Inborn error of metabolism precipitated by COVID-19: challenges in the absence of an expanded newborn screening as state health programmes

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SUMMARY

Inborn errors of metabolism constitute a differential diagnosis in infants presenting with encephalopathy in developing countries where expanded newborn screening is not a state health programme. Acute neurological presentation with encephalopathy is documented in paediatric COVID-19. The pandemic has also altered parents' healthcare-seeking behaviour, leading to delays in emergency care. We illustrate the challenges faced in diagnosing and managing an 18-month-old child who presented with acute metabolic crisis due to methylmalonic acidaemia on the background of the COVID-19 pandemic. We discuss the current global status of expanded newborn screening services for inborn error of metabolism and the impact of the pandemic on the healthcare of children.

BACKGROUND

Inborn errors of metabolism (IEM) result from deficiency of a critical enzyme or cofactor in the intermediary pathways of carbohydrate, protein and fat metabolism. These complex inherited disorders numbering >1000 have diverse clinical presentations and are rare individually.[1] The global prevalence of IEM is 50.9 per 100 000 live births contributing to 0.4% of all childhood deaths.[2] The true prevalence in India is not known but is higher than the global estimate due to the high birth rate and consanguinity.[3 4]

About 140 million infants are born every year worldwide. Newborn screening (NBS) programmes for detecting presymptomatic infants with selected endocrine, hematologic, and metabolic disorders became available several decades ago.[5] The introduction of tandem mass spectrometry (MS/MS) in the 1990s helped to 'expand' the screening to more than 40 IEMs from dried blood spots collected on filter paper by heel prick. Expanded NBS is a state health programme in developed countries. India is yet to implement any form of NBS as a universal state health programme.[4 6] The three Indian states that offer NBS have excluded IEM in their panel.[6] Expanded NBS is offered only to the urban affordable in private health sectors, thus benefiting less than 3% of all newborns born in the country.

The COVID-19 pandemic has altered healthcare seeking behaviour, leading to delays in emergency care, especially for conditions like IEM.[7] In addition, acute neurological manifestations with encephalopathy are reported in children with COVID-19 complicating the clinical scenario.[8 9] We present a child with acute metabolic crisis due to methylmalonic acidaemia (MMA) precipitated by COVID-19. On the background of the pandemic and delayed healthcare-seeking behaviour, we discuss the challenges in diagnosis and management of children in a developing country where expanded NBS for IEM is not a state health programme. We also discuss the current status of NBS services in India and the global scenario.

CASE PRESENTATION

An 18-month-old male child was brought to the emergency department with a 48-hour history of recurrent vomiting, fast breathing and altered consciousness. He was a previously well child, third in order, born of consanguinity; the two previous conceptions were spontaneous abortions. About 4 weeks before this acute episode, he had an influenza-like illness diagnosed as COVID-19 by throat swab RT-PCR. Soon after, he started to regress in motor milestones. The child who was walking unsupported could only stand with support and had head lag. His parents did not seek medical attention at this time. On examination, the child had signs of encephalopathy with a modified infant Glasgow Coma Scale of 10 over 15. He also had tachycardia, delayed capillary filling, tachypnoea and acidotic breathing. All growth measurements and occipitofrontal circumference were within the normal percentile range. He had bilateral pyramidal signs and firm hepatomegaly.

Investigations (table 1) showed partially compensated metabolic acidosis with moderate hyperammonaemia, wide anion gap and ketosis suggestive of organic acidaemia. Serum lactate and sugar levels, liver and renal function were normal. MRI of the brain showed hyperintensity in globus pallidus in T2/fluid attenuated inversion recovery (FLAIR) images with diffusion restriction (figure 1). Tandem mass spectroscopy revealed high propionyl carnitine with a differential diagnosis of propionic acidaemia or MMA.

We managed the acute metabolic crisis with bicarbonate correction, empirical megavitamin therapy (pending MS/MS report), carnitine, sodium benzoate and broad-spectrum antibiotics. Encephalopathy and metabolic acidosis resolved over 72 hours of admission. During recovery, extrapyramidal features such as rigidity, dystonia and tremors were prominent. The child had lost all his motor milestones. We confirmed the diagnosis of MMA by whole-exome sequencing. A novel homozygous,

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Table 1 Laboratory profile at admission

Parameter	Observed value	Reference range
Haemoglobin (mg/L)	1.6	1.63–2.17
Leucocyte count (×10^9 cells/L)	18.5	
Neutrophilia (80%)	6.0–14.0	
Platelet count (×10^9/L)	648	150–400
Blood glucose (mmol/L)	6.6	3.3–5.5
Calcium (mmol/L)	2.2	2.2–2.7
Magnesium (mmol/L)	0.71	0.65–1.05
Urea (mmol/L)	15.1	1.8–6.4
Creatinine (µmol/L)	50.3	2.65–44.2
Alanine transaminase (U/L)	34.6	12–45
Aspartate transaminase (U/L)	41.5	22–63
Sodium (mmol/L)	137	134–143
Potassium (mmol/L)	4.05	3.3–4.6
Chloride (mmol/L)	98.1	98–106
Arterial blood gas		
pH		
$PaCO_2$ (mm Hg)		
Bicarbonate (mmol/L)		
Lactate (mmol/L)		
6.9		
9		
<3		
1.9		
7.35–7.45		
27–41		
21–28		
0.8–1.5		
Anion gap (mmol/L)	36	7–16
Ammonia (µmol/L)	163.7	11–35
Urine ketone bodies	2 +	Nil

likely pathogenic, missense variant, c.1996G>A [p.(Val666Met)] was observed in exon 12 of the MMUT gene; both the parents were carriers of the same variant.

We initiated specific therapy with protein restriction, vitamin B_{12} (1000 mcg/day) and carnitine (100 mg/kg/day in divided doses) daily with metronidazole (30 mg/kg/day in divided doses) for ten days a month. At 6-month follow-up, the child has regained head control and can sit with support. He is yet to regain age-appropriate milestones but has not had a metabolic crisis. He has residual dystonia of the limbs. Hyperintensity of globus pallidus in MRI T2 images is a feature of MMA but not unique to it. Symmetric basal ganglion is specifically reported in metabolic disorders. Basal ganglion involvement is not reported in COVID-19.[8] In the index case, screening at birth or early health-seeking might have prevented neurological sequelae.

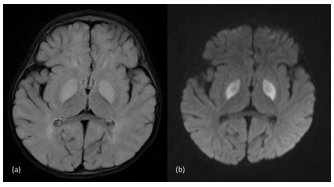

Figure 1 MRI of the brain (A) T2 coronal, and (B) diffusion-weighted sequences showing symmetric hyperintensity and diffusion restriction in bilateral globus pallidi.

GLOBAL HEALTH PROBLEM LIST

- With 25 million births per year (18% of global annual births) and an approximate 10% consanguinity rate, India is yet to establish any form of NBS as a nationwide public health programme.
- There is a low priority for establishing universal IEM screening by spectrometry analysis compared with endocrine and haematological conditions.
- COVID-19 has impacted healthcare-seeking behaviour of the parents; further acute neurological manifestations with encephalopathy are seen with infection add to the challenges in diagnosis and management of children presenting to the emergency department.

GLOBAL HEALTH PROBLEM ANALYSIS

The infant mortality rate in India has declined from 47.3 to 28.3 per 1000 live births between 2009 and 2019.[10] Notably, the newborn mortality rate among infant deaths has increased from 70.2% (33.2 per 1000 live births) to 76.7% (21.7 per 1000 live births) during the same period. India strengthened newborn care with special care units in all districts, which helped bring down infant mortality.[11] With the declining proportion of newborn deaths due to prematurity, sepsis and birth asphyxia, any further reduction in newborn deaths requires the implementation of NBS.

The Indian Council of Medical Research, Government of India, funded a multicentric study that screened 100 000 children between 2008 and 2013 and established congenital hypothyroidism and congenital adrenal hyperplasia as priority disorders for NBS.[11] The prevalence of IEM in India was not established in this study.[4 11] The Department of Biotechnology, Government of India, launched the National Inherited Diseases Administration (NIDAN) kendras (centres) to manage inherited disorders.[12] The NIDAN kendras are to function as regional centres for NBS. The NBS panel does not yet include IEM screening.

Expanded NBS for IEM is believed to make only a minor contribution to the global burden of infant mortality and morbidity, especially in a populous country like India.[13] Also, MS/MS does not detect all IEMs. Presently, only three of the 28 Indian states offer NBS as a state-sponsored health programme.[4 6] The Goa state screened IEM until 2014; presently, expanded NBS is selectively offered only to the symptomatic.[6] It is crucial to diagnose IEM in a presymptomatic state to prevent neurologic morbidity and mortality. However, there are concerns that many of the disorders detected by MS/MS are untreatable or require special diets. Lack of metabolic specialists, cost and low priority are other key issues.[14]

At present, IEM screening is offered only to those who can afford this. Today, India boasts several laboratories that provide expanded NBS in the private health sector.[6] Despite two previous pregnancy losses, the index case with MMA was not screened at birth. Vitamin B_{12} responsive MMAs have favourable outcomes with early diagnosis[15] and in our own experience.[16]

Table 2 summarises the current global status of expanded NBS for IEM as part of national health services.[17–20] There is no uniformity in the screening panel in developed countries, and the primary and secondary targets are variable.[17] Several factors, including political will, policy development, fund allocation, infrastructure, logistics and technical advancement, exist in implementing universal screening in low-income and middle-income countries.[18]

The first wave of the COVID-19 pandemic saw a decline in paediatric outpatient and emergency room visits and a decline

Table 2 Worldwide status of newborn screening for inborn errors of metabolism by tandem mass spectrometry

Region	The approximate number of countries and annual births	Screening status
North America[17 19]	Two and 4.5 million	► The states of the USA have a consensus on primary target metabolites to be screened; there is a wide variation for screening secondary target metabolites ► MS/ MS screening is only partially funded by most states and requires health insurance coverage ► In Canada, only a few provinces like Ontario offer IEM screening, and it is yet to be a federal programme
Latin American and Caribbean islands[17–19]	20 and 11 million	► Offered by Costa Rica ► In most other countries, available partially under public health services/ pilot projects/private sector
Europe[17 19]	48 and 9.5 million	► Diversity among European countries for the conditions screened; under national health service or a statutory health insurance ► Very few countries like Austria, Hungary, Iceland, Portugal, Spain and Sweden screen for both primary and secondary target metabolites ► In the UK, only primary target metabolites are screened ► France started IEM screening as recent as 2015 and limited primary targets; not covered by National Health Services ► Screening is non-existent in Southeast European countries like Bulgaria, Croatia, Serbia
Middle East & North Africa (MENA)[17 18 20]	21 and 11 million	► Available in Israel, Qatar, Saudi Arabia, United Arab Emirates and other Arab countries ► Pilot programme completed in Lebanon, Jordan, and Tunisia ► Non-existent in Sudan and Somalia
Sub-Saharan Africa (Eastern, Western and Southern)[17–19]	50 and 38 million	► None offer as a national health programme; available in the private sector in countries like South Africa
Asia Pacific[17–19]	24 and 67 million	► Offered by Australia, New Zealand, Singapore, China, South Korea, Taiwan and Japan ► A pilot programme in the Philippines ► In India, available in the private sector to the affordable; not covered by health insurances

IEM, inborn errors of metabolism; MS/MS, mass spectrometry.

in inpatient admissions. In multicentre studies from paediatric hospitals, Lee *et al*[21] and Markham *et al*[22] report around 35% decline in emergency room visits during the COVID-19 period compared with the corresponding pre-COVID 19 year. Children with new-onset diabetes mellitus,[23] appendicitis,[24] and cancers[25] were brought late with complications and suboptimal outcomes.

Children with rare metabolic disorders require continuity of clinical care, biochemical monitoring, special diets and medications. The COVID-19 pandemic impacted healthcare delivery to IEM, which included disruption of clinical and laboratory services, non-availability of special diets, metabolic crisis due to infection and discontinuation of therapy.[7 26–29] Online surveys show increased missed follow-up appointments by 3.2 times during the first wave.[7 26] Demographic determinants that influenced parental healthcare-seeking behaviour included travel restrictions, fear of exposure when visiting a healthcare facility, affordability and poor communication on restructured clinical services.[30]

Learning points

- The current global review suggests that newborn screening (NBS) for inborn errors of metabolism (IEM) is a low priority in developing countries and requires focused efforts from all stakeholders.
- Promoting a prospective approach for healthy newborn by presymptomatic screening is essential rather than adhering to a reactive approach to a clinically abnormal child.
- IEM screening should be offered to the affordable until the time expanded NBS becomes a national health programme.
- COVID-19 has disrupted the continuity of healthcare delivery to children, especially those with rare disorders requiring specialised care.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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