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AADARSH®

CONTENTS

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Aims and Scope of Indian Journal of Developmental and Behavioural Pediatrics (IJDBP)

IJDBP is a specialty journal in Developmental and Behavioural pediatrics published by Indian Academy of Pediatrics Chapter of Neurodevelopmental Paediatrics

The Journal welcomes Original papers, Review articles, Case reports and other articles relevant to child development & Behaviour including :

- Neuro developmental disorders,
- Developmental delays,
- Behavioural issues,
- Autism,
- Attention deficit hyperactivity disorder,
- Learning difficulties,
- Intellectual disabilities,
- Evidence based role of early intervention,
- Family centred multidisciplinary intervention,
- Neurogenetic disorders affecting child development,
- Neuroimaging & Neurological issues affecting child development,
- Corrective and assistive surgeries
- Home environmental and environmental issues affecting child development,
- Medical conditions
- Low birth weight and High-risk neonate requiring neonatal intensive care & its outcome,
- Preventive aspects in adolescents and pregnancy.
- Management of conditions covered in Rights of Persons with Disability Act,2016 of GOI.

It aim to promote advances in research in the field of child development and Behavioural issues so that latest evidenced based information is shared to enhance the quality of care and improve lives of children with special needs and their families.

The journal will be National Double Blind Peer review Open access journal published Quarterly. We will accept for publication manuscripts that were not published earlier in any form. The journal is devoted to publishing quality papers based on original innovative and most advance research in the field of developmental behavioural pediatrics.

The Journal aims to have the highest possible ethical and publication standards by scrutinizing the papers, through peer review assisted by eminent experts from prestigious teaching institutes from the country. For all Manuscripts submitted the journal will employ a plagiarism detection system for detecting plagiarism against previously published work.

INVITED GUEST EDITOR

SOCIAL SKILLS FOR ACADEMIC SUCCESS IN CHILDREN WITH ASD

Academic achievement is known to be highly dependent on social skills. Children with strong social skills are more driven to learn and establish personal objectives. In their pursuit of academic goals, they are more driven and tenacious. Social skills are a major indicator of their propensity to pick up reading. Long into their academic careers, students with weak social skills from their early school years frequently struggle with literacy. On the other hand children with strong social skills exhibit less negative behaviours in the classroom, less use of drug and alcohol misuse, violence, and bullying, as well as a higher proportion of positive actions as they go into the teen years. It enables them to be a team player thus helps them to solve issues as a group, work through obstacles, and achieve goals as a team. Collaboration is an essential ability for success in school.

Children with strong social skills are able to listen intently, articulate their thoughts clearly, and thoughtfully answer to others. These skills are a major asset to learning and academic success in the classroom. Therefore children with good social skills do better academically, particularly in foundational courses like reading and math. Develop qualities as inquisitiveness, perseverance, self-discipline, and accountability which are potent markers of success in school. As a result enhancing children's attitudes, actions, communication, and teamwork, social skills are critical for academic performance.

Children with ASD have considerable difficulty in developing social skills. Even high functioning children with Autism spectrum disorder have difficulty in communicating their thoughts though they can cope with academics in the school setting. They need a program to develop social competency through social cognitive activities so as to develop social thinking to be flexible social thinkers and social problem solvers.

The editorial board of IJDBP is doing exemplary work of providing platform for quality research articles in the field of Developmental paediatrics with local adaptability and applicability.

With Regards & Best Wishes,

Nandini Mundkur, MD
Advisor IJDBP
Director : Centre for Child Development & Disabilities
Sangamitra early learning centre, Bengaluru

EDITORIAL

We all are encountering in our developmental clinics more and more cases of neurodevelopmental disorders with no identifiable known risk factors. What are we missing?

The answer may lie in the Environmental influences on Child Health & Neurodevelopmental Outcomes. A dominant mechanism thought to underlie the association between antenatal factors and child outcomes. The Barker, Foetal programming hypothesis. This hypothesis assumes that exposure to adverse conditions (e.g. poor maternal mental health or adverse lifestyle factors) during the antenatal period (i.e. a time of rapid neurodevelopment) can impact brain functioning, thereby influencing children's developmental outcomes later on in life.

Specifically, this adverse gestational environment can occur as a result of

Maternal nutrition (e.g. antenatal supplements)

Hormones (as a result of stress or depression)

Exposure to toxins (e.g. smoking or alcohol)

In addition, Neurodevelopmental Delay in Children Exposed to Maternal SARS-CoV-2 needs to be worked up. Multiple studies highlighting the negative Impact of screen time on suboptimal neurodevelopment in communication & Daily living skills are well document. A social campaign on Zero screen time till Two years of life & promoting a language-rich home environment, can be a simple but very efficient prevention strategy. More emphasis on quality research on various environmental issues affecting neurodevelopment, developing evidence-based intervention techniques & Paediatrician awareness about risks to normal neonate for atypical outcome can help us in finding the correct answer.

I am happy to share that as a team we successfully got our E ISSN.

Best Regards

Dr. Zafar Mahmood Meenai
FRCPCH(UK), MSc paediatric Neurodisability (UK)
Editor-in-Chief, IJDBP

Criterion Validation of 'ASD Related Items' in INCLEN NDST – Research Form Against AIIMS Modified INDT-ASD as Gold Standard

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Abstract

Introduction: Autism Spectrum Disorder (ASD) is an important developmental disorder wo rldwide with a prevalence of 0.09% - 1.07%, in the Southeast Asia population including India.

Aims and Objectives: The primary objective of the study was criterion validation of 'ASD-related items' in NDST as a screening tool for ASD against AIIMS-modified INDT-ASD as gold standard and to calculate sensitivity, specificity, predictive values, diagnostic accuracy, and likelihood ratios.

Materials and Methods: This is a descriptive study - diagnostic test evaluation, which was carried out from January- July2022, at NIMS Spectrum-CDRC, Thiruvananthapuram, a tertiary care centre for children with neurodevelopmental problems. Fifty children, who came to CDRC with suspected developmental problems were screened with ASD-related items in NDST by an experienced Developmental therapist and evaluated with AIMS Modified INDT-ASD by a Developmental Nurse Counsellor trainee, blind to the results of the screening.

Result: On doing criterion validation of ASD related items in NDST, the psychometric properties were as follows: Sensitivity of 100%, Specificity of 80%, Positive Predictive Value of 95.24 %, Negative Predictive Value of 100%, Positive Likelihood Ratio 5; and Negative Likelihood Ratio 0.0. Diagnostic Accuracy of the test was found to be 96%. The prevalence of ASD as per screening tool NDST items was 84% and as per the gold standard is 80.00%.

Conclusion: ASD-related items in NDST is a simple screening test, with good psychometric properties, to screen for ASD among children suspected with developmental problems.

How to cite this article:
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Keywords:
- ASD
- NDST
- INDT-ASD
- Psychometric properties.

Introduction:

Autism Spectrum Disorder (ASD), refers to a range of impairments in areas of social interaction and communication skills along with the presence of repetitive and restricted behaviours as its important features.Centre for Disease Control

and Prevention (CDC)'s latest data suggest that 1 in 36 children have been identified with autism [1]. In a study conducted in India and other Southeast Asia populations, the prevalence of Autism Spectrum Disorders ranged from 0.09% to 1.07% among children in the age group of 0–17 years [2]. As per the latest studies done by INCLEN Trust International,about one in a hundred children in India under the age of 10 have autism[3].A study conducted in Kerala revealed that there isa 20times greater chance for a child to become autisticif there are no children of the same age to play with [4].

The Neurodevelopmental screening tool-Research form (NDST-R/F), a 39-item screening tool developed by the INCLEN-NDD study team led by Arora NK, screens for 10 neurodevelopment disorders such as Neuromotor impairment, ASD, ADHD, Epilepsy, Speech and language disorder, Intellectual disability, Learning disability, Cerebral palsy, Vision impairment, and Hearing impairment. NDST-R/F has 13 specific questions related to ASD and credit for each question can be given by direct observation of the child or by the report from the mother or caregiver. If the child has failed any one item, it is considered that the child has failed the test.

AIIMS-modified INDT-ASD with modifications made from INCLEN-INDT-ASD [5] was validated against the Childhood Autism Rating Scale (CARS), which demonstrated a sensitivity of 98.4% and specificity of 91.7%with acceptable diagnostic accuracy to diagnose ASD [6].

Rationale: ASD is considered as a condition with increasing prevalence as the years go by and both genetic and environmental risk factors have been attributed to it. In the current COVID-19 pandemic, the chances for children to have peer interactions were very low, affectingtheir social and communication skills. If desirable criterion validity measures are obtained against AIIMS Modified INDT-ASD, NDST-R/F can also be used by peripheral health workers to identify a child with ASD. Thus, the current study is undertaken to validate 'ASD-related items' in the Neurodevelopmental Screening Tool-Research form (NDST-R/F) against AIIMS-modified INDT-ASD, a diagnostic test for autism spectrum disorder among consecutive children with suspected social and communication problems.

Objectives:

The primary objective of the study was criterion validation of 'ASD-related items' in NDST-R/F as a screening tool for ASD against AIIMS-modified INDT-ASD as the gold standard and to calculate sensitivity, specificity, predictive values, diagnostic accuracy, and likelihood ratios.

Primary Objectives: -

1. To administer NDST-R/F, on all consecutive children of 2-6 years with suspected social and communication problems, attending NIMS -Spectrum CDRC.
2. To administer AIIMS-modified INDT-ASD diagnostic tool on the same children.
3. Criterion validation of NDST- R/F screening tool against INDT-ASD as the gold standard and to calculate sensitivity, specificity, positive predictive value, negative predictive value diagnostic accuracy, likelihood ratio positive and likelihood ratio negative.

Materials & Methods:

The present study was a hospital-based criterion validation study carried out from January toAugust 2022 for 8months, at Thiruvananthapuram NIMS-Spectrum-Child Development Research Centre (CDRC), Noorul Islam Centre for Higher Education (NICHE), Deemed-to-be University. Institutional Ethical Committee clearance was obtained (Regn. No. ECR/218/Inst/Ker/2013/RR-16 and Approval No. NIMS/IEC/2022/01/05, dtd. 10/01/2022). Fifty consecutive children 2-6 years of age with suspected social and communication problems, coming to NIMS-Spectrum-CDRC, a tertiary care center for children with neurodevelopmental problems, were included after getting parental consent.

Data was collected by interview method. Evaluation with NDST-R/F wascarried out by a Developmental Therapist and then the AIIMS Modified INCLEN tool INDT-ASD was done by a Developmental Nurse Counsellor blind to the screening results. The analysis was performed using Statistical Package for Social Science (SPSS version 20).

Results:

Out of the study population of 50 children,

- Age: 24-35 months – 13; 36-47 months – 16; 48-59 months - 11; 60-72months – 10.
- Gender: Male 42 (84%); Female 8 (16%).

Table 1: Distribution of 'ASD related items' in NDST-Research form (n= 50).

NDST No.	NDST Research form Items	No*	Some-times	Most times#
	Socialisation questions			
39a.	Does your child make common age appropriate gestures to greet familiar people?	**18**	3	29
40a	Did/does your child ever seek your attention by pointing?	**21**	6	23
41a	Does your child look at your face & maintain eye contact when you are talking to him/her?	**16**	17	17
42a	Does your child ever engage in role plays or games involving role play?	**30**	7	13
43a	Like other children of his/her age, is your child able to do his/her ADL by himself/herself?	**26**	12	12
66a	Does your child pay attention when you address him/her by name?	**16**	9	25
67a	Does your child give attention to common sounds?	**12**	5	33
	Communication related questions			
60a	Has your child now stopped speaking/learning new words/sentences?	26	12	**12**
63a	Does your child often repeat the same word/phrase over and over in the same manner?	27	8	**15**
68a	Do you always need to speak loudly to get the attention of your child?	28	14	**8**
	Behaviour related questions			
70a	Does your child insist on sameness and actively resist any change in his/her routines?	44	3	**3**
71a	Does your child appears to be lost in his/her own world, no matter what he/she doing?	16	12	**22**
72a	Does your child do activities that are purposeless, repetitive and excessive?	21	9	**20**

Using NDST-research form, 42 (84%) children had at least one question positively suggestive of ASD.'No'is suggestive of ASD for the first 7 questions related to Socialization, 'Most times'is suggestive of ASD for 3 questions related to Communication, and 3 questions related to Behaviour. (Table 1)

Table 2: Evaluation by AIIMS Modified INDT-ASD.

Domains	**2 or less**	**3**
INDT ASD A1 – No of criteria fulfilled in A1 of the section A (Social interaction & communication)	7	43
Domain	**Nil or one**	**Two or more**
INDT ASD A2 – No of criteria fulfilled in A2 of the section A (restrictive and repetitive)	9	41

Domain	**NO**	**YES**
INDT ASD 3 – Is there onset at early development?	8	42
INDT ASD 4 – Is there an impaired functioning?	7	43
Domain	**4 or less**	**5 or more**
INDT ASD 6- Total number of criteria fulfilled in A1 and A2 together.	9	41
Domain	**No ASD**	**ASD**
INDT ASD 5 – Interpretation of questionnaire (1 to 4)	9	41
INDT ASD 7 – Summary assessment of ASD	10	40
Domain	**NO**	**YES**
INDT ASD 8 – Can these symptoms be solely explained by intellectual disability	49	1
AIIMS Modified INDT-ASD Impression= No ASD: 10 (20%); ASD=40(80%)		

The prevalence of ASD using AIIMS Modified INDT-ASD. (Table 2). As per the criteria for interpreting AIIMS Modified INDT-ASD. [5]

- Out of section A, subsection A1, 43 children met 3 criteria.
- In subsection A2, 41 children met 2 or more criteria.
- 42 children had onset at an early age of development.
- Among 50 children, impairment of functioning was seen among 43 children.
- Ruling out the one child whose symptoms were solely explained by Intellectual disability, by using AIIMS modified INDT-ASD, the number of children with ASD was found to be 40 (based on responses in question7), and 10 children were found to have no ASD.

TABLE 3: 'ASD Related items' in NDST-R/F vs AIIMS Modified INDT-ASD.

NDST-Research form Impression	**AIIMS modified INDT-ASD Impression**		Total
	ASD	No ASD	
ASD	**40 (TP)**	2 (FP)	42
No ASD	0 (FN)	**8 (TN)**	8
Total	40	10	50

On doing criterion validation of related items' in NDST-R/F against AIIMS modified INDT-ASD (Table 3), the psychometric properties were as follows; sensitivity of 100%, specificity of 80%, positive predictive value (PPV) of 95.24 %, negative predictive value (NPV) of 100%, positive likelihood ratio 5.00 and negative likelihood ratio 0.00. Diagnostic Accuracy of the test was found to be 96%.

Discussion:

Though, ASD is probably the most common neurodevelopmental disability presenting to a child development centre, providing specialized diagnostic and intervention services, the reported community prevalence is not that high. A meta-analysis evaluating the prevalence of ASD in the community setting of India showed a pooled percentage prevalence from rural settings of 0.11(95% CI 0.01-0.20) and urban settings of 0.09 (95% CI 0.02-0.16) [7]. The increasing prevalence of autism may be due to the inclusive definition of autism spectrum disorder, the availability of better screening and diagnostic tools, or a change in the family structure witha minimum number of children to play with. The reported modifiable risk factors for ASD, apart from excessive use of mobiles include; (i) the child does not play with children of the same age (OR=19.6); (ii) no outings

(OR=3.4); (iii) does not tell stories/sing songs to the child (OR=3.2); and (iv) breastfeeding duration nil/ <6 months (OR=3.4)[4].Parental awareness of ASD has improved in recent times, especially after the worsening situation with COVID-19.They are also more aware and motivated about the benefits of early intervention and therapies. The presence of the District Early Intervention Center (DEIC) under RBSK has opened upassessment and therapy facilities for the same.

Hence, this criterion validation study of ASD-related items in NDST-R/F against AIIMS Modified INDT-ASD is timely, as it has showna PPV of95.24% and NPV of100%. Thus, the ability of the NDST-Research form to correctly identify children with ASD is 100% and the ability to correctly identify children without ASD is 80% which is acceptable for a screening test. The probability that a person who receives a positive test result has the disorder is 95.24% and the probability that subjects with a negative screening test truly do not have the disorder is 100%. The accuracy of ASD-related items in NDST to diagnose correctly or the proportion of subjects who give the correct result is 96%.

Conclusion:

The results of this study showed that criterion validation of 'ASD-related items' in NDST-R/Fhas good psychometric properties when validated against AIIMS Modified INDT-ASD taken as the gold standard, validating its use in a developmental clinic /child development center.

Ethical Approval: Institutional Ethics Committee clearance (NIMS/IEC/2022/01/05, dated 10/01/2022)

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Conflicts of interest : There are no conflicts of interest

What this study adds

This study demonstrates that the ASD-related items in the NDST-Research Form are highly sensitive and accurate in identifying ASD in children when compared to AIIMS-modified INDT-ASD.

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Criterion Validation of 'ADHD Related Items' in INCLEN NDST Against AIIMS Modified INDT-ADHD Among Children with Developmental Problems

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Abstract

Introduction: Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood with a global prevalence of 3-5% in school-aged children.

Aims and Objectives: The primary objective of the study was to assess the criterion validity of ADHD-related items in the Neurodevelopmental screening tool (NDST) against AIIMS-modified INDT-ADHD as Gold standard using sensitivity, specificity, predictive values, diagnostic accuracy, and likelihood ratios.

Materials and Methods: This was a descriptive study - diagnostic test evaluation carried out at NIMS Spectrum-CDRC, Thiruvananthapuram, a tertiary care center for children with neurodevelopmental problems. 50 consecutive children who came to CDRC for suspected developmental problems were screened initially with ADHD-related items in NDST by an experienced developmental therapist and evaluated with AIIMS modified INDT-ADHD by a developmental nurse counselor trainee, blind to the screening results.

Result: On doing criterion validation, the psychometric properties were as follows sensitivity of 90%, specificity of 80%, positive predictive value of 94.74%, negative predictive value of 66.67%, positive likelihood ratio of 4.50 and negative likelihood ratio of 0.13 with diagnostic accuracy of 88%. Prevalence of ADHD as per screening NDST items was 76% and with gold standard AIIMS modified INDT-ADHD was 80%.

Conclusion: ADHD-related items in NDST had acceptable psychometric properties, to screen for ADHD among children suspected with developmental problems.

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Keywords:

- Attention deficit hyperactivity disorder (ADHD)
- NDST
- INCLEN

Introduction:

Most children may have times when their behaviour becomes out of control like; crashing into everything around them, drifting as if in a daydream, failing to finish what they have started, failing to pay attention, making noise, refusing to wait their

turn, and speed about in constant motion and all these are normal at certain ages[1]. On the other hand, children with Attention-Deficit Hyperactivity Disorder (ADHD) have behavior problems that are so frequent and/orso severe that they interfere with their normal life routines. Their impulsive nature may put them in actual physical danger and those who have trouble paying attention usually have trouble learning. ADHD is typically observed by 4 years of age. However, younger presentations of symptoms are being increasingly reported. Symptoms typically increase over the next 3 to 4 years, peaking between 7 and 8 years of age. The percentage of children ever diagnosed with ADHD increases with age.If left undiagnosed and untreated, ADHD can lead to serious, lifelong problems such as; (i) poor grades in school, (ii) trouble with the law, (iii) failed relationships, (iv) substance abuse, and (v) inability to keep a job.

ADHD is one of the most common neurodevelopment disorders of childhood, with a global prevalence of 3 – 5% among school-aged children, as against 1.7% reported in India as per an INCLEN study[2,3]. Globally, the International Classification of Disease-10 (ICD-10) and the Diagnostic and Statistical Manual of Mental Health Disorders (DSM) criteria are used to diagnose ADHD[4,5]. DSM-5, the latest version consists of two symptom domains-hyperactivity/impulsivity(H/I) and inattention(I), associated with impaired social, academic, adaptive, and occupational functioning[6]. The Neurodevelopmental screening tool (NDST-Research form) a 39-item screening tool developed by INCLEN trust, screens for 10 neurodevelopment disorders with 3 specific questions related to ADHD. INDT-ADHD, the International Clinical Epidemiology Network (INCLEN) Diagnostic Tool for Attention Deficit Hyperactivity Disorder was developed and validated for the age group of 6–9 years based on the DSM-IV criteria as the gold standard [7].ADHD is associated with impaired academics, dysfunctional peer relationships, and school dropouts[8-11].In the present study, a feasible approach was taken using the Neuro-developmental Screening tool (NDST-Research form) developed by the INCLEN NDD study team and led by Arora NK to screen for 10 neurodevelopmental disorders, and specifically use those items relevant for ADHD as a screening tool and validate the same against AIIMS modified INDT-ADHD as gold standard. After validation, ADHD-related items in the NDST-Research form can be used by community doctors and health workers to identify a child with ADHD early.

Objectives:

Primary Objectives: -

1. To administer (NDST-Research form) Neuro-developmental Screening tool, on all consecutive children4-12 years with complaints of inattention and/or hyperactivity, attending NIMS -Spectrum CDRC.
2. To administer AIIMS-modified INDT-ADHD Diagnostic tool on the same children.
3. Criterion validation of ADHD-related items in NDST-Research form (NDST R/F) against AIIMS modified INDT-ADHD as the gold standard and to calculate sensitivity, specificity, predictive value, diagnostic accuracy, likelihood ratio positive and likelihood ratio negative.

Materials & Methods:

The present study is a hospital-based criterion validation study carried out from January 2022 to July 2022 over a period of 6 months, at Thiruvananthapuram NIMS-Spectrum-Child Development Research Centre (CDRC), Noorul Islam Centre for Higher Education (NICHE), Deemed-to-be University. Fifty consecutive children 4-12 years of age with complaints of inattention and /or hyperactivity, coming to NIMS-Spectrum-CDRC, a tertiary care centre for children with neurodevelopmental problems, were included. Institutional Ethical Committee clearance was obtained (Regn. No. ECR/218/Inst/Ker/2013/RR-16 and Approval No. NIMS/IEC/2022/01/06, dtd. 10/01/2022) and the study was initiated with due consent from each parent.

The diagnostic tool used was the All India Institute of Medical Sciences modified AIIMS-INDT-ADHD tool, validated against DSM-5, which is easy to administer and requires minimal training[11,12]. The AIIMS Modified-INDT-ADHD tool has 18 items, 9 items each in two domains inattention and hyperactivity-impulsivity. To be diagnosed as ADHD child must fulfil 6 out of 9 criteria in inattention (A1) and hyperactive/impulsive domain (A2) with symptom onset in less than 12 years of age, lasting for greater than 6 months duration and

in more than 2 settings. The tool also mentioned that Intellectual Disability Disorder (IDD) must be excluded.

Data was collected by interview method. The NDST-Research form was administered by an experienced Developmental Therapist and AIIMS Modified INDT-ADHD by a trained Developmental Nurse Counsellor, blind to the screening results. The analysis was performed using the Statistical Package for Social Science (SPSS version 20).

Results:

Out of the study population of 50 children, 37 were of 4-9 years and 13 were of 10-12 years; 42 were male and 8 were female.

Table 1: Prevalence of ADHD using 'ADHD related items' in NDST-Research form.

NDST No.	NDST-Research form Items	No	Sometimes	Most of the time
75a	Is your child excessively active and appears to be 'on the go'?	6 (12%)	6 (12%)	38 (76%)
76a	Does your child appear to act, speak, or behave without thinking?	15 (30%)	8 (16%)	27 (54%)
77a	Does your child have difficulty sustaining attention on activities at school, home, or play?	5 (10%)	13 (26%)	32 (64%)
	NDST-Research form Impression: N (%) = ADHD: 38 (76%); No ADHD:12 (24%)			

Using ADHD-related items in NDST-R/F; 38 children were excessively active and appeared to be on the go; 27 appeared to act, speak or behave without thinking; and 32 were having difficulty in sustaining attention on activities at school, home, or play. Altogether, 38 (76%) children were positive for ADHD using NDST-R/F.(Table 1)

Table 2: Prevalence of ADHD using AIIMS Modified INDT- ADHD.

Domains	<6	6 or more
INDT ADHD A1-Inattention	13	37
INDT ADHD A2 –Hyperactivity/Impulsivity	13	37
	NO	**YES**
INDT ADHD 3 – Symptoms start before 12 years	12	40
INDT ADHD 4 – Symptoms present for at least 6 months	12	40
INDT ADHD 5- Symptoms present in at least 2 settings	12	40
INDT ADHD 6- Frequent fights/no new friends/frequent injuries/ frequent scolding by parents/complaints from teachers/poor school performance	12	38
INDT ADHD 7 – Symptoms be explained by ID	--	50
INDT ADHD 9 – Whether child can be diagnosed as ADHD	10	40
INDT ADHD 10- child on any medical/ non-medical intervention	29	21
AIIMS Modified INDT-ADHD Impression: N (%) = ADHD: 40 (80%); No ADHD: 10 (20%)		

Using AIIMS Modified INDT-ADHD, 37 children had inattention, and 37 had hyperactivity/impulsivity. Altogether, 40 children were found to have ADHD using AIIMS Modified INDT-ADHD. (Table2)

Table 3: ADHD Related items in NDST-Research form Vs AIIMS Modified INDT-ADHD.

NDST-Research form Impression	AIIMS Modified INDT-ADHD Impression		Total
	ADHD	No ADHD	
ADHD	**36 (TP)**	2 (FP)	38
No ADHD	4 (FN)	**8 (TN)**	12
Total	40	10	50

On doing criterion validation (Table 3) of 'ADHD related items' in the Neurodevelopmental screening tool (NDST-Research form) against AIIMS modified INDT-ADHD, the psychometric properties were as follows; sensitivity of 90%, specificity of 80%, positive predictive value of 94.74 %, negative predictive value of 66.67%, positive likelihood ratio 4.50 and negative likelihood ratio 0.13. Diagnostic Accuracy of the test was found to be 88%.

Discussion:

According to this criterion validation study,38(76%) children had ADHD as per the screening tool NDST, and 40 (80%) children had ADHD as per the diagnostic tool AIIMS Modified INDT-ADHD. The psychometric properties of ADHD-related items in NDST-R/F against AIIMS-modified INDT-ADHD is more than satisfactory. The ability of the NDST tool to correctly identify children with ADHD is 90% and the ability to correctly identify children without ADHD is 80%which is acceptable for a screening test.

A study revealed that older boys with ADHD showed fewer peer problems than younger boys with ADHD, but older girls with ADHD had similar peer problems as younger girls with ADHD[13,14]. In the present study, of the total 40 children who tested positive for AIIMS Modified INDT-ADHD,34children(85.0%) in the age range 4-9 years had ADHD features, while 6 children(15.0%) in the age range of 10-12 years had ADHD.A meta-analysis by Gershon J et al., states that ADHD girls have lower ratings on hyperactivity, inattention, impulsivity, and externalizing problems in comparison to ADHD boys[15].

Conclusion:

The results of this study showed that criterion validation of ADHD-related items in the Neurodevelopmental screening tool (NDST-Research form) has good psychometric properties when validated against AIIMS Modified INDT-ADHD taken as the gold standard. This suggests that ADHD-related items in the NDST-Research form can be used to screen for ADHD among children suspected of developmental problems in a Child Development Centre setting.

What this study adds ?

- The study validates the effectiveness of ADHD-related items in NDST-R/F, showing good psychometric properties against the gold standard AIIMS-modified INDT-ADHD.
- It supports NDST as a feasible community-level screening tool for early ADHD identification.

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Conflicts of interest

There are no conflicts of interest

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Early Intervention in Autism Spectrum Disorder: Models, Evidence, and the Com-DEALL Approach

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Abstract

Background: The prevalence of Autism Spectrum Disorders is steadily on the rise with its global prevalence at 1 in 36 children as of May 2024. There has been a rapid change in our understanding of ASD as being a psychological condition characterized by hallucinations and fantasy to being a profound abnormality of language development with ritualistic behaviour to its present identity as a neurodevelopmental variant with sensory-perceptual difficulties. Evolution in the theories of autism mandates an evolution in interventions aimed at its management.

This article aims to highlight the core beliefs, benefits, and drawbacks of the different models of intervention and to explore a comparatively new model of early intervention in children with Autism called Communication Developmental Eclectic Approach to Language Learning (Com-DEALL).

Method: Recent literature in the last 25 years on the various intervention models of ASD were analysed and a detailed literature review with regards to the inception, principle, team and program attributes of the Com-DEALL program were surveyed.

Result: While other models of intervention such as ABA, Floor-time (Developmental Interventions) and Early Start Denver Model (ESDM, a form of NDBI) have proven positive outcomes the shortage of trained experts and their cost are some inhibiting factors for their effective administration in a resource-limited setting such as ours. Com-DEALL program is an Indigenous program which is an efficacious and relatively inexpensive alternative.

Conclusion: The overarching theme of neurodiversity and acceptance should be kept in mind. The basis of any treatment plan should come from a thorough evaluation of the child's strengths and weaknesses. Com-DEALL program offers such an individualized and culturally acceptable alternative to the more traditional intervention

models.

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Keywords:
- Autism
- Intervention
- Children
- Com-DEALL
- Communication

Introduction:

The prevalence of Autism Spectrum Disorders is steadily on the rise with its global prevalence at 1 in 36 children as of May 2024[1]. Although this increase in diagnosis

among 0 to 5-year-olds has often been attributed to the liberal coding of the International Classification of Diseases, 10th Revision in 2015, studies state that the increased screening for autism is the likely reason [1].

The theories of Autism have been evolving since the early 1900s. With the evolution in understanding the etiopathogenesis of autism, there has been an evolution in the intervention strategies employed in its management. The initial perception of autism as a psychological condition has rapidly changed, especially near the turn of the century, to its current perception of it being a neurodevelopmental variant [2]. Autism Spectrum Disorder went from being understood as a disorder of hallucinations and fantasy in infancy to being a profound abnormality of language development associated with ritualistic and compulsive phenomena [2]. This view has further undergone a transformation wherein the sensory-perceptual difficulties which have long been believed to be associated with ASD have now been recognized as the core deficit in autism, which accounts for children with autism processing the world differently from their peer group

Broadly there are three broad intervention models in the management of ASD, namely, Behavioural therapy (Applied Behavioural Analysis), Developmental Education, and Naturalistic Developmental Behavioural Intervention (NDBI). With the evolution of our understanding of ASD, behavioral therapies which were once held as the gold standard for the management of children with autism for over two decades, are now being gradually phased out to give way to developmental education and NDBI models of intervention. This article aims to highlight the core beliefs, benefits, and drawbacks of each of the above models and to explore a comparatively new model of early intervention in children with Autism called the Communication Developmental Eclectic Approach to Language Learning (Com-DEALL).

Applied Behaviour Analysis:

ABA is based on the principles of learning and behaviour postulated by B. F. Skinner and Darwin's theory of natural selection, which believes that all behaviours occur as a consequence of outcomes. That is, any behaviour that results in a favourable outcome will perpetuate the behaviour further through reinforcements whereas those behaviours which do not have any favourable outcomes will diminish and eventually be extinguished [3]. Skinner established that new skills or behavioural responses may be either developed or changed via operant conditioning procedures such as shaping, prompting, and modeling [3].

Ivar Lovaas developed the first intensive ABA treatment model called Early and Intensive Behavioural Intervention based on Discrete-trial Teaching (DTT) which focuses on teaching by giving discrete/distinct instructions repeatedly. Correct responses to these instructions would be reinforced using praise and/or rewards while incorrect responses would be met with correction or absence of praise. In young children with ASD, it is recommended that the DTT model be applied to teach basic skills for at least 25 hours per week or more. As the child progresses, a shorter duration of therapy (15 hours per week) is recommended to target more complex behaviours, for example, social pragmatic skills. Maximal benefits have been noted with individualized and teacher-implemented approaches to ABA rather than parent-implemented approaches.

With the development of naturalistic models of ASD management, the focus has shifted from DTT as the primary mode of managing behaviours in ASD to more developmentally based naturalistic methods of teaching like the Natural Language Paradigm (NLP), Pivotal Response Training (PRT) and Early Start Denver Model (ESDM) with specific recommendations as to how the two may be blended [3]. While children on naturalistic intervention methods were found to have early requesting behaviour and compliance, DTT was found to be superior to it in teaching targeted skills [3].

Naturalistic development behavioral interventions:

NDBIs are a set of intervention models that combine behavioral principles with insights from developmental psychology. The term NDBI has only been around since 2015 [4] but treatments that use NDBI principles have been around far longer [5,6]. Naturalistic behavioral interventions provided a different perspective and approach to handling unwanted and challenging behaviors, which led to a diminishment of their frequency

[5,6]. NDBI serves as an umbrella term that includes several similar treatment models, such as the Early Start Denver Model (ESDM), Pivotal Response Treatment (PRT), Enhanced Milieu Teaching (EMT), Incidental Teaching (IT), Improving Parents as Communication Partners (Project ImPACT), Social ABCs, Joint Attention, Symbolic Play, Engagement and Regulation (JASPER) [4,7].

The core components of all NDBIs include

1. Interactions should take place face-to-face and at the child's level.
2. The therapist/caregiver should follow the child's lead and actively participate in the activity chosen by the child.
3. The therapist/caregiver /caregiver should use a positive affect and animation to meet the child's sensory needs.
4. The therapist/caregiver should model appropriate language and behavior to match the child's developmental level.
5. The therapist/caregiver should respond to all of the child's attempts to communicate by repeating, clarifying, or expanding on them.
6. The therapist/caregiver should use natural rewards to encourage communication.
7. The therapist/caregiver should provide frequent episodes of direct teaching for new and emerging skills.
8. The therapist/caregiver should provide high-quality direct teaching such as using clear instructions and teaching when the child is motivated [4,7,8].

Implementation of NDBIs should occur in natural environments, throughout the child's daily routines, at home, or at school. This was to tackle what clinicians noticed with more typical, highly structured ABA, such as lack of motivation and generalization. Family involvement is also an integral part of NDBIs. Parents should be involved in goal setting as well as the intervention implementation and most NDBIs specifically incorporate parent training such that parents can act as intervention providers [4,7,8].

Metanalysis of outcomes using NDBI shows significant positive effects in the areas of social engagement and cognition [9]. NDBIs may increase language, social communication, play skills, and cognition in young children with autism. In general, NDBI methods are well-suited to improve outcomes for young children [10].

Communication Developmental Eclectic Approach to Language Learning (Com-DEALL):

Communication DEALL program is an indigenous early intervention program started in Bangalore in 2000 intending to meet the need of the exponentially increasing prevalence of ASD and to re-patriate these children into mainstream schools once the intensive intervention has been established.

Principle

The Com-DEALL program is based on the principle that the core underlying cause of autism is biological (and not psychological) [11]. Whatever this biological cause may be (genetic or environmental or a combination of both), it is found to cause sensory perceptual difficulties in hearing, vision, touch, smell, and kinaesthetic senses. It is these sensory perceptual differences that account for autistic children perceiving the world around them differently from their neurotypical counterparts [11]. Some of the core deficits of ASD such as language delay, poor social communication skills, and some stereotypies can be explained by these differences in perception. For example, a child on the spectrum may have an unusual talent in music due to a prolonged auditory perception time but this perceptual difference may impair his ability to process speech in real-time, thereby accounting for poor speech perception [12].

Autistic children also exhibit difficulties in motor executive functions such as planning, working memory, impulse control, inhibition, initiation, and monitoring of action. This may impair gross and fine motor functions such as carrying out actions when requested to do so. It may also impair the fine oro-motor movements crucial for speech production [13]. Thus, the communication-social-emotional deficits which are often believed to be the core deficits in ASD are, in effect consequences of these differences in sensory-motor processing. When these difficulties manifest early during development they may affect the entire process of language acquisition, thus impairing communication.

Behavioural challenges seen in such children are

considered mere reactions to the various sensory-motor perceptual differences and communication difficulties that they face. The program thus targets the sensory-perceptual, motor, and communication difficulties which consequentially help overcome the behavioural challenges.

Team

The ComDEALL Program includes a team of occupational therapists, physical therapists, speech-language pathologists, developmental psychologists, and educators.

Program

Before enrolling a child, a detailed developmental profile of the child is generated using the CDDC (ComDEALL Developmental Checklist), and the parents are counselled regarding their child's profile and the target interventions required. The Program enrols a small group of children diagnosed with ASD ranging from 18 months to 6 years for a period of eleven months. The initial 6-8 weeks of intervention target prerequisite learning skills such as eye contact, joint attention, sustained attention, sitting tolerance, and compliance. This is followed by individualized interventions based on the child's profile targeting the sensory-motor perceptual difficulties. Language intervention is based on the developmental approach. It focuses on intensive stimulation in a communicative environment based on the motto "Communicate WITH the child, not ABOUT the child". Behavioural challenges are tackled during the therapy as they occur with uniform reinforcements being used by all therapists [11].

Evidence states that the Communication DEALL program results in significant gains in the skills in all eight developmental domains of the CDDC with a parallel improvement in the overall behaviour [14]. Early intervention was also found to be associated with higher rates of children with ASD being enrolled and retained in mainstream schools [15].

While other models of intervention such as Applied Behaviour Analysis, Floor-time (Developmental Interventions), and Early Start Denver Model (NDBI) have proven positive outcomes there is a shortage of experts trained to administer them and are expensive for a resource-limited setting such as ours. It is also imperative that the intervention model is individualized and culturally appropriate to the population that it is targeted at, for maximal benefits. Communication DEALL program is a home-grown indigenous program that has proven to be an efficacious and relatively inexpensive alternative [14].

The approach to ASD has evolved and improved over time. It is important for clinicians and therapists to understand the need to adapt their therapy regime and tailor it individually for each child. The goals of therapy have often been based on neurotypical standards decided by non-autistic people. This has often caused "autistic masking", the phenomenon whereby autistic people often feel the need to mask their autistic features to fit in [16]. Another concern is also the short-term outcomes. While this is essential, it is also equally important to look out for their long-term mental health [17].

Conclusion:

The overarching theme of neurodiversity and acceptance should be kept in mind. The basis of any treatment plan should come from a thorough evaluation of the child's strengths and weaknesses.

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Conflicts of interest

There are no conflicts of interest.

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‘Brain Fogging’ in Special Needs Children: A Post-COVID Neurobiological Enigma

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Abstract

COVID-19 is associated with clinically significant symptoms- post-Covid syndromes, despite its immediate resolution. COVID-19 cases continue to experience the after-effects of the disease including multi-system dysfunctions, thus causing a drain-out of health resources in dealing with its aftermath. Post-COVID-19 syndrome is determined as signs and symptoms that appear during or after an infection consistent with SARS-CoV-2 disease, persist for more than 12 weeks, and are not explained by an alternative diagnosis. This review presents the most frequent neurological complaints associated with COVID-19 along with a recondite of brain fog. In the context of post-COVID-19, Pediatricians, as well as parents, should be aware of a wide spectrum of neurological COVID-19 signs and its association with impairments, commonly called ‘ brain fog’. Further, investigation of the molecular mechanism behind brain fog is suggested. Targeting the newly identified mechanisms may aid in finding newer molecules for treating brain fog. Though in adult Montreal cognitive tests for executive dysfunctions and Mini-mental state examination may help in suspecting it, in children, especially those with neurodevelopmental disorders it remains a challenge to differentiate it in the background of deterioration in performance. A careful history and clinical examination, especially assessing the short attention span in disorders like ADHD, clinches the diagnosis against the post-Covid brain fog. Demonstrating disruption of the blood-brain barrier and sustained inflammation in the brain by dynamic contrast-enhanced MRI may not be always feasible. Most other medical investigations are inconclusive or non-contributory. A battery of psychological tools may help decipher the differences post-covid may help in analyzing the effects and subsequent corrective actions.

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- Brain fog; Brain invasion
- Cognitive impairment
- COVID-19
- Post-acute COVID-19 syndrome
- Brain fog
- Long-COVID syndrome
- Neurological problems
- Neurodevelopmental disorders.

Introduction:

COVID-19 caused by infection with the Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is known for its increased risk of neurological complications like encephalopathy, encephalomyelitis, ischemic stroke, intracerebral hemorrhage, anosmia, and neuromuscular disorders. Sometimes these symptoms following the infection may remain persistent [1] and were known differently as Post-Covid syndrome, permanent COVID-19, Long Covid syndrome, Brain fog, etc.; but of late they have been bought under the umbrella term- Post Acute COVID-19 Syndrome(PACS) [2,3]. This entity is defined by various studies as the continuation of acute SARS-CoV-2 infection symptoms and/or sequelae for more than 4–12 weeks following the start of initial

symptoms [4,5]. A recent meta-analysis presents the global prevalence of PACS as 43%, with 54% of it occurring after hospitalization and 34% occurring in outpatients [6,7]. Brain fog was reported between 2% and 44% of children with long COVID, in a recent study [8]. A recent meta-analysis by Lopez-Leon et al. looked into 21 cohort studies covering a total population of 80,070 and found the persistence of Long COVID symptoms in 25.2% of children affected by acute COVID-19 [10]. This systematic analysis also throws light on neuropsychiatric symptoms in children, accordingly, mood swings, fatigue, sleep disorders, and cognitive dysfunctions (manifested by learning difficulty, lack of concentration, memory loss, and confusion) contribute to the pre-existing problems in children with NDD's.

Numerous neurological issues, such as encephalitis, cerebral venous embolism, micro- and macro hemorrhage, and encephalopathy, manifesting as delirium, altered levels of consciousness, and loss of various memory are reported with COVID-19 infection. This is collectively called "Cognitive Covid" [9]. Brain fog is a general nonmedical term used to describe cognitive impairment and confusion. A 6-month neurodevelopmental follow-up using the Bailey Scale of Infant Development done on high-risk new-borns who had Covid infection during the neonatal period showed significant deficits in the various developmental domains with motor domain (62.5%), cognitive domain (56.25%) and language domain (62.5%) affected [11]. Children with severe infections had more neurologic symptoms such as impaired vision, skeletal muscle impairment, and an elevated level of C-reactive protein in the plasma which may be related to macrophage activation syndrome [12]. A study done by Munblit et al. gives recommendations for selecting outcomes for assessment and quality data, based on which for the domain of cognitive functioning, outcomes to be quantified are confusion, concentration impairment, and memory impairment [13]. Unlike in adult studies that used the Montreal cognitive assessment or the MMS examination, in children, such tools have age and accuracy limitations [14]. A recent systematic review identified that post-Covid children developed concentration difficulties, indicating possible impairments in memory, and information processing speed, poor attention control, delirium, and psychiatric symptoms [15].

These observations were supported by other studies that reported that concentration difficulties, attention impairment, and memory deficits were common in children with long-Covid syndrome. Further, they noted that cognitive symptoms were more common among female children, with cognitive and neurological symptoms being more common [16,17]. Deficits like attentional issues, working memory deficits, decreased processing speed, and executive dysfunctions were reported in a recent study [18]. This can have devastating effects on academic performance, more so in children with neurodevelopmental disorders. Long Covid syndrome was not found to be different in children when compared with adults, especially in the concentration and memory domains, which was proven by a recent study in which [18F]-FDG PET scan showing hypo metabolism in the pons, cerebellum, and bilateral amygdala, uncus, and parahippocampal gyrus [19]. The hippocampus is an important part of memory formation. The parahippocampal cortex (PHC) is a major part of the medial temporal lobe which lies between the hippocampus and fusiform cortex. It helps in visuospatial processing and episodic memory, in addition to networking with multiple areas of the brain. PHC is been attributed to emotional processing, center-periphery organization along with the ventral visual stream, and a host of other functions including contextual associations [20]. Hence, the devastating effect COVID-19 can have on the developing brain concerning skill acquisition can be understood, especially in social and educational aspects.

Brain fog- a PACS nightmare or separate entity:

Executive functioning, memory encoding, processing speed, category fluency, recall, and post-COVID-19 course deficits are some of the cognitive impairments found during both the subacute phase and the subsequent course with both initially moderate and severe COVID-19 [21]. Fatigue and cognitive deficiencies coexist, frequently resulting in highly restricting, excessive, subjective exhaustion on a physical, cognitive, and/or psychological background [22,23]. The neuropsychological basis of "brain fog" can be explained by the slower information processing speed. Information processing speed is very much

crucial for securing academic goals and overall social growth in children. A recent study on the prevalence of brain fog after the Omicron variant found that 7% of post-Covid children had brain fog and 70% had cognitive impairment at 12 months' post-infection with disturbed sleep and behavioral issues complicating it [23]. It may be noted that researchers have found that the 'cognitive covid' also varies with the strain affected. With the original virus and with every subsequent strain cognitive decline was noted when compared to controls. The greatest decline in IQ was noted with the original strain (before December 1, 2020) and the early B.1.1.7 (alpha) variant (from December 1, 2020, to April 30, 2021). A 3- 3-point loss equivalent of cognitive decline in those with mild infection and a 6-point equivalent decline in IQ was noted in those with persistent symptoms [24].

It has been observed that many neuro-divergent conditions like ADHD and Autism children experience "brain fog" even otherwise, often related to sensory overload, meltdown, and stress. Brain fogging also has been reported before with chemotherapy and other illnesses. Brain fog can also be brought on by stress, overworking, and sleep deprivation. Long-COVID (Brain fog) symptoms may mimic ADHD, but ADHD can be distinguished by a short attention span, difficulty in focusing and multitasking, and executive dysfunction. The differentiation becomes difficult in the predominantly inattentive form of ADHD as forgetfulness, difficulty in concentrating, and following instructions are shared commonalities between the two conditions. Analysis of a few neurodevelopmental disorders revealed that ADHD had a causal relationship with 'hospitalized' COVID-19, while tuberose sclerosis conferred a causal relationship with 'critical admissions' for COVID-19, whereas Autism did not demonstrate any causal relationships [25]. Quite often, many neuropsychiatric symptoms of long COVID may be dismissed as common autism symptoms in ASD children. A recent case series reports that such presentations are common in ASD and the possible long-term activation of monocyte cytokines as a cause [26]. Whether this is a consequence of hypoxia, inflammation, or vascular damage to various connected regions of the brain or a separate entity in itself, like encephalopathy, continues to be an enigma.

Brain fog- due to direct viral invasion or consequence?

Brain fog may also be referred to as Neuro-fatigue; common in those who have had a brain injury, posttraumatic stress disorder (PTSD), or other mental or neurological problems. This fatigue or sleepiness is not the same as exhaustion caused by physical activity, insufficient sleep, or overworking. Confusion, forgetfulness, and a lack of attention and mental clarity characterize it.

Confusion, forgetfulness, loss of concentration, and mental clarity are symptoms of brain fog. Stress, sleep deprivation, and excessive internet usage among children with special needs can all contribute to this. This will manifest as poor concentration, spacing out, insomnia, confusion, thinking more slowly than usual, mood swings, fuzzy thoughts, forgetfulness, lost words, mental fatigue, etc. [27, 28]. This difference is glaring in NDD, especially in those well-behaved children with specific learning disabilities.

According to research, brain inflammation is the root cause of brain fog [29]. Brain fog is thought to be cellular, induced by high levels of inflammation and hormonal changes that affect mood, energy, and focus. An infection with SARS-CoV-2 can cause the body to produce immunological molecules that harm vascular endothelium, causing platelet aggregation and forming clots. Additionally, proteins seep out of the blood vessels, causing inflammation and neuronal death. When exposed to COVID, the immune hyperactivates, causing a simmering but eventually subsiding inflammation in the brain, or the virus itself directly damages the brain [30]. Though post-COVID cognitive impairment has been reported in many studies, including a few review articles, with most occurring in severe COVID-19 infection requiring ICU care, cognitive issues including decreased attention, and memory loss had been reported even in mild patients managed on an OP basis [31].

Mechanism of Brain fog:

Though a lot of studies have been done to examine the various aspects of cognitive symptoms, no single source has provided a thorough explanation of all the variables and how they interact that could contribute to the "brain fog" that patients feel. Scientists have attributed this to many

aspects like hypoxia-induced damage, a surge in proinflammatory mediators, autoimmune activation leading to neuronal damage, microglial activation, and direct nerve tissue invasion [32]. Recent studies have shown that neuropilin-1, a membrane protein that is highly expressed in neurons, is one of the factors that helps SARS-CoV-2 enter nervous system cells. Researchers also found microstructural alterations in the hippocampus and other brain regions, following Covid-19; which makes one believe that cognitive deficits might potentially be caused by these alterations [32]. However, SARS-CoV-2 RNA was not found in CSF in most published studies, and intrathecally produced SARS-CoV-2-directed IgG antibodies cannot be blamed for PCS [33]. In addition to usual mechanisms like hypoxia, and hippocampal atrophy following a vascular injury or after severe lung damage, there can be other contributors like a surge in proinflammatory mediators/ immune response or chronic inflammation. Interestingly, neurofilament, a marker of neuronal degeneration, is frequently elevated during acute infection with neurological manifestations, but not in PACS patients. This shows that an ongoing damage of neurons may not be the reason for brain fog; rather, it would result from a functional impairment of neurons. Neurons in the brain that are injured can't interact with one another. This may be one of the factors contributing to brain fog [34].

The orbitofrontal cortex controls emotion, pleasure, mood swings, depressive feelings, reasoning, and decision-making. The PHC also plays a critical role in emotion regulation, processing of spatial awareness, and memory recall [20]. An infection with COVID-19 affecting these areas can result in depression and anxiety, which can impair memory in a child- known as brain fog. Atrophy of the brain was also reported following Covid-19. They found that the virus especially in mild infection, did not affect the neurons, and produced brain fog through the mechanism with the cytokines/chemokines like CCL11. This supports the view that 'brain fog' acts through a mechanism similar to 'chemofog' a similar condition that presents in those who undergo chemotherapy for malignancy [32]. Of late a very recent study has come out with evidence for the reasons for brain fog. By doing dynamic enhanced contrast MRI, it was found that long-term blood-brain barrier disruption and sustained systemic inflammation result in Brain fog [35].

In related research on long-Covid, researchers have found that symptoms were related to lower circulating levels of serotonin through RNA virus-driven activation of type 1 interferon which decreases absorption of tryptophan (precursor of serotonin) and circulating serotonin (inside platelet) through hypercoagulability. This reduction in circulating serotonin levels by impeding the vagal stimulation impairs the hippocampal responses and memory. Considering the shreds of evidence available so far, a pictorial expression of the possible mechanism leading to this new issue affecting humans is proposed as in Figure 1.

Thus brain fog has been explained with a combination of various neurobiological processes, but a conclusive opinion remains elusive making it a continuing enigma.

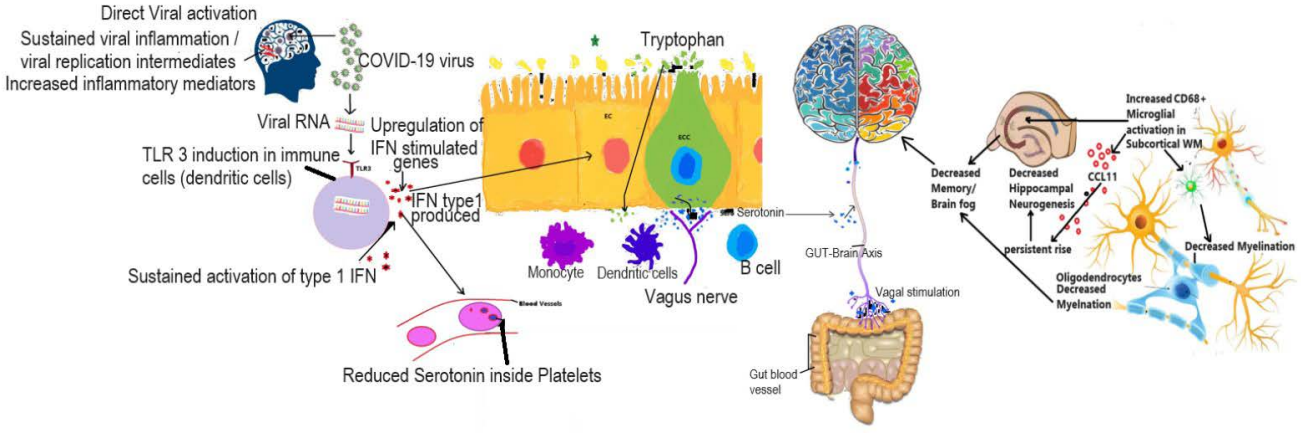

Figure:1 Pathophysiology behind Brain fog- neurochemicals, & role of Gut-brain axis

Management:

Managing brain fog can be quite challenging, but there are no specific medications designed solely for treating it. However, addressing underlying factors and maintaining overall well-being can help alleviate brain fog. A multi-pronged approach for the evaluation of cognition, neuro-inflammatory markers, psychological factors, and sleep disorders should be used in the treatment of brain fog [36]. If sleep problems are present, assess disorders such as insomnia, obstructive sleep apnea, or restless legs syndrome in addition to late screen exposure.

Investigations:

Usual Brain MRI, awake and sleep EEG, and cardiological evaluation may be ordered, but are usually non-contributory to the issue at hand. Managing this challenge requires considerable effort on the part of a Developmental Pediatrician/ Pediatrician, as often they have to collaborate with a psychologist/psychiatrist. Parent especially the mother's concern for the child's health may be measured formally using some tools like the "thoughts" subscale of the "Health anxiety scale by proxy scale" or similar tools available. This is a 26-item Likert scale that addresses the intensity of thoughts, feelings, and behaviors of parental concern for the child's health [37]. Similarly, the child's mental health also may need to be assessed using the "*Strength and Difficult Questionnaire*" and Maternal perceptions of child health anxiety can be measured by "Health Anxiety Symptoms," a subscale of the *Soma Assessment Interview*. It is a parental interview assessing children's functional symptoms [38]. Memory may be checked by calculating age-appropriate digit span and clinical judgment. A formal cognitive battery testing may be useful as it often brings out deficits in memory, reasoning, and executive functioning in Brain fog children. Agata et al., have validated a Brain fog scale (BFS) with mental fatigue, impaired cognitive acuity, and confusion which has six items loading on the mental fatigue factor, nine items loading on the impaired cognitive acuity factor, and eight items loading on the confusion factor [39]. Deterioration of the autistic symptoms and the effect of interventions can be reliably quantified using the T-score of CARS-2 rather than the raw score-based severity ratings. ADHD often has severe manifestation due to the inherent nature of the disorder with 'brain fog', even otherwise part of it. Brown ADD scale may become handier in assessing school-going children affected by COVID-19 brain fog than the Vanderbilt ADHD rating scale. Its components viz, activation (organizing and activating to work), attention (sustaining attention& concentration), effort (sustaining energy& effort), affect (managing affective interference), and memory (using working memory and accessing recall) help in quick assessment of the functional impact on the child. PTSD and depression assessment may be considered especially in children admitted to ICUs for a long duration and may be quantified using relevant tools for the same.

Treatment: The few possibilities available for treatment tried in adults are antiviral, Ensitrelvir, which was found to reduce the risk of long COVID-19 when started in the acute phase of COVID-19, and Metformin, when started within 7 days of COVID-19 infection, was shown to reduce the risk of long COVID in an RCT [40].

Brain fog is often accompanied by symptoms of fatigue which makes it difficult especially in activity-based learning attempted in children with special needs. This becomes more troublesome in hypoactive children with genetic autism or clumsy children as in developmental coordination disorder (DCD). Hence while attempting therapy sessions or assessing the deterioration this factor should be in the back of the mind of the paediatrician.

Neuropsychological evaluations are designed to detect cognitive impairments compared to an individual's peer group. They can also serve as a measurable outcome to address the impact of interventions in the treatment of brain fog post-COVID-19. Cognitive rehabilitation used for traumatic brain injury is often recommended for individuals with cognitive complaints. This includes patient education or "psychoeducation" along with training of cognitive skills which were deemed to be a weakness for that individual. This concept may be used by clinicians in the treatment of brain fog in adolescents and may be included as an educational component to provide an overview of brain fog. Such psychoeducation can detail the definition of brain fog, possible etiology, and general factors impacting the recovery process. When this psychoeducation is supported with group intervention with the patient's peers, the

validation, reassurance, and access to qualified healthcare providers can facilitate recovery [41]. Using visual representation to make the learning disabled or NDD child understand will help in the process of counseling.

A brief cognitive-behavioral therapy (CBT) may be considered for older children with primarily cognitive complaints without a clinically significant mental health condition, to support adjustment to illness or disability. Such a brief CBT may include the applying skills required to manage cognitive complaints. Also, mildly symptomatic borderline IQ adolescents disinterested in individual psychotherapy may be offered support through formal or informal groups of other people experiencing persistent COVID-19 symptoms. While a formal evidence-based group treatment can alleviate symptoms, peer-led support groups offer connection and help to decrease feelings of isolation [42].

Other options and lifestyle modifications that could assist in overcoming brain fog include lowering brain inflammation through an anti-inflammatory diet (whole grains, lean meat, and plant-based foods) may help with symptoms of brain fog. Getting regular exercise -150 minutes of physical activity each week is recommended by the Centers for Disease Control and Prevention. Sleep deprivation can either increase or cause brain fog. Though the requirement of sleep for younger children is higher, a typical adolescent may require seven to eight hours of sleep every night to maintain their physical and mental health. Tech-savvy children and adolescents may benefit from strategic online chess. mindful breathing meditation, learning a new language. Guided imagery exercises can reduce stress and reduce brain fog by changing the focus of the mind to peaceful and positive images.

In a recent study on understanding the basis of Brain-fog due to Long Covid syndrome, it was found by single-nucleus RNA sequencing (snRNA-seq) analysis that COVID-19triggered the immune reactions in both microglia and astrocytes, and exacerbated oxidative stress in oligodendrocytes, oligodendrocyte progenitors, and neurons. It was found to inhibit mitochondrial oxidative phosphorylation and suppress the expression of some mitochondrial complex genes. They suggested a holistic approach to protecting mitochondrial complex function, rather than targeting a single molecule, as an effective therapeutic strategy to prevent and treat the long-term consequences of "long COVID" [42]. It is in this context that the information on benefits and fast recovery following intake of some food supplements is to be considered. Fish oil containing long-chain Omega-3 fatty acid-DHA may help in recovery from inflammation [43]. Choline Bitartrate is chemically connected to the vitamin B group. Cell membranes and the synthesis of the neurotransmitter acetylcholine, which is involved in memory and muscular function, both depend on choline. γ-oryzanol was demonstrated to increase the central nervous system's neurotransmitter levels. Additionally, it encourages peaceful sleep and emotional relaxation. Ginkgo Biloba extract with its potent anti-inflammatory, antioxidant, platelet-forming, and circulation-boosting properties has been suggested to enhance mood, bring higher energy, and better memory, enhance cognitive function, and decrease symptoms associated with certain chronic illnesses [44]. Vitamin A, and B complexes not only help in better immune functions, but they also help in healthy cell development and proliferation. Its antioxidant properties shield cells from harm caused by free radicals, which is a further essential role. However, how far these theoretical benefits help in actual management is not conclusively proven.

Conclusion:

Even mild COVID-19 infection can result in a sustained inflammatory response resulting in sustained cytokine/chemokine elevations and disruption of the blood-brain barrier leading to brain fog in children. The effect of serotonin on the hippocampus also adds to the effect resulting in brain fog. The changes in memory, concentration, and confusion seen in children post covid has to be distinguished from the "brain fog" seen in some of the NDDs like ADHD or ASD. In the absence of an effective tool to measure it in children, identifying it clinically may be an option for differentiating it, especially in ADHD and ASD children. Currently, the options are mainly supportive and cognitive rehabilitation with psychological support.

Conflict of interest statement:

We hereby declare that there is no conflict of interest.

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Highlighting the Importance of Newborn Screening in India by Comparative Analysis of Inborn Errors of Metabolism in High-Risk Babies with Methylmalonic Acidemia.

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Abstract

This is a comparative analysis of 7789 high-risk IEM cases, using the example of methylmalonic acidemia (MMA), a rare metabolic disorder to emphasize the critical role of newborn screening in early diagnosis and management. Case 1 involves a patient not diagnosed at birth through newborn screening, while Case 2 involves a patient diagnosed in the neonatal period due to symptom presentation. The differences in their clinical outcomes underline the importance of early detection through newborn screening programs. The MMA was the most common organic aciduria with an incidence of 1:26 diagnosed among 12 common IEMs causing developmental delay, disabilities, or death in high-risk neonates & children. These 12 IEMs (incidence 1: 26 to 409) with high incidence are strongly recommended as candidate disorders for newborn screening programs in India. This paper compares two cases of MMA to illustrate the significant impact of newborn screening.

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Keywords:
- Newborn screening
- IEMs
- High-risk babies
- MMA
- Prevention

Introduction:

Methylmalonic acidemia (MMA) is an inborn error of metabolism (IEM) inherited as an autosomal recessive metabolic disorder [(1)]. The prevalence of MMA is still unknown in Asian countries like India and China but in European countries, USA& Canada, it is around 1/29000 to 1/ 26000[(2)]. MMA is characterized as a genetically heterogeneous disorder of methyl malonate and cobalamin (cbl; vitamin B12) metabolism. MMA occurs due to a defect in mitochondrial enzyme methyl malonyl-CoA mutase (MCM) which converts methyl malonyl-coenzyme A (CoA) into succinyl-CoA, or a defect in the metabolism of 5'-deoxyadenosylcobalamin, the cofactor of MCM methyl malonic acid that leads to Methylmalonic acid in the blood [(3)]. It leads to various health issues which range from lethal to severe including developmental delays, feeding problems, metabolic crises, and death in severe cases. Early diagnosis and intervention are crucial in managing MMA and preventing severe complications.

Currently, universal newborn screening for metabolic disorders is neither a Government health policy nor is it routinely performed in India [(4)]. Diagnosing and managing Inborn Errors of Metabolism (IEM) in India and other developing countries is challenging, as most advanced comprehensive metabolic tests using mass spectrometry are not routinely available. Metabolic evaluation is typically done only in very sick neonates or children with high suspicion of symptoms

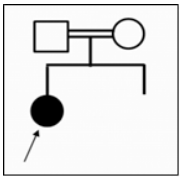
like lethargy, coma, metabolic acidosis, seizures, hyperammonemia, etc [5]. This paper compares two cases of MMA to illustrate the significant impact of newborn screening. The given case comparison underscores the importance of newborn screening programs in India in preventing severe childhood complications and enhancing the quality of life for patients with MMA and best clinical outcomes.

Case presentation:

Patient Details: In the present study, the two cases of MMA are clinically & metabolically compared as below-

Case 1: A female child born of a consanguineous marriage was referred by a pediatrician for Whole Exome Sequencing at 1 year of age due to a history of lethargy, vomiting respiratory distress since day 1 of life, and severe metabolic acidosis. The patient had not undergone newborn screening as it was not routinely available as a government health policy for newborn screening. Unfortunately, the child passed away by the time the exome report was available (Case 1-Pedigree) (Figure 1).

Figure 1: Case 1-Pedigree analysis



The Whole Exome Sequencing by NGS revealed a mutation in the MMAA gene, but no screening or metabolic workup had been performed initially (Table 1).

Table 1: The Whole Exome sequencing of Case 1 showing details about gene mutation

Gene (Transcript)	Location/ Variant	Zygosity	Disease (OMIM)	Inheritance/ Classification
MMAA (NM_172250.3)	Chr4:146575176 c.850G>T / p.Asp284Tyr)	Homozygous	Methylmalonic Aciduria, cblA Type (OMIM#251100)	Autosomal Recessive, Variant of Unknown Significance

Case 2: A 20-year-old boy has been following with us for the last 20 years with his parents (Figure 3). He had undergone newborn screening by urinary GCMS testing at 1 month of age during NICU. During the neonatal period, he presented with metabolic acidosis, refusal to feed, and failure to thrive. The mother noticed similar clinical symptoms in an earlier sibling who had died at the neonatal stage with severe metabolic acidosis and other similar symptoms (Figure 2) and hence became alert of the situation & informed the neonatologist.

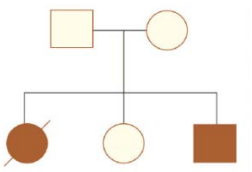


Figure 2: Pedigree analysis of Case 2

The metabolic workup was quickly undertaken and urinary GCMS analysis confirmed the diagnosis of MMA. The therapy management of the baby was quickly started with a high dose of cobalamine, folate &carnitol, etc. along with Sodium benzoate for acidosis over a long period and normal growth was achieved (Figure 3). He has been since then appropriately put on a low protein & high carbohydrate diet and periodic monitoring with urinary GCMS analysis every 6 months to monitor the abnormal biomarkers of MMA. The diet & dose adjustments were done if high abnormal markers of MMA were detected.

(A) **(B)**

Figure. 3: A) Neonate diagnosed with MMA; B) Same patient at the age of 20 years.

Investigation:

The urine samples of high-risk cases were sent to the laboratory along with detailed family, birth & clinical history. The pedigree charts were drawn as shown for Cases 1 & 2 (Figures 1 & 2). The routine metabolic tests for ammonia, lactate, ABG analysis, etc. were informed. The urine-soaked, air-dried filter paper was sent in the envelope for Gas Chromatography/Mass Spectrometry (GCMS) metabolic profiling which is a non-invasive method for simultaneous analysis of 140+ metabolic conditions (Figure 4). The urine sample was processed for GC/MS analysis & data was analyzed using the method of Matsumoto &Kuhara (1996) [6].

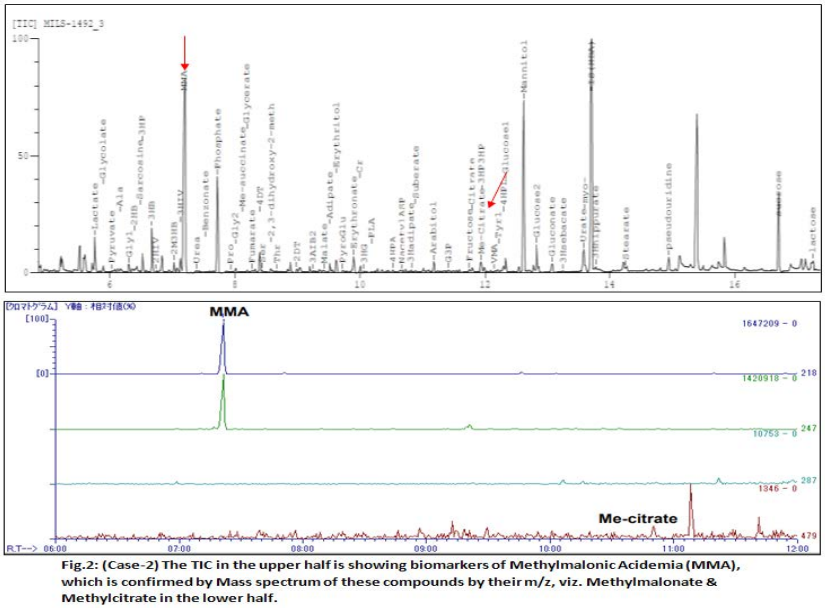


Fig.2: (Case-2) The TIC in the upper half is showing biomarkers of Methylmalonic Acidemia (MMA), which is confirmed by Mass spectrum of these compounds by their m/z, viz. Methylmalonate & Methylcitrate in the lower half.

Figure 4: The TIC in the upper half shows biomarkers of Methylmalonic Acidemia (MMA), which is confirmed by the Mass Spectrum of these compounds by their m/z, viz. Methylmalonate & Methylcitrate in the lower half.

Management & Outcome:

Later, at the age of 19, genetic counseling was done to the family members, emphasizing the identification of mutation for familial inherited condition which is significant for further prevention of the disease in the family. Next-Generation Sequencing (NGS) identified a mutation in the MMADHC gene (Table 2). This gene is involved with Combined MMA and homocystinuria cblD type (MAHCD) and or isolated homocystinuria, and isolated MMA of complementation group cblD. However, as per the phenotypes& mass spectrometry correlation patient was suffering from Combined MMA and homocystinuria cblD type (MAHCD).

Table 2: The Whole Exome sequencing showing details about gene mutation-Case2

Gene (Transcript)	Location/ Variant	Zygosity	Disease (OMIM)	Inheritance/ Classification
MMADHC ENST00000428879	Chr 1p34.1 Exon 3/ c.202C>T(p.Gln68Ter)	Homozygous	Combined MMA a and homocystinuriacblD type (MAHCD), isolated homocystinuria, and isolated MMA of complementation group cblD	Autosomal recessive, Pathogenic

Early detection and precise diagnosis at 3 months of age led to appropriate therapy with vitamin B12, carnitine, and biotin, along with periodic metabolic profiling. The patient's clinical status has shown improvement, and he is currently being monitored at the age of 20 years; going to college for finance studies indicating normal intellectual development.

Discussion:

The periodic data analysis revealed MMA as the most common organic aciduria in 7789 referral high-risk cases with an incidence of 1:26 among 12 IEMs which showed high incidence varying from 1in 26 to 1 in 409 (Table-3).

The results of this comparative analysis offered evidence of the profound impact of newborn screening on the outcomes for patients with MMA. In Case 1, the absence of newborn screening resulted in a delayed diagnosis, leading to severe metabolic acidosis and the eventual death of the patient (refer to Case 1 Pedigree – Figure 1). The lack of early intervention and metabolic workup significantly contributed to the poor outcome. The exome report, which came too late, confirmed a mutation in the MMAA gene which revealed VUS but strongly correlated with the clinical phenotypes. The case offered evidence that early detection and intervention could have potentially altered the clinical course.

Table 3: Recommendation of 12 NBS Disorders Based on Overall Incidence of IEMs in 20 Years

High- Risk Screening Data by GC/MS Comprehensive Test (2005-2024)

* Overall Incidence of 12 IEMs is 1: 26 to 1: 409 (2024 Analysis)

Total N = 7789; Normal = 5805 (75 %); IEM Abnormality = 942 (12 %)

Sr. No	Inborn Error Of Metabolism	2005 N= 2040 Abn = 176 - 8.6%	2015 N= 3341 Abn= 291- 8.7%	2020 N= 6510 Abn=681 – 10%	2024 N= 7789 Abn= 942-12%
1.	Methylmalonic Acidemia (MMA)	1: 55 (37)	1: 64 (52)	1: 30 (214)	1: 26 (291)
2.	Tyrosinemia / Hepatic Dys	1: 78 (26)	1: 88 (38)	1: 72 (55)	1: 90 (86)
3.	Hyperglycinemia	1: 146 (14)	1: 119 (28)	1: 171 (38)	1: 185 (42)
4.	Glutaric AciduriaType1	1: 102 (20)	1: 90 (38)	1: 90 (73)	1: 94(82)
5.	Galactosemia	1: 136 (15)	1: 176 (19)	1: 130 (50)	1: 86 (90)

6.	Maple Syrup Urine Disease(MSUD)	1: 156 (13)	1: 239 (14)	1: 99 (66)	1: 89 (87)
7.	Propionic Acidemia (PA)	1: 170 (12)	1: 176 (19)	1: 105 (62)	1: 101(77)
8.	Urea Cycle Disorder (UCD)	1: 170 (12)	1: 134 (25)	1: 186 (35)	1: 194 (40)
9.	Fructose-1,6-Diphosphatase Def. (FDPD)	1: 136 (15)	1: 134 (25)	1: 217 (30)	1: 149 (52)
10.	Multiple Carboxylase Def. (MCD)	1:510 (4)	1: 257 (13)	1: 260 (25)	1: 216(36)
11.	Isovaleric Acidemia (IVA)	1: 680 (3)	1: 835 (4)	1: 591 (11)	1: 409 (19)
12.	Beta-Ketothiolase deficiency	- -	1: 304 (11)	1: 383 (17)	1: 194(40)

In contrast, Case 2 benefited from newborn screening, which facilitated early diagnosis and prompt initiation of appropriate therapy. The newborn screening by GCMS at 1 month of age allowed for the identification of MMA, enabling timely treatment with vitamin B12, carnitine, and biotin and normal development. The patient's condition was closely monitored through periodic metabolic profiling, ensuring the absence of abnormal markers and preventing severe complications. The subsequent NGS at age 19 years provided further insights into the pathogenic mutation in MMADHC gene at Chr 1p34.1 Exon 3/c.202C>T (p. Gln68Ter) inherited as autosomal recessive responsible for the congenital metabolic disorder (Table 2). The patient has shown significant clinical improvement and continues to lead a better quality of life; at present studying for finance graduation and is well aware of his diet and regular medicine, highlighting the efficacy of early detection and ongoing management.

Conclusion:

The study highlights a dire need for comprehensive newborn screening programs for preventable IEMs using mass-spectrometry to ensure early detection and management of not only Methylmalonic Acidemia (MMA) but also 12 common preventable metabolic disorders. Early diagnosis through newborn screening facilitates timely and appropriate interventions, substantially improving patient outcomes and quality of life. The significant contrast in outcome between the two cases in this study emphasizes the life-saving potential of newborn screening in preventing severe complications associated with MMA. Thus, it is imperative to adopt widespread newborn screening practices to promptly identify and manage various preventable childhood congenital metabolic disorders like MMA. This proactive approach can prevent fatalities, reduce morbidity, and enhance the overall health and well-being of affected individuals.

Since the majority of the IEMs are also autosomal recessive genetic disorders, genetic counseling about the recurrence risk& nature of inheritance is essential for families who have/ had one affected child. Many cases are asymptomatic and undetected; hence, we report this case to underscore the importance of newborn screening programs, including MMA for early detection and intervention. Early screening, confirmed diagnosis, and preventive measures can improve survival rates, prevent childhood morbidity & mortality, and thereby subsequently reduce a national burden.

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Conflicts of interest : There are no conflicts of interest.

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