communication impairment is likely to be more common in children with IEM, and these children are at increased risk of developing various communication-related impairments.

This is one of the first studies documenting communication impairments in a group of children with IEM. The present study was a preliminary attempt to profile the communication impairments in a group of children with IEM by retrospectively reviewing the medical records of children over a 10-year period. The data revealed an array of communication impairments and relevant details such as clinical signs and risk factors. However, this study had certain potential limitations such as the absence of a control group and statistical treatment of the data. Future research is thus essential to understand the mechanism and nature of communication disorders resulting from individual types of IEMs.

CONCLUSION

Nearly half of the children with IEM were identified to have communication impairments, where the majority of them showed an overall delay in speech and language development, while others presented with specific disorders such as autism, attention deficit hyperactivity disorder, and cerebral palsy. While communication disorders are common in children with IEM, it is not routinely assessed and, therefore, goes unnoticed in many children, placing them at risk for later cognitive disadvantages.

Conflicts of interest
There are no conflicts of interest.

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