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Official Journal of IAP Chapter of Neurodevelopmental Pediatrics

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Editorial Board

EDITORIAL ADDRESS

Dr. Zafar Mahmood Meenai
Director, Ummeid Child Developement Centre,
Z-30, Meena Tower, Polytechnic Main Road, Civil Lines, Bhopal-462002
Mobile : +91-8989039786 **Email :** editor.ijdbp@gmail.com
Journal Website : https://ijdbp.in **Chapter Website** : https://iapndp.org

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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

Leveraging Indian Socio-Cultural assets in Neurodevelopmental Intervention

Neurodevelopment is the acquisition of new skills for new functions commensurate with the age of the growing child. Normal Development depends on neuronal maturation as well as environmental sustenance. Neurodevelopmental disorders are group of conditions associated with an insult to the developing brain which results in impairment of normal neurological functional developmental skills.

While the role of genetic and biological factors is well recognised, the role of social risk factors is largely underestimated, inadequately addressed or submissively dismissed. In India, given the difference in family structures and values as well as societal norms, the entire gambit of social operation is significantly different, especially compared to developed countries. The latter have a completely different social milieu; it is pertinent to comprehend that the western journey of developmental disorders has been shaped in that mileu.

When we read western literature, we appreciate the methodologies for therapy. But we are confounded by the limitation of resources as prescribed by western methods- both professional and financial. To us, the battle then swings towards a socio-economic perspective and we set our measures of success by the ability to provide western methods in a 'resource-limited' 'lower and middle income country' setting. Indeed, these have now shaped our agenda- how best can we provide western interventions in an Indian setting. Our deliberations then veer towards awareness of this limitation, followed by provision within limited resources. Almost most research space is occupied by this struggle. Research is then set in the context of providing western methods in an Indian setting.

And hence, while there is a need to validate western methodologies to our population, there is a greater need to set up constructs and paradigms within our own socio-cultural mileu.

For example, if we consider ABA or sensory integration in autism, we set our measure of clinical success by how much we can provide ABA or sensory integration therapy with our limitation of trained personal and finances. Our efforts are driven towards bridging this gap, our success defined by our ability to provide them. To do this, we recruit the parents and families. We train our parents to 'do therapies'. Parents do their best to replicate the same methods. Involving families so deeply allows us to label these Endeavour's as holistic- another word which has been coined to lend credibility to our efforts. Thus, socio cultural strengths are leveraged to bridge socio economic liabilities. Local research proceeds to scientifically document the success of these measures, thus validating them. We have succeeded in providing western science in Indian settings. That becomes the outcome.

However, socio cultural differences have far greater strength than that which is being leveraged for. Mechanical mimicry is a low hanging fruit and does not make the intervention holistic. Holistic is when the intervention goes beyond engaging professional help. Cloaking family support in the garb of therapy is far from that. Holistic would truly mean using the inherent social strength of families to directly impact the difficulties the child has - not merely to repeat therapeutic activities. Can the ordinary and regular parents and families intervene with the child within the ambit of the home and neighbourhood to enable the child to overcome her difficulties, without turning into therapists first? - this then would make it truly holistic. This would be effectively leveraging socio cultural norms like family values and bonding in the Indian setting to make the intervention holistic, rather than just replicating professional therapy at lesser cost.

Western paradigms are far different from Indian ones, especially when it comes to developmental behavioural pediatrics. The effect of the behaviour of care givers is surely far greater than in other medical disciplines. The role of parents, families, homes, neighbourhoods, schools- indeed society, is of far greater impact than in say, pediatric cardiology or even neurology. The role of the chacha, bua, kaaki, maamaa (uncles and aunts) in promoting or restoring normal development is of enormous important. Even the norms and the questions that establish these normative evaluations, assessments and interventions – the very tools- need to be indigenised to reflect our environment.

Thus, harnessing the inherent and powerful mahashakti (great power) of families and the community in the Indian scenario is likely to be the next area of work in the field of neurodevelopmental disorders. The next decade will decide if we continue in approximating the methodologies of western science or indigenise intervention to leverage our socio cultural strengths. I am hopeful prudence will overcome.

Dr Samir Hasan Dalwai,

Advisor, Indian Journal of Developmental Behavioral Pediatrics.

Developmental Behavioural Pediatrician, Director : New Horizons Child Development Centre,

Mumbai

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EDITORIAL

The Mantra for every child with special needs should be inclusion & empowerment. For this to happen ICF (International Classification of Functioning, Disability and Health) checklist, it's wide application and extensive use can be a game changer. This is a checklist of major categories of the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization, The ICF Checklist is a practical tool to elicit and record information on the functioning and disability of an individual. It is important to understand the difference between ACTIVITY LIMITATIONS & PARTICIPATION RESTRICTION

Activity is the execution of a task or action by an individual. Participation is involvement in a life situation. Activity limitations are difficulties an individual may have in executing activities. The Capacity qualifier indicates the extent of Activity limitation by describing the person ability to execute a task or an action. The Capacity qualifier focuses on limitations that are inherent or intrinsic features of the person themselves. These limitations should be direct manifestations of the respondent's health state, without the assistance. By assistance we mean the help of another person, or assistance provided by an adapted or specially designed tool or vehicle, or any form of environmental modification to a room, home, workplace etc. The level of capacity should be judged relative to that normally expected of the person, or the person's capacity before they acquired their health condition.

Participation restrictions are problems an individual may have in involvement in life situations. The Performance qualifier indicates the extent of Participation restriction by describing the persons actual performance of a task or action in his or her current environment. Because the current environment brings in the societal context, performance can also be understood as "involvement in a life situation" or "the lived experience" of people in the actual context in which they live. This context includes the environmental factors – all aspects of the physical, social and attitudinal world that can be coded using the Environmental. The Performance qualifier measures the difficulty the respondent experiences in doing things, assuming that they want to do them.

It is in this backdrop that individualised intervention program for attainment of maximum potential for every child with special needs should be planned.

Best Regards

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

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Guidelines on Oral Health Management for children with special health care needs (SHCN)

Dr. Shilpi Tiwari [1] , Dr. Parimala Kulkarni [2], Dr. Zafar Meenai [3], Dr. Shikha Mali [4], Dr. Anoop Kumar [5], Dr. M Srinivas [6], Dr Pallavai Shrivastava[7], Dr Deepak Dwivedi[8], Dr Medha Panchanadikar[9], Dr Noopur Panchanadikar[10], Dr Leena Srivastava[11]

1. Professor, Department of Pedodontics and Preventive Dentistry, People's College of Dental Sciences & Research Centre, Bhopal-462037, Madhya Pradesh, India. E-mail: shilpi.tiwari1@gmail.com, 2. Professor and Head, Department of Pedodontics and Preventive Dentistry, People's College of Dental Sciences & Research Centre, Bhopal-462037, Madhya Pradesh, India. E-mail: drtyagip@gmail.com, 3. Head and CEO, People's Department of Child Development and Early Intervention, People's College of Dental Sciences & Research Centre, Bhopal-462037,Madhya Pradesh, India. E-mail: drzafarah@gmail.com, 4. Reader, Department of Pedodontics and Preventive dentistry, People's College of Dental Sciences & Research Centre, Bhopal-462037. Madhya Pradesh, India. E-mail: shikha9290@gmail.com, 5. Senior Lecturer, Department of Pedodontics and Preventive dentistry, People's College of Dental Sciences & Research Centre, Bhopal-462037.Madhya Pradesh, India. E-mail: pedodonticsdr.anup@gmail.com, 6. Senior Lecturer, Department of Pedodontics and Preventive dentistry, People's College of Dental Sciences & Research Centre, Bhopal-462037. Madhya Pradesh, India. E-mail: moudgalya.king@gmail.com, 7. BDS, MDS, LLB, Director, Chirayu Hospital & Research Centre, Rewa, 8. MD, PGDDN, Professor Pediatrics, SS Medical College, Rewa, 9. Medical Dental Sciences, Consultant Pediatrics Dentist, 10. MDS, Consultant Pediatric Dentis, Panchanadikar Clinic, Pune, 11. Head, Division of Developmental & Behavioral Pediatics, Department of Pediatrics, Bharati Vidyapeeth University Medical College and Hospital Pune

Corresponding Author: Dr Zafar Mahmood Meenai, Editor-In-Chief, Indian Journal of Developmental & Behavioral Pediatrics (IJDBP), Bhopal. E-mail: editor.ijdbp@gmail.com, Phone: +91 8989039786

Introduction:

Children with special health care needs (SHCN) are those who have medical, developmental, behavioral, or emotional conditions that require more extensive and specialized health care than typically developing children(1).The importance of oral hygiene maintenance for children with Special health care dentistry cannot be overstated.(2) Good oral health not only prevents dental problems but also contributes to better overall health, improved social interactions, and a better quality of life.However, due to the unique challenges faced by these children, it is essential to develop tailored oral hygiene guidelines that take into account their specific needs and abilities. (3) In this guide, we will provide evidence-based recommendations for maintaining good oral hygiene in children with special health care needs, based on the latest research and best practices in pediatric dentistry.(4) Table number 1 discuss different dental problems faced by children of special needs.(5)

Table no 1 General oral and dental problems faced by children of special needs and there predisposing factors

Poor oral hygiene
- Cognitive and motor concerns leading to dependence on others
- Parental neglect
- Pseudobulbar palsy
- Oral aversion due to sensory issues
- Reduced food clearance due to oro-motor impairment

Dental plaque and caries
- Poor oral hygiene
- Chronic administration of syrups
- Gastroesophageal reflux
- Enamel hypoplasia due to kernicterus
- Reduced food clearance due to oro-motor impairment
- Xerostomia due to drugs

Periodontal disease and gingivitis
- Poor oral hygiene and dental caries
- Gingival hyperplasia commonly with long-term phenytoin and less common with valproate, phenobarbitone or carbamazepine.
- Alveolar bone loss with carbamazepine or phenytoin.

Traumatic dental injuries
- Fall associated with seizures.
- Hyperactivity and other behavioral issues.
- Self-mutilation behaviors.

Chronic dental erosions
- Bruxism.
- Malocclusion

Hypodontia

Sedation and anesthesia

General Guidelines For Children With Special Health Care Needs

Maintainance of Daily Oral Hygiene: The most important part of maintaining good oral health for special children is daily oral hygiene. It includes brushing teeth, tongue cleaning, rinsing,and a healthy diet.

Brushing Teeth: Supervised brushing should be done twice dailly(6)it should be started as soon as possibleThe American Academy of Pediatric Dentistry (AAPD)recommends using a smear or rice grain-sized amount of fluoridated toothpaste for children under three years of age .For children three to six years old, a pea-sized amount of fluoridated toothpaste is recommended.However,

it is crucial to consider the specific needs and circumstances of each child and consult with their dentist for personalized guidance(7).

Adapt Toothbrush: Caregivers can adapt toothbrushes to make brushing easier for children with special needs. They can use a toothbrush with a larger handle or attach a grip to the toothbrush handle to make it easier to hold. They can also use an electric toothbrush that can help children with limited dexterity(8).

Tongue Cleaning: Tongue cleaning, using tongue scrapers or brushes, should be incorporated into the oral hygiene routine of children with special healthcare needs. It helps remove bacteria and debris from the tongue surface, promoting oral health. Individualized approaches, adaptations, and supervision may be necessary based on the child's abilities and preferences.

Rinsing: Rinsing withwater after meals and snacks can help remove food particles and reduce the acidity in the mouth(6). Close supervision is essential to ensure safe and effective rinsing. Adapted Approach for rinsing can be utilized which includes using a specialized rinse cup, visual cues or instructions, or utilizing assistance from caregivers. Use a rinse solution recommended by the dentist or healthcare professional that is safe for children and addresses specific oral health needs. Avoid rinses with alcohol content, as it may cause irritation or discomfort(8–10).

Healthy Diet: A healthy diet that is low in sugar and high in vitamins and minerals can help maintain good oral health. Caregivers should avoid giving sugary and acidic foods and drinks that can erode tooth enamel.(11)

Dental Check-Ups: According to the AAPD, children with special healthcare needs should have routine dental checkups every 3 to 6 months, depending on their individual needs and oral health status. These frequent visits allow for close monitoring of oral health, preventive care, and timely intervention if necessary.(8) Depending on risk category high/moderate/low Caries risk screening can be eased to six months interval for those who do not have Caries and every three months for moderate and high risk caries patients.

Stages of prevention of dental disease in children: In paper published in Indian pediatrics chandna et al has divided different stages of prevention of dental diseases in children. (6)

Stage 1- Pregnancy : This stage needs to managed same as it is for a typically developing healthy child and is beyond the scope of this review. Readers are advised to read the abovementioned review for the same.

Stage 2 - Infancy : Infants with SHCN are at increased risk for oral diseases because of compromised immunity, cardiac conditions, defective oro-facial complex, etc as mentioned in table no 1. When parent of these children visit then a detailed patient assessment of infants condition should be done and discussed with parents regarding risk of the child for having various dental problems. Box. 1 mentions guidelines for parents to check there infants oral cavity .

Box no 1. Parental guidelines for checking infants mouth (12)

1. Parents should begin checking their child's mouth once a month as soon as teeth begin to appear.
2. Wash your hands before you begin.
3. Lift your child's upper lip.

4. Look at their gums and teeth.
5. Try to examine the inside and outside of the tooth surface.
6. As the child gets older, check back teeth.
7. Early decay may appear as white or brown spots.
8. Contact your dentist if you notice any problems.
9. Make sure to schedule regular dental check-ups every 3 to 6 months, depending on their individual needs and oral health status to ensure early detection and treatment of any oral health issues.(12)

Brushing Your Infant and Toddler's Teeth

- **Before Teeth Arrive:**

Using a clean wet cloth or gauze, gently wipe the gums, inside the cheeks, outside the lips, and along the tongue twice a day.(13)

- **After Teeth Begin to Arrive:**

Continue wiping your child's mouth with clean wet cloth or gauze until teeth arrive.

After more teeth have arrived, brushing should be done twice daily using a soft bristle, small head toothbrush/ finger toothbrush with a smear layer of fluoridated toothpaste.(14)

- **Technique of brushing to be followed:**

Choose a time after feeding when your infant is not fussy or overly tired.Cradle your infant's head with one arm and wipe or brush with the opposite hand.Place your infant on a changing table, bed, floor, or lap.Sing, talk, and smile with your infant while cleaning his teeth to make it a positive experience.

Be an example; allow your toddler to watch you brush your teeth. This helps teach and reinforce the importance of good oral hygiene.(15)

Ensure that the child spits out the toothpaste after brushing to avoid swallowing too much fluoride18

Talk to your dentist or pediatrician about any concerns or questions you may have about brushing your infant's teeth.

- **Teething and the Child with Special Needs**

1. Teeth may come in at different rates for all children, and children with developmental problems may take longer to get their baby teeth and adult teeth.
2. Children with developmental problems have a greater chance of bite problems.
3. Common signs of teething include discomfort, restlessness, irritability, loss of appetite, and waking during the night. Chewing on toys and fingers is very common. The amount of saliva may increase, causing your child to drool more and cough as they try to clear their throat.
4. To sooth your infant while teething give your child chewing objects such as a cold, wet washcloth or a hard, solid teething ring.
5. Make sure to schedule regular dental check-ups every 3 to 6 months, depending on their individual needs and oral health status to ensure early detection and treatment of any oral health issues.(12)

- **The Pacifier and Your Infant's Dental Health(16)**

1. Choose a pacifier that is solid and made of a nontoxic material with a ventilated shield to prevent swallowing.
2. Do not tie the pacifier to clothing.

3. Avoid dipping the pacifier in sweetened foods like sugar, honey, or syrup.
4. Discourage pacifier use after your child reaches 18 months of age to reduce the risk of dental problems.

Dental home concept: The dental home concept (10,12)was developed analogous to the concept of 'medical home'. Patients with SHCN who have a dental home are more likely to receive appropriate preventive and routine care. The dental home provides an opportunity to implement individualized preventive oral health practices and reduces the childs risk of preventable dental/oral disease. The dental home is inclusive of all aspects of oral health that result from the interaction of the patient, parents, nondental professionals, and dental professionals. Establishing a dental home should be done within 6 months of eruption of the first tooth and no later than 12 months of age.

Stage 3 - First dental visit : The American Academy of Pediatric Dentist recommends that the first oral examination should occur within 6 months of the eruption of the first primary tooth, and no later than age 12 months of age. Thereafter the child should be seen according to a schedule recommended by the dentist, based on the child's individual needs and susceptibility to disease.(6)

Stage 4 - Care of deciduous dentition : It should be done as per typically developing children.(6)

Brushing Your Preschooler And Middle Schooler Child:

- Supervised brushing should be done twice daily using a soft bristle, small head toothbrush with a Pea sized of fluoridated toothpaste in a circular motion for 3-6 years old children. (14)
- Provide assistance and supervision: Some children with special healthcare needs may require assistance or supervision during brushing. Caregivers should be actively involved in the process to ensure thorough cleaning and proper technique.
- Create a toothbrushing routine with music, a favorite cup for rinsing, and a consistent daily routine.
- Ensure that the child spits out the toothpaste after brushing to avoid swallowing too much fluoride18
- Rinsing-Demonstrate and assist by showing the child how to rinse their mouth properly. Assist them as needed, guiding them to swish the rinse around their mouth and spit it out into a sink or cup.If the child is unable to rinse and spit effectively, start with small amounts of water or a diluted mouth rinse and gradually increase the volume as their skills improve. Always supervise the child during rinsing to ensure they are using the rinse safely and not swallowing it. If necessary, use a fluoride rinse specifically recommended by the child's dentist.(8,15)
- Tongue cleaning-Select a tongue cleaner or scraper that is suitable for the child's age and abilities. Look for tools with a small head and a handle that is easy to grip.Show the child how to clean their tongue properly. Assist them as needed, guiding them to gently scrape the surface of their tongue from back to front to remove any buildup or debris.If the child has difficulty using a tongue cleaner, start with alternative methods such as gentle brushing of the tongue using a soft-bristled toothbrush. As the child becomes more comfortable, introduce the tongue cleaner gradually.Always supervise the child during tongue cleaning to ensure they are using the tool safely and not causing any harm to their mouth. Teach them to rinse their mouth thoroughly with water after tongue cleaning. (8)
- Healthy diet-Encourage a well-balanced diet that includes a variety of nutrient-dense foods from different food groups. Include fruits, vegetables, whole grains, lean

proteins, and healthy fats in their meals.Work with the child's healthcare team, including their pediatrician and dietitian, to develop an individualized meal plan that takes into account their specific health condition, dietary restrictions, and nutritional needs.(11)

- Consider the use of remineralizing agents such as Casein phosphopeptide--amorphous calcium phosphate (CPP-ACP) in the management of early childhood caries or tooth demineralization. (9,17)Instruct parents or caregivers on the proper application of CPP-ACP. It can be applied topically as a paste or cream directly to the teeth or incorporated into other dental products such as toothpaste or mouth rinses.

Make brushing easier for Special Health Care Need Children:

- Use a lying down position to brush your child's teeth.
- Place your child's head on your lap or on the floor while keeping their head steady with your legs.
- If your child is standing, have them stand with their back to you and their head tilted slightly, resting against your body.
- Have your child stand in front of a bathroom mirror while brushing their teeth so they can see what is being done.
- Establish a toothbrushing routine that includes playing music, setting things up, and using a favorite cup for rinsing. Singing a song during brushing can also be helpful.
- If your child is able, let him brush his own teeth first, then brush them again yourself. Encourage him to spit out the toothpaste after brushing.
- Depending on risk category high/moderate/ low Caries risk screening can be eased to six months interval for those who do not have Caries and every three months for moderate and high risk caries patients.

Brushing Your Adolescent:

- Supervised brushing should be done twice daily using a soft to medium bristle(13), small head toothbrush with a full length of fluoridated toothpaste for 10-19 years old children.(14)
- Brushing technique-Assistive devices and adaptations like electric tooth brushes,modified toothbrush handles, adaptive grips, or specialized toothbrushes designed for individuals with special needs can be used to encourage effective brushing(18,19) These adaptations can improve their ability to grasp and maneuver the toothbrush effectively. Visual and tactile cues can also be incorporated to guide the adolescent during teeth brushing.
- Consider the most comfortable and effective positioning for the adolescent during teeth brushing. This may include using a supportive chair, adjustable headrests, or cushions to ensure proper alignment and effective positioning for optimal access to the mouth.
- Encourage 45-degree angulation of the toothbrush bristles along the gumline and ensure adequate time is spent on each quadrant of the mouth. 45-degree angulation involves positioning the toothbrush bristles at a 45-degree angle to the gumline. It allows for effective cleaning at the gumline, where plaque tends to accumulate. It may be suitable for adolescents who have sufficient motor skills and can manage the angulation without causing discomfort or injury.Encourage brushing for a minimum of 2 minutes during each brushing session. This ensures adequate time to clean all tooth surfaces thoroughly. (10,20)
- Gentle circular motions can also be done if 45 degree angulation is not possible
- Ensure that the child spits out the toothpaste after brushing to avoid swallowing too much fluoride.(12)

- **Rinsing Technique:**Encourage the adolescent to take a small sip of water and swish it around the mouth for about 30 seconds before spitting it out.Teach them to tilt their head slightly forward to prevent water from going down the throat and causing choking.
- Tongue cleaning should be practiced in a similar way as mentioned for preschoolers and middle schooler children.

Oral Hygiene Practices For Children In A Wheelchair

- Method 1: Stand behind the wheelchair. Use your arm to brace the individual's head against the wheelchair or against your body. Consider using a pillow so that the person is comfortable.
- Method 2: Sit behind the wheelchair and, remembering to lock the wheels of the wheelchair for safety, tilt the wheelchair back into your lap.

Changing A Toothbrush:

- Change toothbrushes every three months or sooner if the toothbrush bristles are worn out(21).
- Provide Replacement Toothbrushes: Ensure that an adequate supply of replacement toothbrushes is available for the child or adolescent.
- Educate caregivers about the importance of regularly replacing toothbrushes and provide guidance on appropriate toothbrush selection.

Guidelines For The Application Of Fluoride Supplements

- In the case of children with special health care needs, the decision to use fluoride supplements should be based on their individual circumstances, oral health status, and consultation with a healthcare provider or pediatric dentist who is familiar with their specific needs.
- When considering fluoride supplements for children with special health care needs, the healthcare provider or pediatric dentist will take into account factors such as the child's age, risk for tooth decay, fluoride exposure from other sources, and any medical conditions or medications that may affect their oral health.
- The American Dental Association (ADA) and the American Academy of Pediatric Dentistry (AAPD) provide some general guidelines regarding the use of fluoride supplements:

-Infants: Fluoride supplements are not typically recommended for infants younger than 6 months old. At this age, if the water supply is deficient in fluoride, it may be appropriate to use ready-to-feed formula with fluoride or consider breastfeeding.

-Children 6 months to 3 years: If the child's primary source of drinking water contains less than the optimal level of fluoride (less than 0.6 parts per million), fluoride supplements may be considered after consultation with a healthcare provider or pediatric dentist. The decision to use supplements should be based on an assessment of the child's risk for tooth decay.

-Children 3 years and older: Fluoride supplements may be considered if the child's primary drinking water source is deficient in fluoride. The decision to use supplements should be based on an assessment of the child's risk for tooth decay and consultation with a healthcare provider or pediatric dentist.(7,22,23)

Management of children suffering from dental illness:Children who are diagnosed to have dental illness should be referred to a pedodontist for further management.

Conclusion: In conclusion dental illnesses are an important ailment for children with special needs. Brushing and oral hygiene should be started as soon as possible. There are various modifications required in SCHN population for brushing. These children should be screened timely and should be referred to a pedodontist is any feature of dental illness is recorded.

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RESEARCH ARTICLE

Prevalence and pattern of specific learning disabilities among middle school students in Chennai city

Rabindran Chandran [1], Darshini Madanagopal [2], Rema Chandramohan [3]

From: 1 Assistant Professor, Department of Neonatology, Sri Ramachandra Institute of Higher Education and Research, Chennai, TamilNadu, India, 2 Assistant Professor, Department of Allied Health Sciences, Sri Ramachandra Institute of Higher Education and Research, Chennai, TamilNadu, India, 3 Professor of Pediatrics, Director, Institute of Child Health, Egmore, Chennai, TamilNadu, India

Correspondence:
Rabindran Chandran, Email: rabindranchandran@gmail.com

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Abstract:

Purpose: Specific learning disability (SLD) impedes ability to learn specific academic skills. The objective of study was to determine SLD prevalence among middle school students in Chennaiand estimate difference in prevalence based on gender and age & relationship between various types of SLD.

Methods: A Cross Sectional Survey using Expost Facto research design was adopted. Source population was government middle school students of fifth, sixth and seventh standards. Study period was November 2019-November 2020. Using purposive random sampling, 344 students were enrolled. Those with score average, above average and intellectually superior in Raven's Progressive Matrices IQ Assessment were included and those with defective and below average were excluded. NIMHANS Index was used to assess SLD. Using confidence interval (95%), relative error(5%), z for 95% C.I. (1.64), ε(5%), N(11645), p̂(15%), required sample size was 138. Data was analyzed using SPSS-19, MedCalc, Descriptive statistics, Pearson Product Moment correlation, ANOVA and 't' test.

Results: Among 144 students, Spelling Dyslexia (13.88%), Reading Dyslexia (16.66%), Dysgraphia (7.63%), Dyscalculia (2.08%), memory deficits (10.41%) and attention deficits (10.41%) were noted. All SLDs were more in boys. Significant gender difference occurred in mean scores of Spelling Dyslexia and Memory Deficit and percentage scores of Reading Dyslexia and Dysgraphia. Spelling and Reading dyslexia had significant correlation with Memory deficit. Significant difference in Spelling Dyslexia, Memory deficit and Raven's score was noted in various age groups.

Conclusion: The study provides insight to higher SLD prevalence and advocates developing school curriculums, inclusive of this population.

Keywords: Specific learning disability, NIMHANS index, Dyslexia, Attention Deficit

Introduction: Specific learning disability (SLD) is a type of Neurodevelopmental Disorder that impedes ability to learn or use specific educational skills [DSM-5 315 &; ICD-10-CM] [1]. SLD includes difficulties in specific processing areas like "Dyslexia, Dysgraphia,

Dyscalculia, Dyspraxia, Perceptual disabilities and Developmental aphasia"[2]. Children with SLD are unable to acquire their age appropriate cognition, language and analytical skills inspite of adequate learning opportunities, intellectual capacity, appropriate sensory systems and physical abilities. Children who have learning problems due to visual/hearing defect, motor handicaps, mental retardation, emotional disturbance, environment, cultural or economic disadvantage are not considered to have SLD. The spectrum of SLD consists of 1) Reading dyslexia, which is the commonest affecting 80% of all those identified as learning-disabled [3]. They have errors in oral reading skills like omissions, substitutions, distortions or additions of words; slow reading rate, long hesitations, word reversals and deficits in reading comprehension; 2) Dysgraphia - Dysgraphic children have problems in handwriting, spelling or organizing concepts. It affects around 4% of school children [4]; Dyscalculia - These children have lack of understanding of mathematical signs and numerical symbols. Prevalence ranges from 3-14% [4]. SLD Prevalence is influenced by factors such as heterogeneity of definitions, clinical assessment tools, study design and population demographics. Tests for SLD have two major components: Testing for Potential: Performance Discrepancy and Testing Processing skills. A two-year discrepancy between potential and performance is an indicator of possible SLD [5].

Rationale for study: No other disabling condition affects so many people and yet has such a low public profile and low level of understanding as SLD [6]. Given the immense consequences of SLD in academic performance & issues with its identification in Indian schools, there is a need to gain insight about extent of presence of SLD among middle school students. It is vital to identify SLD early before poor school performance and its attendant emotional sequelae sets in. Prompt diagnosis and timely intervention will improve their self-confidence and social competency. Prevalence of various types of deficits of scholastic skills was reported to be 3-10% among Indian student population [7]. Moreover, prevalence studies are rare with respect to SLD as compared to general learning disabilities due to general lack of awareness of its symptoms. Since there is a paucity of studies on SLD done in Chennai, present study was conducted to fill in research gap.

Aims and Objectives:

1. To estimate prevalence of various types of SLD among middle school students in Chennai.

2. To determine difference in prevalence of SLD if any between gender and age.

3. To find out relationship between various types of SLD.

Material & Methods:

Study Design: A Cross Sectional Survey using Expost Facto research design was adopted. This studywas conducted in two levels. In level one, overall prevalence was surveyed. In level two, connection between various types of SLD and impact of gender and age on SLD was studied.

Study Setting: Government schools in Chennai. Chennai was purposively sampled for two reasons. First, there was few number of studies on prevalence of SLD and secondly, Chennai covers a large number of Government Schools.

Source Population: Middle school students studying in fifth, sixth and seventh standards.

Study Population: Study population included 344 students of which 140 (59 boys,81 girls) were from Corporation Middle School (CMS) Manjakollai, 133 (72 boys, 61 girls) were from CMS Arumbakkam and 71 (44 boys, 27 girls) were from CMS Aminjikarai. Totally 175 boys and 169 girls were studied. Consent was taken from parents and assent was taken from participating students.

Study Period: The study was conducted from November 2019 to December 2020.

Selection Criteria: Raven's Progressive Matrices was administered to selected students (N= 344) toidentify IQ level. Those who were intellectually defective (N=32) and below average (N=168) were excluded. Students who were intellectually superior (N=2), above average (N= 25) and Average (N=117) were then administered part of NIMHANS Index of SLD.

Inclusion Criteria: Students studying in fifth, sixth and seventh standards whose score was average, above average and intellectually superior in IQ Assessment who consented for the study were included.

Exclusion Criteria: Students whose IQ Assessment score was defective and below average, those with intellectual disability, sensory deficits (Visual/ Hearing impairment) and physical impairment and those diagnosed with any other psychiatric conditions were excluded from the study.

Sampling Design:Written permission was taken from commissioner of education for conducting study. Random sampling was done. Study was conducted in 3 schools randomly allotted by education officer.

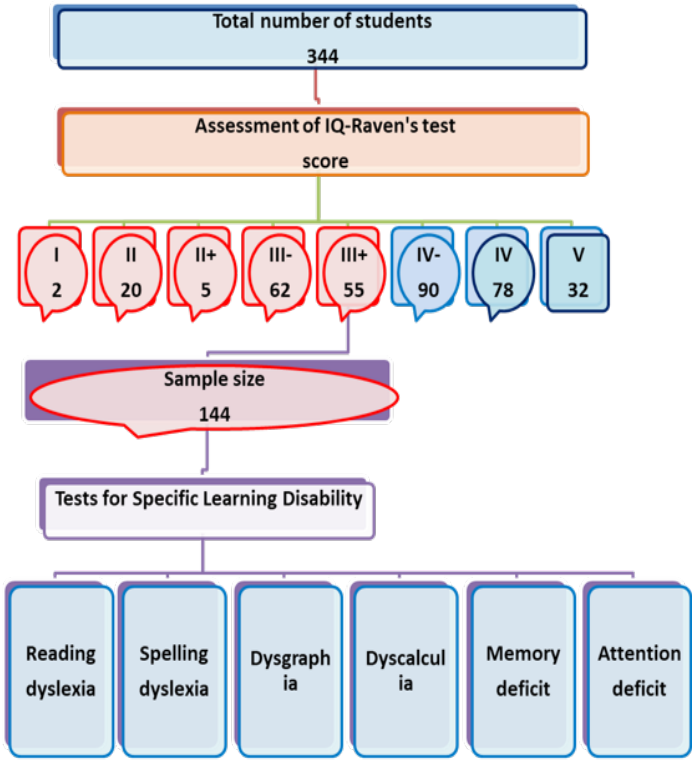
Sampling Procedure:

Sample Size :According to Government of Tamil Nadu Department of Economics and Statistics-District Statistical Hand Book Chennai District 2016-2017 there are 185 institutions in Chennai providing middle school education, with 11645 students studying middle school out of which 6260 were boys and 5385 were girls. So middle school population strength was taken as 11645 [8]. Being a finite population, following formula was used for sample size estimation.

$\acute{n}$ = n divided by 1+ [$\{z^2 x\ \hat{p}\ (1-\hat{p})\}/\ \varepsilon^2 N$]

where z is z score; ε is margin of error; N is population size; $\hat{p}$ is population proportion. Sample size was calculated based on reported SLD prevalence of 15% [9]. Being a social study with small total population 95% confidence interval and relative error of 5% was taken. z for a95% confidence level is 1.64; ε, margin of error is 5%; N, population size is 11645; $\hat{p}$ proportion is 15%. Applying the formula, required sample size for this study is 138children.

Figure 1- Flowchart of Sampling Process



A total of 144 students with 67 Boys and 77 Girls in age ranging from 9 to 13 years were selected for study.

Research tools used in study: Raven's Progressive Matrices was used for initial IQ assessment. Test-retest reliability (N = 968) of Raven's test ranged between 0.69 and 0.85, while Cronbach coefficients alpha ranged from 0.88 to 0.93, showing acceptable to good temporal stability and good to high internal consistency.

[10]. Raw score results was then converted to percentile ranking. NIMHANS Index is widely used for assessing SLD in India. Reliability is 0.53 and criterion validity 0.75 [11]. It has 2 levels. Level I is for children between 5-7 years and Level II is for children between 8-12 years. Level II comprises of following tests Attention (Number Cancellation); Language Test (Reading, Writing, Spelling and Comprehension); Arithmetic(Addition, Subtraction, Multiplication, Division and Fractions) and Memory (Auditory and Visual). Modified Kuppuswamy scale (Feb 2019) was used to stratify study population [12].

Data Collection: Socio-economic data of study population was collected in standard proformas. Raven's IQ test was administered. Scores from Spelling test, Maths test, Attention test and Memory recall test were collected. Handwritten copies were analysed for dysgraphia. Individually reading test was conducted. All collected data were entered in excel sheet.

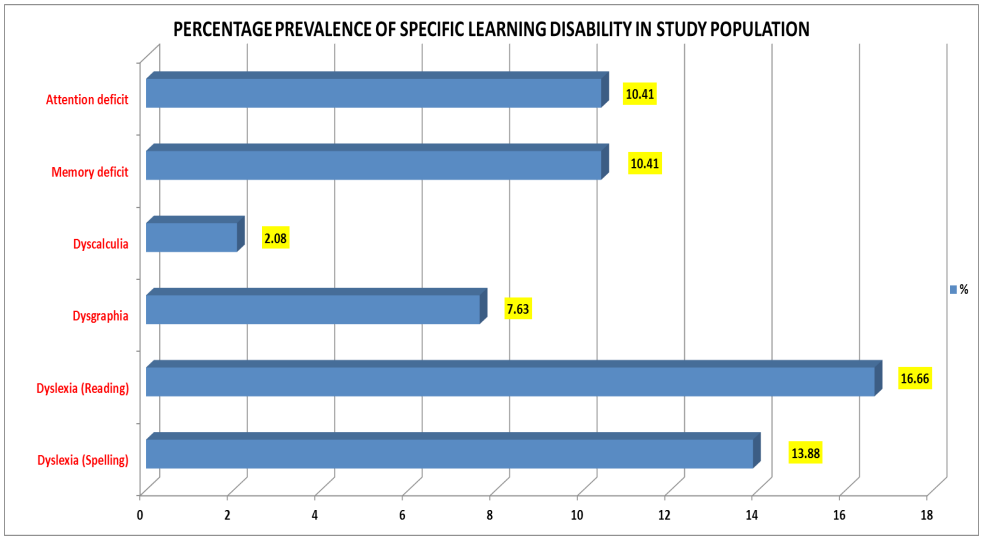
Statistical Analysis: Data collected was analyzed using Statistical package for Social Sciences (SPSS-19) and Med Calc. Quantitative data were analyzed using descriptive statistics. Pearson Product Moment correlation was used to findthe relationship between various types of SLD. Independent 't'-test was done to find out significant difference in SLD between genders. ANOVA was done to find out significant difference in SLD between different age groups and among students with different Raven's scores.

Results:

Among 144 students, 78(54.16%) were from CMS Manjakollai, 43(29.86%) were from CMS Arumbakkamand 23(15.97%) were from CMS Aminjikarai. Majority 77(53.47%) were girls. Around 33(22.91%) were 9 years, 63(43.75%) were 10 years, 16(11.11%) were 11 years, 27(18.75%) were 12 years and 5(3.47%) were 13 years old. Around 99(68.75%) were Fifth standard students, 15 (10.41%) from Sixth standard and 30 (20.83%) were Seventh standard students. Majority107(74.3%) belonged to Socio-Economic status IV and 36(25%) belonged to status III. Among 144 students, 61(42.36%) were first born, 56(38.88%) were second, 17(11.8%) were third and 7(4.86%) were fourth child. Majority (97.91%) were right handed. Majority 90(62.5%) belonged to nuclear family. Around 71(49.3%) belonged to small size family, 67(46.52 %) belonged to medium size and 6 (4.16 %) belonged to large size family.

Prevalence of SLD:

Figure 2- Percentage prevalence of SLD in study population



As depicted in Figure 2, 20 children (13.88%) had Spelling Dyslexia, 24(16.66%) had Reading Dyslexia, 11(7.63%) had Dysgraphia, 3(2.08%) had Dyscalculia, 15(10.41%) had memory deficits and 15(10.41%) had attention deficit.

Table 1- Correlation Coefficient of various types of SLD

	Attention Deficit	Memory Deficit	Spelling Dyslexia	Dyscalculia	Raven	Dysgraphia	Reading Dyslexia
Attention Deficit	-	0.2376	0.2461	0.2473	0.1758	0.1723	0.1967
Memory Deficit	-	-	0.7433	0.2276	0.3007	0.2268	0.5056
Spelling Dyslexia	-	-	-	0.1731	0.3952	0.2579	0.4419
Dyscalculia	-	-	-	-	0.1930	0.0234	0.1589
Raven	-	-	-	-	-	0.0591	0.1822
Dysgraphia	-	-	-	-	-	-	0.2222

As depicted in Table 1, Correlation coefficient between Spelling Dyslexia and Memory deficit was particularly high at 0.7433. Correlation coefficient between Memory deficit and Reading Dyslexia was also high at 0.5056. Hence, null hypothesis-1 stating that, "Various types of SLD will not be related to each other" was rejected.

Prevalence of SLD with respect to gender: Prevalence of various SLD was higher in Boys as compared to girls. Comparing Boys vs Girls, Spelling Dyslexia was 19.4% vs 9.09%, Reading Dyslexia was 23.88% vs 10.38%, Dysgraphia was 16.41% vs none, Dyscalculia was 2.98% vs 1.29%, Memory deficit was 13.43% vs 7.79% and Attention deficit was 11.94% vs 9.09% respectively.

Table 2- Comparison of percentages of SLD between boys and girls

	Boys (%)	Girls (%)	CHI SQ	DF	P
Dyslexia (Spelling)	19.4	9.09	3.162	1	0.0754
Dyslexia (Reading)	23.88	10.38	4.67	1	0.0307
Dysgraphia	16.41	0	13.585	1	0.0002
Dyscalculia	2.98	1.29	0.50	1	0.4796
Memory deficit	13.43	7.79	1.213	1	0.2707
Attention deficit	11.94	9.09	0.31	1	0.5779

As depicted in Table 2, Difference in dysgraphia between boys and girls was most significant with p value 0.0002. Reading dyslexia was also higher in boys as compared to girls with significant statistical difference of 0.0307 which was significant ($p < 0.05$). Hence, null hypothesis-2 stating that, "Boys and Girls will not differ significantly in various types of SLD" was rejected.

Prevalence of SLD with respect to age: Prevalence of Spelling Dyslexia among students of age 9 was 9.09%, age 10 was 17.46%, age 11 was 18.75%, age 12 was 7.4% and age 13 was 20%. Prevalence of Reading Dyslexia among students of age 9 was 6.06%, age 10 was 23.8%, age 11 was 25%, age 12 was 7.4% and age 13 was 20%. Prevalence of Dysgraphia among students of age 9 was 6.06%, age 10 was 6.34%, age 11 was 25%, age 12 was 3.7% and age 13 was 0%. Prevalence of Dyscalculia among students of age 9 was 3.03%, age 10 was 1.58%, age 11 was 0%, age 12 was 3.7% and age 13 was 0%. Prevalence of Memory deficit among students of age 9 was 9.09%, age 10 was 17.46%, age 11 was 0%, age 12 was 3.7% and age 13 was 0%. Prevalence of Attention deficit among students of age 9 was 9.09%, age 10 was 7.93%, age 11 was 25%, age 12 was 11.11% and age 13 was 0%.It was found that prevalence of Spelling Dyslexia was highest among students in 11 years (18.7%) and 10 years(17.4%) age group. Prevalence of Reading Dyslexia and Dysgraphia was highest among students in 11 years age around 25% in each. Prevalence of Dyscalculia was highest among students in 12 years (3.7%) age group. Prevalence of memory deficit was highest among students in 10 years (17.4%) age group and attention deficit was highest among students in 11 years (25%) age group. The score in Memory test was significant ($p=0.043$) when ANOVA analysis was done between age groups 9,10,11,12 and 13 years. Spelling dyslexia was also significantly different between age groups ($p=0.016$). Hence, null hypothesis-3 stating that, "Students of different ages wouldn't differ significantly in various types of SLD" was rejected.

Discussion: Prevalence of SLD: Prevalence of Spelling Dyslexia in our study was 13.88% which was comparable to Kumar and Suman (12.31%) [13] & Mogasale et. al., (11.2%)[14]. Reading dyslexia was note d in 16.66% which is higher than Mogasale et.al (11.2%)[14], Sheetal et al., (10%)[15] and Calicut study (8.2%)[16]. We noticed dysgraphia in 7.63% which was lower

than Mogasaleet.al., (12.5%)[14]. Dyscalculia was lower (2.08%) in our study as compared to Mogasaleet.al., (10.5%)[14] and Dhanda et al.,(15.54%)[17]. Sree Chithira Thirunal Institute of Medical Sciences showed 8-10% of school population had SLD[18].

Prevalence of individual learning disabilities among children with SLD: Among children with learning disabilities 24(48%) had Reading Dyslexia, 20(40%) had Spelling Dyslexia, 15(3%) had attention deficits, 15(30%) had memory deficits, 11(22%) had dysgraphia and 3(6%) had Dyscalculia. Neeraja et al., also found that among children with SLD, majority 94% had Reading problems, 81.7% had writing problems and 78.3% had problems in Mathematics[19].

Prevalence of SLD with respect to gender: In our study Reading dyslexia was higher in boys, 23.88% as compared to 10.38% among girls.Boys: Girls ratio for Reading dyslexia was around (4:1) as per Goswami U et al.,[20], Smith etal.,[21] and Shaywitz, S. et al.,[22]. In our study Dysgraphia was higher in boys, 16.41% as compared to 0% among girls which was similar to Katussic SK et al.,[23], Berninger VW etal.,[24] and Smithet al.,[21]. In our study Dyscalculia was higher in boys, 2.98% as compared to1.29% among girls which was similar to Barbaresi WJ et al.,[25]. Male preponderance was attributed to a referral bias in school-identified children[26].

Prevalence of SLD with respect to age: We found that Reading Dyslexia, Spelling Dyslexia, Attention Deficit and Dysgraphia was highest among 11 years and Dyscalculia was highest among 12 years age group students. Dhanda et al., also observed that SLD was higher in higher age group[17].

Conclusion: Prevalence of Spelling Dyslexia was 13.88%, Reading Dyslexia was 16.66%, Dysgraphia was 7.63%, Dyscalculia was 2.08%, Memory Deficit was 10.41% and Attention Deficit was 10.41%. There was difference in SLD based on Gender and Age. There was a statistically significantly positive relationship between various types of SLD. The study provides insight to higher SLD prevalence and advocates developing school curriculums, inclusive of this population.

Limitations: This study was limited to a sample only from Chennai, only from Government schools, and from fifth, sixth and seventh standards only.

Policy Implications: The study provides an insight to higher rate of SLD which would help teachers and parents to understand the causes of scholastic backwardness. The study results strongly advocate needfor developing school curriculums which are more inclusive of this population.

Suggestions: Future research can be more inclusive with regard to different boards of education, can be done at a younger at-risk age population and in rural setting to get a more holistic picture of SLD. With statistics of present study, Government can definitely think about adapting relevant teacher training courses, bringing changes in curriculum and in methods of teaching.

Key Messages:

What is already known: Our educational system has over emphasis on memory reproduction and theory rather than application which is not suitable for children with SLD.

What this study adds: Present study aimed at finding SLD prevalence apart from being descriptive also gives idea on where to work on to improve conditions of such students.

Keywords: Specific learning disability, NIMHANS index, Dyslexia, Attention Deficit

Abbreviations:

SLD - Specific Learning Disability

NIMHANS-National Institute of Mental Health and Neuro Sciences

CMS - Corporation Middle School

Declarations:

Compliance with Ethical Standards

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Ethics approval: Clearance from Institutional Ethics Committee was obtained on 24/10/2019, Ref Oct 2019 before proceeding to Education Department, Greater Chennai Corporation to obtain permission to conduct research. Written permission was obtained. E.D.C.NO. A3/11650/2019 Dated 07/11/2019.

Consent to participate and to publish; Written informed consent to participate and to publish data was obtained from the parents. Informed assent was obtained from all individual participants included in the study. Participants willingly cooperated in giving required information without coercion or bribery.

Authors' contribution statements: All authors contributed to the study conception and design. Conceptualization, Material preparation, data collection and analysis were performed by Dr. Rabindran Chandran & Dr. Darshini Madanagopal. The study was supervised by Dr. Rema Chandramohan. The first draft of the manuscript was written by Dr. Rabindran Chandran and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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From Cradle to Classroom– The hazardous leap of early childhood

Dr Samir Hasan Dalwai
Advisor, Indian Journal of Developmental Behavioral Pediatrics.
Invited Guest Editor
Developmental Behavioural Pediatrician, Director : New Horizons Child Development Centre, Mumbai
samyrdalwai@gmail.com

The current ideological confusion and obsession with gadgets within the younger generation arises from deeper psycho-socio-cultural changes in society, especially within the realm of parenting, early childhood development and the gradual erosion of neighbourhoods.

"Doctor, I'm worried that my child comes home from school crying that a couple of boys tease him and hit him. How can I make my child hit back?"

This is not an uncommon situation in a pediatrician's clinic. While it is absolutely essential to oppose bullying, is this best done by teaching your child to be aggressive and physically hit back?

Today, parenting is largely left to 'common sense". As can be seen here, the latter is often times a knee jerk reaction, and not the application of intelligence but the reflexive response of the primitive or limbic brain.

As humans evolved within the animal kingdom, genetics worked on the inherited brain to go beyond the 'fight or flight' binary. This modification was largely in terms of what we call 'higher functions' like rational thought, communication, delaying gratification and, as Yuval Noah Harari popularly noted (Sapiens: A Brief History of Humankind) the ability to think as and for a large group. Thus, over hundreds of centuries our brain adapted itself perfectly to settled community living. Children were born in families and reared in neighbourhoods. With 24-hour- days being squeezed more into seconds than minutes, with multi-tasking monotonous rigour, it is easy to lapse into the sordid but easy comfort of binaries- strong vs weak, right vs wrong, good vs evil, and eventually, us vs them. And this happens more than ever in the laboratory of parenting. As our children are born and develop in an increasingly binary world, fraternity, equality, social causes, morality, empathy are all beginning to get coloured with the tunnelled vision of quick-fix, poorly thought through, machismo solutions.

This makes for an interesting regression. What the binary largely does is replace higher order cortical functioning with a paradigm and pervasive shift towards short term, narrow, self-serving, emotional decision-making. The real victims of this lilt are reasoning and empathy and the gradual loss of ability to resist impulsive thinking. Parents increasingly report that their children lack empathy - this is not due to the presence of some evil gene but rather the lack of practice of reasoning and reasonable thinking in multiple social situations involving families and neighbourhoods. Increasing rates of suicides are reportedly due to a lack of resilience- an ability which develops as children are

nurtured within diverse experiences to come to terms with failure. Instant gratification and lack of human engagement at very young ages have led to altered human behaviours like poor attention span and impulsivity and abysmally poor coping skills leading to tantrums and phobias.

Amidst this, the pervasive onslaught of electronic gadgets has vitiated the environment beyond the point that existing genes can deal with, and we have a young population that proclaims itself to be Gen Z but is truly as vulnerable as never before. A mother told me that her eighteen-month old needs the screen to eat; if the network drops or the wi fi falters for a minute, the child flings herself backwards flailing her hands and feet and starts screaming. A visibly stressed father shared that his four year old son was diagnosed to be obese, but he is already habituated to directly order food over popular food apps. Parents of adolescents request help to connect with their children who represent a 'lost generation'- inhabitants of a digital world with poor adaptability and resilience in the real world. This generation, they lament, are unable to connect with others during family get-togethers, are extremely rude and seem to have no insight into their behaviour. Though we have red flagged the impact of climate change, the impact of recent environment on children's mental and behavioural development has gone relatively unnoticed.

Placing a screen before an eight month old is the easiest way to make her finish her porridge- quickly allowing the parent to return to the next work-from-home meeting. The child continues to find solace in the screen. This gradually weakens the infant's skills of interaction within the home. The isolation of children begins in the family home but is complete in the neighbourhood. A child weaned on screens is unlikely to learn social manoeuvring due to scant interaction with diverse neighbours; neither do neighbours have time to indulge little ones. In fact, the neighbourhood is prominent by its absence today. As political scientist, Ajay Gudavarthy describes it, 'living together, separately' is the reality for most of urban India's children. Parents have scant need for neighbourhoods, being focussed entirely on academic carriers. And all the social manoeuvring children should have learned in the neighbourhood is expected to be learned in a few weeks of a swank pre-school! This dangerous leap 'from cradle to classroom' bypasses the scaffolding of family and neighbourhood, hitherto essential components of human rearing over thousands of generations. Lev Vygotsky immortalised the place of both in developmental biology with his theory of the zone of proximal development- the human infant learns from those closest to herself, thus developing early skills that can be used to then connect and learn with those further away. Taking away the human scaffolding renders gaps as children are unable to connect and establish secure and nurturing relationships in the community. This reinforces their attention towards screens. In the proverbial chicken and egg situation, it is difficult to say who came first- the aggressive courting of fragile attentions by screens or the forsaking of gentle minds that were reaching out to those in their proximal environment only to be ignored.

Schools are no longer the inclusive and assimilative spaces they were for all classes and castes. Name calling and prejudice over food or clothing is now common place in classrooms. Children are bullied or boycotted over the choice of food or clothes. Busy parents underestimate and brush them off as just another 'issue that doesn't concern me' - the matter cuts far deeper. A mother complained to me once about the bullying her 7 year old was subjected to since his namesake was a notorious international terrorist. It is not only her child who is traumatised. It is important to understand that the children who

see others being bullied are equally affected - either traumatised into silence and fear, or beginning to enjoy the sadistic terrorising of a weak peer.

Parents lament they are helpless to prevent this. Stopping screens is just not practical today. You cannot deny a generation the fruits of their predecessor's toil. Post –liberalisation, the neo middle class has become the new bourgeois and refuses to give up their share for those they left behind the poverty line not long ago. Similarly, the young cannot be persuaded to give up their bright screens. It is their political inheritance that is at fault here, not just the shiny lights.

Isolation of family members to be replaced with screens, banishing neighbourhoods for the blind dash towards schooling, are sudden changes in the environment we have been exposed to over the past couple of decades- something mankind has not had time to evolve for and deal with. This provokes anxiety and opens the doors towards doubts, fears, and suspicion. Flaws in early childhood are very difficult to rectify later. It may not be apparent at an individual level or in the near term, but will certainly and inexorably lead us towards an increasingly disturbed and hostile society.

And the advice to their child 'to hit and come home, rather than be hit' is where the fault line defines itself. The middle class has been made to give up the luxury of quality time for the carrot-and-stick model of economic survival. Many parents manifest not-so-latent aggression lurking beneath a thin veneer of civility. Tough but common instances in daily life are all it takes to shatter this surface. And the lesson is not lost on the child. Thus, both sides of the parent-child equation are increasingly hostage to narratives that peddle consumerism or toxic hatred and prejudice.

Solutions may not be as impossible as they seem. The potential damage to young minds, either by poor social interaction, affects society as a whole, even trans-generationally, rather than merely harming individuals. Yet, from a developmental perspective, this battle must be fought at the individual level. Every child must be provided a nurturing scaffolding of care, acceptance and love- the only way to draw her into a trusting and conducive relationship with the world around her. Redeeming the priceless worth of families – co inhabiting with a chacha, maama, kaaki, khaala, bua, nanaji - is urgent and imperative, and is doable at least in small aliquots or temporary measures, weekends for instance.

Parents are in a perpetual rush to enrol their children in 'non-academic' classes- swimming, tennis, language, learning an instrument, etc. At New Horizons Child Development Centre, we counsel parents to realise that these may end up making the child better in performing those skills, but to be careful that the child does not end up emotionally more self-focussed and consequently, isolated. In working class families, after school hours while parents are at work, children stay glued to the screen. In order to help parents overcome their child's screen time addition, we suggest parents in a neighbourhood form groups of five or six. Every day, all children go by rotation to one family where that parent takes that much time off from work and decides what games the children will play, what food they will eat- while the other parents are busy at work. This ensures each child stays away from the screen and at the same time experiences and builds relationships with other families. There is something different to learn and the child ends up learning empathy and self-regulation in social situations.

We advocate parents encourage the child to participate in community activities that serve others- without self-gratifying certificates of individual excellence. Interestingly, today in a busy city, these

opportunities are available in gurudwaras, mandirs, masjids and churches. Send your children here not merely to memorise verses, but to help an old uncle up the stairs, to serve at the langar, to sweep the floor or to fold the carpets. Take them to all these religious places. Let them observe that basic beliefs are similar, but practices are different. Learning to adapt to different practices in small measures helps the child develop self-regulation better.

Let these different practices be the many arms of the scaffolding. Your child will be able to grow higher and eventually look over the fence! She will have a life beyond screens. She will be able to learn patience, resist the first impulse that hits her mind, prioritize what she deciphers from many books over an inflammatory social media post, and be able to take failure in her stride. Attitude to attempt and adapt gradually and meaningfully to changes, resilience in the face of failure, collaborating with peers with care, humility and humour are vital. These timeless values and skills that sustain the child as an individual, and at the same time sustain society, cannot be developed in a tuition class or on an app. They can only be developed safely in a thriving, secure diversity. And it is essential that parents take a pause, think beyond binaries and quick machoism and go on to mirror and role model these timeless values and practices.

A proverb tells us that it takes a village to raise a child. It is time to add that it takes a neighbourhood to raise a citizen.

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"Therapeutic Vitamin B12 trial reversing neuroregression– Identifying the right time"

Authors: Dr. Hema Kandru, Dr. Chaitra Govardhan, Dr. Bindu Narayanaswamy, Dr. Maria Lewin, Dr. Sunitha Palasamudram Kumaran,

Department of Paediatrics, St.John's Medical College Hospital

Department of Radiology, St.John's Medical College Hospital

Correspondence: Dr. Chaitra Govardhan, E-mail: chaitragovardhan@gmail.com, Mobile:8861831025

Contribution of each author:

In patient care (establishing clinical diagnosis, planning investigations, management and follow-up) and writing the manuscript. To specify the extent of involvement.

- Dr. Hema Kandruwas involved in collecting the information for the initial draft of the manuscript, assessing and follow up of the child.
- Dr. Chaitra Govardhan prepared the manuscript and revised it.
- Dr. Bindu Narayanaswamy and Dr Maria Lewin reviewed the manuscript, editted it and provided critical feedback for the same.
- Dr. Sunitha Palasamudram Kumaranreviewed and provided critical feedback for the radio imagesand for the manuscript.

Abstract

Background: Vitamin B12 plays a crucial role in the development of the fetal brain. Vitamin B12 deficiency manifests in infancy with varied neurodevelopmental manifestations ranging from nonspecific symptoms to neuroregression. In children with neuroregression, absence of either low serum vitamin B12 levels or macrocytosis, does not rule out a deficiency and may lead to missed diagnosis of a treatable condition with consequent severe neurodevelopmental morbidity. In this boy, the clinical findings along with low maternal vitamin b12 levels in the mother, therapeutic response and radiological recovery on follow up support the diagnosis of vitamin B12 deficiency.

Case Presentation: A 13-month-old boy who was predominantly on breastfeeds, presented with neuroregression and seizures. Initial assessment revealed pallor, skin hyperpigmentation, microcephaly, hypotonia and significant psychomotor delay. Laboratory investigations showed macrocytic anaemia, with elevated urinary methylmalonic acid levels(MMA). Serum vitamin B12 and folic acid levels were however normal in the child. MRI revealed global cerebral atrophy. On maternal screening vitamin B12 levels was significantly low.

Management and Outcome: Both the child and mother were treated withvitamin B12 and lost to follow up due to the pandemic. A review at 3 years 8 months showed significant improvement in the gross, fine motor and cognition, but persistent delay in the language domain. Repeat MRI showed reversal of atrophy and myelination appropriate for age.

Conclusion: Being a single case report, the findings of B12 treatment related reversal of neuroregression and cerebral atrophy will require confirmation with further experimental or analytical studies.

Keywords :

megaloblastic anaemia, neuroregression, vitamin B12 deficiency

Introduction:

Vitamin B12 deficiency in infants though rare can manifest with both haematological and neurological symptoms. In infants, aetiology, clinical features and radio imaging varies in comparison to adults and their presentation is mostly non-specific which can mask the diagnosis. (1) There is a high prevalence of B12 deficiency in Indians, especially among pregnant and lactating mothers ranging between 52% - 74%. (2) Adults may remain asymptomatic for many years despite vitamin B12 deficient diet due to adequate endogenous stores, whereas infants who have very limited hepatic reserves,develop symptoms within months of birth. (3)Affected infants are on exclusive breastfeeding by motherson a strict vegetarian diet, often a poor resource for vitamin B12. The involvement of the central nervous system has been poorly understood, however, demyelination, delay in myelination, impaired methylation or lactate accumulation in peripheral nerves, spinal cord and cerebrum have all been the proposed theories. (4) The affected infants who have normal developmental milestones in the initial 4-6 months of life, later present with non-specific symptoms such as irritability, progressive lethargy, feeding or weaning difficulties, refusal to accept solid foods, pallor, failure to thrive, hypotonia with hyperpigmentation of skin and lustreless scalp hair.(5)If not recognised and treated at this stage, neurodevelopmental slowing and neuro-regression sets in and symptoms are often unmasked as acute neurological deterioration associated with intercurrent infection.(5) Haematological evaluation reveals macrocytic anaemia and megaloblastic bone marrow. Metabolic screening suggests elevated serum homocysteine levels and urinary methylmalonic acid excretion which is the hallmark of the condition with serum low levels of vitaminB12. Mothers are often asymptomatic with low serum vitaminB12 levels when screened. MRI in these infants reveal white matter loss and delayed myelination. (6)secondary to severe vitamin B12 deficiency.\nMETHODS: Twenty-one infants aged 4-24 months with B12 deficiencies who were admitted to our clinic between May 2013 and May 2018 were included in the study. MRI, bone marrow aspiration and the Denver-II Developmental Screening Test were performed in all infants.\nRESULTS: The mean age of the infants was 12.3 months, and the mean B12 level was 70.15 ± 32.15 ng/L. Hypotonia and neurodevelopmental retardation, and anaemia were present in all patients. Their bone marrow examinations were compatible with megaloblastic anaemia. Twelve patients had microcephaly, seven had tremor and one patient died of severe sepsis. Almost all patients were fed with breast milk and their mothers were also malnourished. Nine (42.9% Affected infants respond dramatically to vitaminB12 therapy with rapid improvement with regain of milestones, however, long-term neuro deficits may result if the diagnosis and timely treatment is delayed. (7) We report a 13-month-old toddler with neuroregression and treatment of vitamin B12 deficiency who on follow up showed significant clinical and radiological improvement, however, language deficits persisted.

Case Presentation:

A 13 months old boy, brought with developmental regression and seizures 1 month before presentation. The child was second born tonon-consanguineous parents at term via caesarean section with a birth weight of 2.75kg. He was exclusively breastfed until 8 months of age followed by complementary dietwhich was nutritionally inadequate. Following normal development in early infancy, neuroregression was evident by loss of ability to come to sit or roll over by one year. He continued to respond verbally with the mother with differential sounds and no

loss of visual tracking. Examination revealed an underweight child with skin hyperpigmentation. Neurological examination revealed microcephaly, hypotonia, with brisk reflexes. Developmental assessment was conducted by different trained professionals initially and on follow up using Comm DEALL developmental checklist (CDDC) as mentioned (see Table 1). Ophthalmological and hearing assessment was within normal limits. Baseline investigations, (see Table 2) donesuggestive of macrocytic anaemia and mother had low serum vitamin B12 levels. Screening for metabolic disorders revealedmild hyperlactatemia, hyperammonaemia, normal serum homocysteine levels, and tandem mass spectroscopy was normal. Urineorganic acid levels showed elevated methylmalonic acid levels. Electroencephalogram (EEG) was abnormal with frontal epileptiform discharges, cranial MRI showed diffuse prominent subarachnoid spaces, fissures and cisterns, thinning of the corpus callosum, global cerebral atrophy, leukoencephalopathy with delayed myelination/ hypomyelination. (See Figure 1)

Management and Outcome:

Child was started on parenteral daily vitamin B12 250mcg given intramuscularly for 14 days as per recommendation, followed by slow taper with weekly doses for 4 weeks and fortnightly doses for a month and maintenance dose once a month with monitoringalong with additional folic acid supplements. Mother was given 500mcgvitaminB12 oral supplementationdaily for 2 months.On follow up at six weeks of initiation of therapy, significant improvement was observed with clearing of skin hyperpigmentation, improved feeding, activity and emergence of regressed milestones with improved tone.

Child was lost to follow-up due to covid pandemic. A follow up review at 3 years and 8 months of age child was symptomatically better but mother had discontinued all the medications including vitamin B12 after 2 months of initiation of therapy. In view of clinical seizures, child was started on sodium valproate by a paediatrician elsewhere. A detailed assessment revealed head circumference appropriate for age and normal development for age in gross and fine motor domain, however, delay persisted in a language domain (see Table 1). Investigations revealed a normocytic hypochromic blood picture. (see Table 2) Repeat serum B12 levels were normal. Tandem mass spectroscopy was normal and urine showed persisting elevated methylmalonic acid levels.Follow-up EEG was suggestive of epileptic encephalopathy, a repeat cranial MRI showed a reversal of cerebral cortical atrophy as compared to the previous study with normal spectroscopy. (See Figure 1) Child was discharged on home-based stimulation, speech therapy and continuation of anti-seizure medication.

The child's caregivers were advised long-term anti-epileptic medications but did not comply after a seizure free period. The child suffered a second episode of neuroregression at 5 years of age following recurrent seizures with status epilepticus and severe hypoxic encephalopathy. Neuroimaging repeated during this episode was consistent with severe hypoxic encephalopathy changes and a repeat vitamin B12 and metabolic evaluation including methylmalonic acid levels was within normal limits. Genetic evaluation was completed with whole exome sequencing and was inconclusive. Child was later on supported with intensive developmental therapy and has been regaining milestones assessed on follow up. Need for long term anti-epileptic medications with good compliance has been counselled.

Discussion:

Vitamin B12 deficiency in infants was described in the early 1960s from India by Jadhav et al, prominent findings were megaloblastic anaemia, neuroregression and skin hyperpigmentation among the few case studies reported worldwide. (8)Vitamin B12 a water-soluble complex organic compound, is essential for the production and

maintenance of RBCs and myelination of nerve cells, and plays important role in fetal brain development. Vitamin B12 deficiency can affect infants and children resulting in cognitive and intellectual problems depending upon the area of the brain affected. (9) Various theories have been proposed to explain the underlying mechanism of neurological dysfunction secondary to vitamin B12 deficiency, namely altered S-adenosylmethionine: S-adenosylhomocysteine (SAM: SAH) ratio, cytokines imbalance with increased TNF-a and decreased EGF (Epidermal growth factor) leading to loss of neural integrity that compromises brain development in infants. (10) While most adults remain asymptomatic for a longer duration, breastfeeding infants have limited hepatic reserves become symptomatic within few months after birth and peak by 4-10 months of age. Bicytopenia with anemia and thrombocytopenia is usually observed in vitamin B12 deficiency. However, treatment or supplementation of high dose vitamin B12 or an intercurrent infection can also cause thrombocytosis as observed in our child.(11) Laboratory investigations with the establishment of low serum B12 levels and elevated levels of methylmalonic acid shall be cornerstone of diagnostics, but normal levels of serum B12 or MMA do not exclude symptomatic B12 deficiency similar to our child.(12)Seizuresare reported with B12 deficiency although the exact mechanism are unknown and probably related to increased excitability of the damaged myelinated neuron to glutamate. (13)we aimed to evaluate patients with seizures who were found to have vitamin B12 deficiency and whose seizures resolved with vitamin B12 treatment., Methods: A total of 26 infants were included in this retrospective study. The patients were evaluated in terms of clinical findings, laboratory tests including homocysteine, electrophysiological studies, neuroimaging studies, and other neurological examination findings., Results: Of 26 patients, 14 (53.8%Korenkeet al reported an infant manifested as acute encephalopathy, epilepsy, microcephaly and megaloblastic anaemia at 4 months of age secondary to subclinical pernicious anaemia in mother and showed response to vitamin B12 therapy similarly.(14) Ursula et al, reported a 14-month-old,with severe vitamin B12 deficiency related symptoms who showed complete disappearance of structural abnormalities following therapy, however continued to have cognitive and language delay at the end of 2 years of age. (3) Nadia et al, reported 2 infants with vitamin B12 deficiency who showed complete recovery following therapy. (4) Cezary et al in their case study observed a 7-month-old child with megaloblastic anaemia and neurological regression, who had remarkable response in general condition and blood picture, however, continued to have long-term psychomotor disability due to a delay in diagnosis. A similar trajectory was seen in our index child, as the non-specific symptoms improved within weeks of initiation of treatment but the psychodevelopmental evaluation showed deficits in language domain. Thus, it is evident that the long-term prognosis and outcome of vitamin B-12 deficiency in children depend on the severity and duration of the deficient state. (7) There is limited data on long-term follow-up of developmental outcomes following therapy in these children. Pearson et al followed a 32-month-old child, found to have an intellectual delay at the end of 6 years of age. (7) The neuroimaging features in vitamin B12 deficiency can vary from diffuse or focal cortical atrophy, thinning of the corpus callosum, structural abnormalities and delayed myelination. (1) Asipayam et al, studied 21 hypotonic infants aged between 4- 24 months with B12 deficiency, who were predominantly breastfed, and had similar findings comparable to our index case, and all responded to therapy but lacks follow up of long-term sequelae. Among 21 children, 12 had microcephaly, and all had retardation in personal social, language, fine and gross motor abilities. MRI findings in

his study also revealed cerebral atrophy in all infants, corpus callosum thinning, frontoparietal, frontotemporal atrophy and delayed myelination in 2 infants each. (6) Neuroimaging in our child showed remarkable recovery which also correlated with clinical improvement, language deficits persist requiring therapy.

Limitation:Neurodevelopmental follow up and speech stimulation could not be done as the child was lost to follow up during the covid pandemic. Since this is a single case report with follow up, similar studies to compare the radiological recovery is limited.

Conclusion:

Early recognition of infants with vitamin B12 deficiency is critical because treatment can partially or completely reverse the neurological and radiological impairment, thus preventing the progression of irreversible neurological deficits, and this needs to be substantiated with further experimental or analytical studies.

Lessons learnt:

Vitamin B12 deficiency when recognised early and treated can prevent irreversible neurological damage.

Long term follow-up of these children is essential to identify persistent deficits requiring continued intervention.

Paediatricians need to have high suspicion and screen all breastfed infants with developmental concerns for vitamin B12 deficiency.

Figures

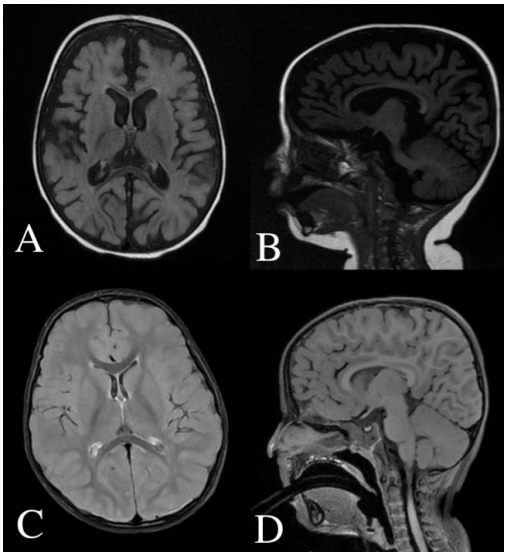

Figure-1

A- T2 Flair(axial)- Global cerebral atrophy with diffuse sulcal space widening in bilateral cerebral hemispheres with prominent subarachnoid spaces and fissures and basal citerns.

B- T1 Flair(sagittal)- Thinning of corpus callosum and myelinated.

C- T2 Flair (axial) Showing previously noted prominent cortical sulcal spaces, basal cisternal spaces appearsto be normal with reversal of cerebral cortical atrophy.

D- T1 Flair(sagittal)- Corpus callosum appears normal in size

Tables:

Table-1– Developmental profile

DOMAIN	At initial presentation* Chronological age: 13 months 6 days		On follow up* Chronological age: 3 years 8months (44m)	
	Milestones	Developmental quotient (DQ)	Milestones	Developmental quotient (DQ)
Gross Motor	Head Holding-3m Rolling over-6m Sitting with support-7m Crawling-11m Regression at 1 year Lost the ability to crawl, sitting independently and rolling over	DQ-47	Walking and running Climbs stairs and jumps Plays ball	DQ-97:
Fine Motor	Reaches out for objects-6m Transfer objects-7m Plays with toys-8m Stopped reaching objects	DQ-46	Spontaneous scribble Opensdoors, draws Plays with clay Picks thread	DQ-77
Language	Cooing - 3m Babbling - 8-9 months Stopped babbling	DQ-26	Follows simple commands Communication through pointing Jargon speech	DQ-32
Cognition	Recognizes mother Plays with rattle Stopped exploring	DQ-42	Recognizes self in photograph. Knows where things usually belong. Chooses picture books.	DQ-84

*Assessment performed using COMMDEALL developmental checklist

Table-2 - Laboratory profile

Laboratory Parameters	At initial presentation	On follow up
Hemoglobin (10.5-14g/dL)	9.2	11.4
White blood cell count, (6-14x10^3 mm^3)	11510	12110
Neutrophils (54-62%)	24%	50%
Lymphocytes (25-33%)	70%	44%
Platelet count (150-400x10^3 mm^3)	656	415
Red blood cell count (4.5-6.5x10^6 mm^3)	2.76	5.08
Hematocrit (32-42%)	30	35.9
ESR (0-10mm/hr)	9	
Mean corpuscular volume (72-88fL)	108	70
Serum Vitamin B12	313 (187-883pg/ml)	40.8 (25.1-165pmol/L)
Serum Folic acid, (3.1-20.5ng/mL)	17.6	
Plasma Ammonia (11-35 µmol/L)	136	39
Serum Homocysteine (5.46-16.2µmol/L)	9.54	
Plasma Lactate (0.5-1.6mmol/L)	5.6	1.2
Tandem Mass Spectrometry (TMS)	Normal	Normal
Urinary Methylmalonic acid levels (<3.6mmol/mol of creatinine)	8.46	24.86
Peripheral blood smear	RBC- Normocytic normochromic with oval macrocytes, target cells, tear drop cells, polychromatophils WBC- Normal in number, few hypersegmented neutrophils Platelets- Increased	RBC- Normocytic hypochromic with few polychromatophils WBC- Normal Platelets- Adequate

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GRIN1– Related neurodevelopmental disorder–Autism with Epilepsy – A case report

Authors
Dr Prabhavathi R1, Dr Nandini Mundkur, Dr Ravikumar, Dr Parag M Tamhankar

Centre for Child Development and Disabilities, Malleshwaram, Bangalore, India

Corresponding Author : Dr Prabhavathi R, email -drprabha81@gmail.com

Introduction

GRIN1-related neurodevelopmental disorders are a group of rare paediatric encephalopathies,with estimated prevalence of 1:5000 births [(1)]. Genetic variation in the GRIN1 gene have been associated with a wide range of neurologic and neuropsychiatric disorders .GRIN1 (Glutamate Receptor Inotropic, NMDA 1) is the name of the gene that is affected..GRIN1 -related disorders, the so-called grinpathies, is caused by mutations affecting *GRIN* genes (mostly *GRIN1, GRIN2A* and *GRIN2B* genes), which encode for the GluN subunit of the *N*-Methyl D-Aspartate (NMDA) of glutamate receptors[(2)]. NMDARs play critical roles in normal brain function, such as neural development, synaptic plasticity, learning, memory, and motor function [(3)].Phenotypes associated with de novo GRIN1 pathogenic variants include severe early onset psychomotor delay in all reported patients and epilepsy in up to 70% of these patients [(4)]. Mutations of the NMDAR subunits are associated with a different neurodevelopmental phenotypes, including intellectual disability (ID),epilepsy, and Autism spectrum disorders (ASD), and psychiatric diseases. [(5)] Other common manifestations are muscular hypotonia, movement disorders, spasticity, feeding difficulties and behaviour issues. A subset of individuals shows a malformation of cortical development consisting of extensive and diffuse bilateral polymicrogyria. [(6)]

The symptoms and severity of the disorder vary widely. There are no typical clinical signs and symptoms of a *GRIN1*-related disorder that enable a diagnosis based on clinical features alone. Genetic study is required to diagnose a *GRIN1*-related disorder. Implementation of next-generation sequencing to clinical diagnosis has allowed reporting of a growing number of both neutral and disease-associated *GRIN1* variants [(2)] To date, 72 individuals with *GRIN1*-NDD have been reported, including 64 individuals with de novo heterozygous pathogenic missense variants and eight individuals from four families with biallelic pathogenic missense or truncating variants[(6)]

This case report highlights the importance of GRIN1 mutations in the etiology of isolated cases of early onset encephalopathy, and the valuable role of whole exome sequencing in identifying these mutations.

Keywords: GRIN1 gene; Autism; Epilepsy

Case report

A 5 year old male child presented with history of speech delay, convulsions and inability to sit in one place. He is a first child born out of nonconsanguineous marriage, he is a term baby delivered by LSCS, birth weight was 3.3 kgs, baby cried immediately after birth, breast fed on day 1 of life. There was no family history of developmental delay or seizures in three-

degree pedigree charting. Child had a normal developmental trajectory upto 1 year 4 months of age.

Developmental history : Gross motor milestones - child achieved neck holding at 3 months, sitting by 7 months, standing by 1year, later there was a mild delay in walking, started walking by 1 year 4 months, running by 2 years, presently child can't jump, they feel his movements are bit clumsy. Fine motor milestones - child achieved pincer grasp by one year and by one and half year of age, parents noticed abnormal shaking movements of hand, shaking toys and household items near his ears to hear sounds, banging things to hear sounds, biting and mouthing things following which child didn't achieve much fine motor skills, now child can scribble with pen. Language milestones: child used to follow simple one step commands by one year of age, used to talk in words, he had a vocabulary of around 7 to 10 words and had good name-call response also.

Around 1 month after 1st episode of convulsion parents noticed regression of his language milestones, child stopped talking in words, used only sounds to communicate, stopped responding to commands, stopped responding to name, started engaging in repetitive movements and child seemed to be in his own world gradually. Presently his receptive and expressive language is around 8 -9 months. Child used to play peek a boo and simple ball game by 1 year of age. But by one and half year child started repetitive behaviour and stopped playing meaningfully. Now his play skills are poor with only mouthing and exploratory play. Social milestones are poor with no pointing, no joint attention, no shared joy...

Behaviour history – Sleep is adequate, appetite is good, not toilet trained, no problematic behaviours. Sensory issues: Child prefers to move always, loves banging and shaking toy to make noise, hypersensitive to cooker and mixer sounds, closes his ears for the same. On examination there were no obvious neurological deficits. Child was diagnosed to have Autism and started on speech and occupational therapy from 3 years of age onwards. Currently child is taking speech, occupational therapy and behavioural therapy classes daily since one year. Parents are not noticing much improvement in his speech and overall behaviour. –

Seizure had varied semiology. Seizures started as typically febrile seizure at the age of 1year 4 months, followed by recurrent febrile seizures once in two months ,around total 5 episodes till the age of 2 years10 months which was treated with Clobazam prophylaxis only. Later around 3 years of age parents noticed recurrent sudden loss of tone for <20 seconds, following which child used to get up and walk. These episodes occuredonce in 20 days around 3-4 episodes in 3 months, EEG was abnormal and diagnosed as Absence seizures and started on carbamzepine after which symptoms subsided. At the age of 4 years 4 months again child had two episodes of unprovoked generalized tonic seizures lasting for <1 min with transient loss of consiousness. Repeat EEG was abnormal so Sodium Valproate was added, carbamazepine was tapered and stopped. Around 4 years 11 months parents noticed jerky movements 2-3 times a day and diagnosed to have myoclonic epilepsy and topiramate was added. But intensity of jerks increased. So clobazam was added. But myoclonic jerks persisted and hence leviteracetam was added to Sodium Valproate and topiramate and clobazam were tapered and stopped. Presently child is on Sodium Valproate and leviteracetam and symptoms are under control.

Investigations showed the following findings. EEG showed multifocal and generalized interictal epileptiform discharges(myoclonic jerk noted during EEG), **MRI** brain was normal. Clinical exome : revealed a heterozygous missense variation in exon 19 of the GRIN1 gene (chr9: g.137163846G>T GRCh38 format;

c.2594G>T) that results in the amino acid substitution of Leucine for Arginine at codon 865 (p. Arg865Leu) was detected in the indexpatient. Arg865Leu is reported as pathogenic mutant as per ACMG criteria PM1, PM2, PM5, PP2, PP5 (Clinvar database reference 598966). Another pathogenic variant at same site Arg865Cys has also been described (Clinvar database reference 521354)

Neurodevelopmental assessments showed the following. Based on observation on the Autism Diagnostic Observation schedule module 1, Pranav obtained a total score of 25 which met the ADOS 2 classification of autism and the level of symptoms being high, Mullens scale of early learning showed overall T score on the early learning composite is interpreted as very low functioning, child had associated sensory issues

Discussion

GRIN1-neurodevelopmental disorder (*GRIN1*-NDD) should be considered in individuals with Mild-to-profound developmental delay or intellectual disability and any of the following symptoms in infancy or childhood which includes epilepsy, Autism spectrum disorder, Microcephaly, Cortical visual impairment, hypotonia or spasticity, dystonic, dyskinetic, or choreiform movement disorder[6] De novo mutations in the GRIN1 gene have been recently reported as the molecular cause of a broad-spectrum early-onset neurodevelopmental delay. In this study, we report one patient who presented with early onset seizure and developmental delay and autism due to a *de novo* pathogenic variant in the *GRIN1* gene. Here we have a five-year-old boy with normal development till 1.4 years had seizures on and off many times till now, initially GTCS but now myoclonic seizures which required trial of multiple antiepileptics associated with regression of acquired speech and features of Autism. Whole-exome sequencing identified a novel p. Met641Leu de novo variant in the GRIN1 gene as the cause of the phenotype. Child also had abnormal EEG- multifocal and generalized interictal epileptiform discharges.

We reviewed literature available on the topic. Tim A. Benke, et al reported patients with *GRIN1*-related neurodevelopmental disorder showing multiple deficits, including ID, epilepsy, hypotonia, movement disorders. All affected individuals evaluated to date show variable levels of ID, 65% had epilepsy, hypotonia (66%), movement disorders (48%), cortical visual impairment (CVI, 34%), oculogyric crises (11%), features of autism spectrum disorders, or stereotypic movement disorder (32%), sleep problem (15%), and self-harm behaviour (7%). The onset of seizure ranges from birth to 11 years of age, and two thirds demonstrated resistance to conventional antiseizure treatment. Seizure types include generalized seizures (68%; with multiple semiologies), focal seizures (2%), and epileptic spasms (13%). some individuals showed cortical malformations like extensive bilateral polymicrogyria, ventriculomegaly, reduced thickness of the corpus callosum, basal ganglia dysplasia, and decreased white matter volume. In our case child has autism and seizures of multiple semiologies presently requiring trail of multiple antiepileptics. MRI was normal despite developmental delay and Seizures[7]. Konrad et al, reported 72 individuals with *GRIN1*-NDD, including 64 individuals *denovo* heterozygous pathogenic missense variants and eight individuals from four families with biallelic pathogenic missense or truncating variants. All affected individuals have a variable degree of DD or ID (profound in 17%, severe in 71%, moderate in 7%, mild in 5%). No active speech has been noted in 48% of individuals. Seizures occurred in 65% of individuals. Some affected individuals presented with different seizure types over time. In 27 individuals with seizures, 17 had refractory seizures and 10 were well controlled with standard anti-seizure medication. Signs of autism spectrum disorder were observed in 22%.

Other behavior issues observed were stereotypic movements (32%), self-injurious behavior (7%), and sleep disorder (15%). ([6]). Johannes R. Lemke, et al, study on 23 patients carrying de novo *GRIN1* mutation presented with profound global developmental delay, 71% had hypotonia , spasticity in 29%, dyskinetic movement disorders (61%), Nonspecific stereotypic movements in 33%. 70% had epilepsy with different. Seizure semiology (infantile spasms, tonic and atonic seizures, hypermotor seizures, focal dyscognitive seizures, febrile seizures, generalized seizures, status epilepticus), and the associated EEG pattern (hypsarrhythmia, focal, multifocal and generalized spikes and waves). 31% therapy-resistant epilepsy, 2 patients became seizure-free, 2 patients responded to topiramate, levetiracetam, and clobazam. 8(35%) *GRIN1* patients were diagnosed with ASD or ASD-like features (5). Jin Zhang et al reported 20 patients with 26 pathogenic variants in the *GRIN1* gene. Phenotypes associated with *de novo GRIN1* pathogenic variants include severe early onset psychomotor delay in all reported patients and epilepsies in up to 70% of these patients. [(3).] Fry et al. recently reported *de novo* pathogenic variants in the *GRIN1* gene in 11 patients with extensive bilateral polymicrogyria. Our case here has pathogenic variant GRIN1, with Autism with seizure with movement disorder. Brain MRI is normal in our case[(8)]. ChihiroOhba et al - study on GRIN1 mutations in children with unclassified early onset epileptic encephalopathy, with nonsyndromic intellectual disability and concluded that Clinical features of infantile involuntary movements, seizures, and hand stereotypies, suggesting that GRIN1 mutations cause encephalopathy resulting in seizures and movement disorders[(9)]. Yuchen Xu, et all assessed the effects of a set of FDA-approved NMDAR channel blocker memantine, which significantly improved the patient's seizure burden, with evidence that seizures worsened considerably during transient discontinuation of memantine and concluded that appropriate clinical trials including more *GRIN1* patients are necessary to further establish the safety and efficacy, especially with respect to neurodevelopmental outcomes, for long-term use of memantine and considered as future hope for children with GRIN mutations[(10),]

Conclusion : De novo GRIN1 mutations are being identified more often cause of neurodevelopmental delay with seizure. Our case report suggests that the novel *de novo GRIN1* variant (type variant) is associated with developmental delay, autism and epilepsy. GRIN1-encephalopathy should be suspected in early onset seizures with neurodevelopmental delay. Whole Exome Sequencing (WES) will help in diagnostic testing in suspected cases.

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Autism spectrum disorder in a child with Oculocutaneous Albinism

Author

Chaitanya Varma*, Nandita de Souza, Alisha Narvekar.
Sethu Centre for Child Development and Family Guidance, Saligao, Goa.

Correspondence : Dr Chaitanya Varma, Sethu Centre for Child Development and Family Guidance, Dhonwaddo, Saligao, Goa-403511. Email-chaitanya.varma@sethu.in, Contact no- 077200 13749.

ABSTRACT

Oculocutaneous albinism (OCA) is a collection of autosomal recessive conditions of melanin biosynthesis that rarely presents with multiple systemic signs. Autistic spectrum disorder (ASD) is characterized by impaired communication, social interaction, and repetitive behaviours. ASD has been reported in association with several inherited medical and psychological disorders. The association of ASD and OCA is rarely reported in the literature. Herein, we report the joint occurrence of these conditions in a three year old boy. This rare association might offer pointers about the genetic relationship between ASD and OCA.

Key Words:

Autism spectrum disorder, Oculocutaneous albinism, melanin synthesis, hypopigmentation, nystagmus, genetic testing.

Introduction:

Oculocutaneous albinism (OCA) is a group of rare inherited disorders characterized by a reduction or complete lack of melanin pigment in the skin, hair and eyes.[1]Autism spectrum disorder (ASD) is a neurodevelopmental disorder where the child has social communication difficulties and repetitive behaviours.[2] There are very few case reports of OCA and ASD presenting as co morbidities. We present a 3 year old child diagnosed with albinism who presented with symptoms of ASD.

Case Report:

History

A 3-year-old boy was referred to Sethu Centre for Child Development and Family Guidance, Goa with complaints of decreased response to name call and poor eye contact. Parents shared that their son never initiated conversations or shared his interests. He would communicate by leading them by their hand, screaming or occasionally using single meaningful words. He did not use gestures to communicate. The child spent a lot of time playing alone, being in a world of his own and ignoring his peers.

When excited, he would repeat words and flap his hands. He had rigid thinking and would throw tantrums if things were not done according to his liking. He was fascinated with colors, observed objects closely and liked to arrange incense sticks in the shape of alphabets. He also had tactile defensiveness and did not allow haircutting or toothbrushing.

The child was born full term by Caesarean section, cried immediately at birth and had a birth weight of 2.5 kgs. As the child was born with hypopigmented skin, blond hair, and blue eyes he was examined by the pediatrician at the government hospital during a routine well baby visit and was diagnosed as Albinism but was not evaluated further. He had no previous history of hospitalization.

Gross motor and fine motor milestones were

attained age appropriately. He started reciting alphabets by the age of 18 months and could name multiple body parts/fruits and vegetables by the age of 2 years. He can presently use 2-word phrases occasionally (need based). He is dependent on his parents for his eating, toileting, and dressing needs.

The child is first born to a non-consanguineous marriage. There is no family history of language delay, developmental regression, seizures or albinism.

Examination:

The child was active alert with stable vitals during examination. His weight was 13 kgs (0-25th centiles), height was 94 cms (25th-50th centile) and head circumference was 50 cms (50th centile). His hair, eyebrows and eyelashes were blond (Fig 1). Iris was hypopigmented with blue color. Nystagmus was noticed with a fast component towards the right side. His skin was hypopigmented over his entire body (Fig 2). Neurological examination done was normal with no cerebellar or meningeal signs. The systemic examination was also normal.

A developmental assessment revealed that his gross motor and fine motor milestones were age appropriate. His language was limited to occasional 2-word phrases, grunts, and screams. He did not follow any verbal instructions or visual schedules cues during assessment. Name response, joint attention and eye contact were absent. He was engaged in solitary play, was in a world of his own and approached parents only if he needed something. He exhibited hand flapping when he was excited, and frequently used scripted, repetitive phrases like "Oh No". He was interested in playing with the wheels of the toy cars and would squint and look at them closely. An assessment for Autism Spectrum Disorder based on the DSM V criteria was fulfilled. The Indian Scale for Assessment of Autism (ISAA) score was 112 which indicated moderate autism.

Diagnosis And Treatment:

Based on history and physical examination and developmental assessments the child was diagnosed to have Oculocutaneous albinism and Autism spectrum disorder. The parents were counselled about both the diagnosis. They were recommended genetic testing for OCA along with regular ophthalmology reviews and skin care protocols. Early intervention behavioral and communication therapy were advised for ASD.

Discussion:

Though hypomelanotic skin disorders like tuberous sclerosis and hypomelanosis of Ito have been reported in association with childhood autism[3,4], an association between oculocutaneous albinism with autism has been reported rarely. Rogawski et al in 1978 first reported such an association in two boys.[5] Four families of individuals who had childhood autism and the additional feature of oculocutaneous albinism in addition to major affective disorder were described by Delong.[6] A 13 year-old Nigerian boy who had oculocutaneous albinism and autism was described by Bakare and Ikegwuonu in 2008.[7] In the Indian scenario, Sandhya and Aravinda HR described a four year old female child, born of a consanguineous marriage who presented with delayed speech and social skills and clinical features of OCA.[8] Genetic evaluation was normal but visual evoked potentials showed decreased visual acuity. She was diagnosed with autism along with OCA type 1. Raj G et al described a three year old female child with low weight, neonatal ICU stay at birth, delay in fine motor, social cognition and language, and hyperactivity, along with inappropriate behaviours, poor eye contact and solitary play.[9] Ophthalmology consultation showed foveal hypoplasia and she was diagnosed to have oculocutaneous albinism. A thorough literature search has revealed that this report is the first of its kind for a male child and the third report of combined OCA and ASD from India.

Conclusion:

A variety of genetic mechanisms like single gene disorders, copy number variations and polygenic mechanisms may be involved in the etiology of autism.[10] Genetic variation in the GABA(A) receptor alpha 5 subunit gene and GPR143 gene have been found to occur mainly in Ocular and oculocutaneous albinism and to a smaller extent to the development of autism like features [6,11]. Vitamin-D level which is involvedwith melanin production and is also being studied as a risk factorfor autism may further explain the association between autism and hypomelanotic skin disorders [12]. Further research into the role of a common etiology between the two could help with early detection and management of both childhood autism and OCA.

Consent:

A written consent from the parents was obtained for the publication of this case report.

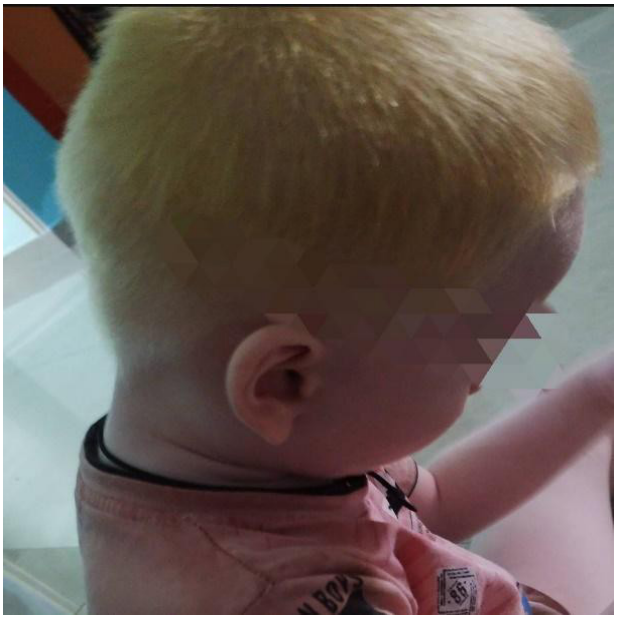

Figure 1

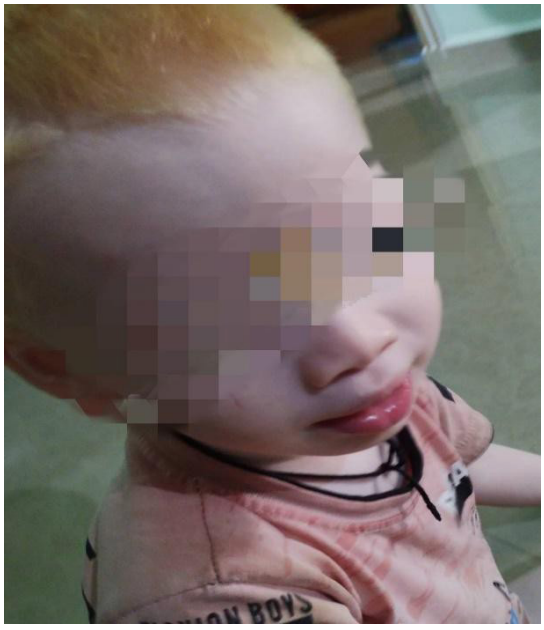

Figure 2

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