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IJDBP

Indian Journal of Developmental & Behavioral Pediatrics

Official Journal of IAP Chapter of Neurodevelopmental Pediatrics

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CONTENTS

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

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

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

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

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

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

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

INVITED GUEST EDITOR

CHANGING DYNAMICS OF PARENTING

Over the last 40 years, scientific interest on parenting has grown exponentially and standards of good parenting have also changed dramatically. This is being driven by the challenges of balancing family and career, societal complexity and changing family structure. There is overload of information both for parents and children, and the constant interference of digital media and third-party caregivers. It is thus prudent to reflect their impact on child development, given the understanding that early nurturance and adverse effects during critical period of one's developmental stages, have long term effects in mental and physical health.

Today, there is so much emphasis on productivity and activity, that the parents are put under pressure to have the smartest, earliest toilet-trained, best performing kid. The fallout of this is the chronic stress that parents and the child go through. This is detrimental to growth, and on the other hand, it pushes parents to take bad decisions with effects of an unhealthy parent-child relationship. Overload of information from various professional perspectives add to their confusion.

We practitioners need to be aware that learning by the child takes place at two levels: growth of visibleknowledge and implicit understanding, and their deductions in conceptualizing life.

The greatest compromise today has been on time and play, on being together, sharing, communicating feelings and responding. These impact emotional development and communication, forcing children to seek alternative modes of release of pent-up emotions. Over the last decade the importance of social determinants of health have come to focus and research on the complex mechanisms involved has come to the fore. The epigenetic model of learning adds that experience could act not only by triggering Hebbian learning but also by epigenetically modifying gene expression relating to behavior.

Additional challenges are placed on the parent if the child has neurodevelopmental problems, with their accompanying problems, to raise them in the present-day milieu. Family structure changes, like divorce, single parenting, remarriage and same sex marriage, all have their own different dynamics of relationship which may affect child development.

Another phenomenon that is on the rise is children in foster care due to death of parents in environmental disasters, conflicts and epidemics. How does this foster care and the burden of parenting affect development outcome?

There are new challenges emerging in bringing up children in cross cultural environment either due to parental work environment, relocation or displacement. This poses a great need for practitioners and caregivers and social support systems to be empowered with culturally competent family interventions and community family practices to support parents.

The pediatrician's role and responsibilities have expanded in the backdrop of the dynamic societal changes. Capacity building of professionals and infrastructure support is the need of the hour.

Studies are warranted on long term follow up of this causal relationship with specific methodologies through a well- coordinated, harmonized network of stakeholders of child care.

Dr. Shabina Ahmed, MD, FIAP
Chairperson
IAP Chapter of Neurodevelopmental Pediatrics

EDITORIAL

At the outset congratulations to the entire editorial board on getting the RNI number for the Journal. It now put the Journal on track for ISSN registration and subsequent Indexing.

This year the theme for Autism Awareness day 2023 is Transforming the narrative: Contribution of Autistic people at Home, at Work, in the arts and in policy making.

In 2023, the CDC reported that approximately 1 in 36 children in the U.S. is diagnosed with an Autism Spectrum Disorder. Most children are still being diagnosed after 4, though Autism can be reliably diagnosed as early as 2years. The importance of Labelling to Enabling needs to be reemphasized.

The CDC also reported 31% of children with Autism have Intellectual disability, 25% are in borderline range and 44% have average to above average IQ. As per WHO International classification of Functioning maximum emphasis should be directed towards Inclusion.

As per CDC stats Developmental Regression or loss of skill occur in 1 in 5 children and typically occur between ages 1 & 3 years and can be one of red flags to start early intervention which can improve learning, communication and social skills, as well as underlying brain development. Early intervention is the best modality till a definitive cure is found.

In keeping up with its commitment to empower families and professionals with updated evidence based information the Neurodevelopment chapter of IAP will come out with the revised National consensus guidelines on Autism soon. The NMC, ICMR, Neurodevelopment chapter, Neurology chapter came out with A White paper clearly stating no role of Stem cell therapy at present as a mode of treatment for Autism.

I hope with the support of my learned editorial board the third issue will be having ISSN number.

Best Regards

Dr. Zafar Mahmood Meenai
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Editor-in-Chief, IJDBP

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How to Write a Review Article?

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The generation of evidence is an ongoing process in the field of medicine. Basic and clinical research have been the pillars of modern medicine and continue to be the strength of a modern medical practitioner. With increasing number of biomedical journals and therefore research articles being published, staying updated with the current evidence is a necessity for the clinician.

One of the five goals of an Indian medical graduate as prescribed by the National Medical Commission is to function as a lifelong learner committed to continuous improvement of skill and knowledge [1]. It would be ideal that any topic of concern is thoroughly searched, read, reviewed and analyzed by going through all the literature. However, this is easier said than done. This task is nothing less than swimming in the middle of an ocean with no land in sight.The variability in the quality and content of the enormous amount of information available confuses the clinician who ends up having more unanswered questions than before. It is for such situations that a state of the art, reliable, well written review article acts like a lifeboat.

A review article is a comprehensive synthesis of published and unpublished material on a topic. It is a well planned and well-organized analysis of all the literature relevant to a topic of interest providing a useful summary and answers to the reader's doubts and questions. It facilitates the medical practitioner to take evidence based clinical judgements and decisions. It is a practical solution to the problems of excessive information, divergent views and lack of consensus on a topic. Review articles aid decision making in clinical practice by summarizing enormous information available, in a coherent and easily understandable form, thereby acting as guides for practicing evidence-based medicine. They facilitate in understanding of recent advances, complex topics and sub topics, which are not a part of the conventional textbooks. They help in the identification of relations, contradictions, controversies and lacunae in the existing literature, and provide a direction for future research.

Types of Review Article

Review articles are classified as Narrative Reviews (NR) and Systematic Reviews (SR). NR are a summary of the evidence obtained from the studies selected and analyzed according to the author's selective literature search and review of literature. They are written in a format which is easy to read and understand. They provide a critical assessment of a wide range of issues on the topic of interest.They are useful even to those readers who may have no or limited knowledge of statistics or research methodology. They provide a comprehensive information about a clinical topic or a decision-making algorithm and are sought after by young clinicians or students for a broad and quick understanding of the topic of interest.

The main weakness of NR has been attributed to the fact that they are more prone to subjectivity in study selection and therefore may be biased.The search by the authors may be limited to freely available full text literature in open databases. NR do not necessarily state or follow strict criteria for search of evidence and arrival at conclusions. The selection bias may be compounded by a synthesis bias whereby the conclusions may be biased towards the personal opinions of the authors.

On the other hand, the broad principle of a systematic review is to apply scientific strategies that limit bias to the systematic assembly, critical appraisal and synthesis of all relevant research studies on a specific topic [2]. SRs formulate a well-defined question, provide a qualitative and quantitative analysis of all the relevant evidence and then may or may not be followed by a Meta-Analysis (MA). MA refers to the statistical analysis of the data from independent primary studies focused on the same question, which aims to generate a quantitative estimate of the studied phenomenon. Because of the fact that special emphasis is put in the methodology of SR to diminish biases, they are considered to be at the top of the pyramid of hierarchy of evidence [3]. SRs synthesize all the available relevant literature to result in an objective, reproducible and transparent conclusion.The research question, search criteria, study inclusion, data extraction, data synthesis and assessment of quality of study are pre-defined and protocol based in a SR.

SR are; however, not free from limitations. The narrow focus of SR does not allow for a comprehensive coverage of the topic of interest. Heterogeneity in the selected studies, biases pertaining to patient selection, evaluation and measurement in individual studies, and publication bias also hamper the quality of SR. Also, the rigorous methodology of SR is labor and time intensive. A comparison of NR and SR is shown in Table1.

Steps of Writing a Review Article

Writing review articles is a good way for a new researcher to enter into scientific writing. Review of contemporary topics which provoke discussion regarding practice guidelines are sought after by all readers. However, it is always advisable that before conducting a NR, the authors must consult and send a proposal to the editor of the intended journal, as similar review articles may already be in submission or the topic may not fall in the scope of the journal.Similarly, registries for SR must also be checked for ongoing reviews in order to avoid redundancy. The following is a general overview of the steps of writing a review. This can easily be remembered by the simple mnemonic **REVIEW** - **R**esearch Question/ Topic of interest selection, **E**vidence search, **V**alue assessment, **I**ntegration and synthesis of descriptive data, **E**xamining quantitative data and **W**riting the review. This is summarized in Table 2.

Step 1: Research Question / Topic of Interest Selection

Framing and addressing the research question is the cornerstone of a good review. This step must be given ample amount of time. The research question must be clear, specific and relevant. The research question for a SR must have the essential 6 elements addressing the **PICOTS** questions i.e.,**P**opulation/ **P**atient/ **P**roblem addressed, **I**ntervention or Exposure being evaluated, **C**omparator for the said intervention, **O**utcomes being assessed, **T**ime frame and **S**tudy design. The topic of interest for NR must preferably address patient-oriented outcomes of emerging or common illnesses, interventions or drugs which concern many readers [4]. They may also be written on new drugs, vaccines, diagnostic tests or guidelines for specific conditions. Broad, non-specific, theoretical, rare and unusual topics must be avoided for review articles, more so for a narrative review.

Step 2: Evidence Search

A comprehensive search for all the possible published and unpublished evidence, which can address the research question, is extremely important. The search must be Systematic, Objective, Reproducible and Transparent

(SORT). Based on the PICOTS components of the research question, searchable concepts must be identified. An exhaustive literature search can be started by using bibliographic databases which contain journal and newspaper articles, conference proceedings and papers, reports, government and legal publications, patents and books. Popular global online databases which provide free or subscription-based access include PubMed, Embase, Web of Science, Scopus, CENTRAL and Google Scholar. In order to retrieve the maximum number of relevant studies and diminish publication bias, the search strategy must employ other methods like 'hand searching' or going through grey literature, textbooks, references and citations or personally communicating with authors of unpublished work and subject experts for brainstorming and further guidance. Suitable search words like controlled vocabulary in conjunction with Boolean operators, truncations, limits and filters must be used to yield best search results. The search time frame, databases searched and the search strategy including search terms used must be mentioned in the methodology section of the review article in order to aid transparency and reproducibility.

The studies found by the search should be screened for eligibility for inclusion in the review. This includes a preliminary screening of the study titles followed by screening of the abstracts. The full text articles of the short-listed abstracts should then be assessed for eligibility based on the PICOTS components of the research question. A data extraction form must then be used to extract data of the eligible articles (after removing duplicates). The common headings of the data extraction form include (i) study information, including geographic location, survey years, research design, sample size, percentage of respondents among eligible participants, and number of institutions included; (ii) characteristics of participants, including mean age, gender, specialties; and (iii) outcomes.

Step 3: Value Assessment

Assessment of the value or quality of every included study is an indispensable component of the review process. It is important to discriminate good quality and poor-quality studies in order to derive correct conclusions based on higher weightage for the results of good quality studies. It may be essential to limit the review to studies which are most appropriately designed to address the topic of interest. The research methodology of individual included studies should be critically appraised to assess for the efforts made by the authors to minimize bias while conducting the study. Attempts must be made to identify poor quality studies having inappropriate study designs or inappropriate study methods.

Several standard tools are available online to assess the quality of studies included in SR. A commonly used tool for assessing the quality of RCTs is The Cochrane Risk of Bias tool [5]. This includes appraising the adequacy of the methodology of the study for random sequence generation, concealment of allocation, blinding of study participants, blinding of outcome assessors, incomplete outcome reporting, and selective outcome reporting. There is also an additional element for appraising any other bias. The Newcastle Ottawa Scale (NOS), Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool and the QUADAS-2 tool are other tools for assessing quality of different types of studies [6-8].

Step 4: Integration & Synthesis of Descriptive Data

The descriptive characteristics of the included studies must be integrated and synthesized as it is rare for all researches to arrive at the same conclusion. This is one of the most difficult steps in which the researcher will need to apply their skills of critical reading and analysis to arrive at a rational, logical, evidence based, and comprehensive synthesis of the selected academic material. This step may be considered as the soul of review writing. The evidence can be categorized and analyzed holistically, as well as individually according to the key concepts or dimensions under evaluation.A comprehensive

table may aid in better understanding of the readers. By the end of this process the researcher would be able to identify the state of existing knowledge and also the lacunae pertaining to the topic of interest.

Step 5: Examining Quantitative Data

This step is usually performed in a SR in order to obtain pooled outcome measures. Quantitative data for each outcome measure are extracted from individual studies. The statistical procedure for pooling data from individual studies is called meta-analysis.Specialized software like the Cochrane Review Manager or RevMan may be used for conducting meta-analysis [9]. It presents the estimate of effect from each included study, relative weightage of each study and the pooled estimate of effect. The relative weight of a study is determined by the expected variance in the result. This is dependent on the sample size and width of the confidence interval of the effect. Pooled estimate of effect is not a mathematical average of the data from individual studies, but a weighted average.

The meta-analysis is graphically represented as a Forest plot. The parts of this graph can be better understood by taking an example of the Forest plot published in a study by Yeung, et al in 2021 [10]. This is given in Figure 1 mentioned. The interventions being compared and the outcome being analysed are mentioned as the title of the figure. In this example, the interventions being compared are systemic and inhaled steroids versus control. The outcome measure is the risk ratio or relative risk for in-hospital mortality. The table shows, the outcome data, effect with confidence interval and relative weight in pooled analysis, of each study arranged in rows chronologically. This is represented in the pictorial presentation by a square at a position representing the effect and of a size representing the weight. A horizontal line through the square represents the confidence interval. In this example, the first row shows that Yeh et al did a study in 1977 which had 35 participants for this outcome. Seventeen received steroids and 18 received control intervention. This study contributed 10.4% weightage in pooled analysis. The risk ratio of in-hospital mortality was 0.53 with confidence interval 0.05 to 5.32 suggesting that steroids could be superior or inferior to control. The pictorial representation shows the low relative weight of the study and wide confidence interval crossing the vertical line of no effect (RR of 1.0). The pooled effect or the weighted average estimate of effect is represented in the row labelled as Total and is shown as the diamond in the pictorial presentation. The centre of the diamond represents the pooled effect and its width represents the confidence interval. In this example, the pooled effect suggests that the risk of in-hospital mortality may be 41% lesser with steroids compared to control. The true value may; however, vary between 72% lesser to 23% higher. The position and width of the diamond represent this pictorially and the fact that the diamond crosses the line of no effect suggest that the effect of the steroids could be superior or inferior to control.

The heterogeneity among studies is the variation in the effect of the studies which may occur due to random chance or other factors. To statistically assess the heterogeneity among studies, the I square (I^2) test is used. Heterogeneity is mentioned in the Forest plot. An I^2 of <50%, 50 – 75% and >75% is considered as low, moderate and high degree of heterogeneity. A P value of <0.10 suggests a statistically significant degree of heterogeneity. In this example, the heterogeneity is of low degree (I^2 = 0%) and is not statistically significant (p = 0.16). The statistical model used for the meta-analysis may be random effect (RE) or fixed effect (FE). The RE model assumes that a distribution of true effects which vary from study to study exists. There is no single common effect. The FE model in contrast assumes that all studies aim to estimate a single common estimate of effect. The model used is mentioned in the column heading of the outcome measure and the pictorial representation. In this example, the random effect model is used for analysis.

Step 6: Writing the Review

This is the final stage of writing the review article in which the synthesis is lucidly presented to the reader in an easily understandable written format. NR should be written in a logical and sequential manner with a proper flow of ideas. The author should be prepared for multiple cycles of writing drafts, reflection after self or peer review, and refinement. It is important to have a structured presentation having sections and subsections without irrelevant repetition or flowery prose that will divert attention from the main focus of the review. Flowcharts, tables and boxes may be used to highlight important points in the review. It is also equally important not to indulge in publication misconduct. The temptation to blindly copy and paste should be strictly curbed and the content should be written in the researcher's own words with due acknowledgement and documentation of all references. SR must be presented in the general format of Introduction, Methodology, Results and Conclusions. The Preferred Reporting Items for Systematic reviews and Meta Analysis (PRISMA) statement may be followed for writing a SR [11].

Table 1: Comparison of Narrative Reviews and Systematic Reviews

Characteristic	**Narrative Review**	**Systematic Review**
Scope	Usually broad scope.	Generally specific.
Research Question/ Hypothesis	To provide an overview of the topic of interest. May not be stated.	Clearly defined or well formulated research question.
Search Eligibility and Strategy	May not be predefined or according to some protocol. Involve subjective selection bias of the authors as the included studies are as per author's intuition and clinical experience.	Predefined and protocol based. Systematic, Objective, Reproducible and Transparent. Intention is that no study that can potentially answer the research question gets missed.
Appraisal of Studies	Qualitative appraisal of the included studies. May be influenced by the personal views of the authors. The methodology of the included studies may not be critically appraised.	Critical qualitative and quantitative appraisal of the included studies to estimate the risk of bias. A potential impact of such bias on the result of the systematic review and meta-analysis is also assessed.
Data Synthesis and Analysis	Simple description of study findings, mainly focusing on studies that the authors selected.	Protocol based qualitative and quantitative methods. Meta-analysis to obtain a pooled estimate of the included data may also be performed.

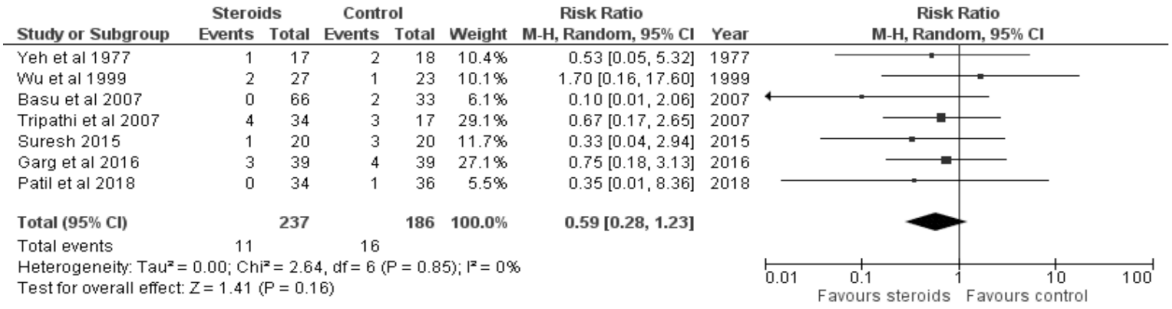
Interpretation	May be biased by author's opinion	Based on the data included.
Advantage	More popular among students, young researchers and practicing physicians. Does not require an in-depth knowledge of statistics or research methodology to write or understand. Offers solutions to problems and controversies based on the perspective and expertise of the author.	Detailed and rigorous methodology. Lesser chance of bias. Reproducible.
Disadvantages	Not very rigorous methodology. Prone to bias. Not reproducible.	Scope is limited by the defined research question/ hypothesis, search strategy and eligibility. Labor intensive. Time intensive. Require knowledge of statistical methods and research methodology to conduct and understand.

Table 2: Steps of Writing a Review Article

Step	**Brief Description**
Research Question/ Topic of interest selection	Clear, specific & relevant research question Should preferably address the PICOTS questions
Evidence search	Comprehensive, Systematic, Objective, Reproducible & Transparent search Should include multiple bibliographic databases Attempts should be made to incorporate all possible studies addressing the topic of interest
Value assessment	Methodology of individual included studies should be critically appraised to assess for possible bias Risk of bias for each study must be assessed
Integration and synthesis of descriptive data	Integration of all aspects of the topic of interest into a rational, logical, evidence based and comprehensive synthesis

Examining quantitative data	Meta-analysis to obtained pooled estimate of effect Depiction of the meta-analysis in the form of a Forest plot
Writing the review	Structured and reader friendly presentation of the synthesis PRISMA guidelines must be followed for SR

Figure 1: An example of a Forest Plot (Source: Yeung T, et al. Indian Pediatrics, 2021)



Supplementary Fig. 1 Comparison of in-hospital mortality in infants with meconium aspiration syndrome receiving systemic and inhaled steroids versus control.

Conclusion

Relevant review articles which are methodologically robust, comprehensive and well written are greatly appreciated by readers. SR are preferred for focused topics whereas, NR are better suited to comprehensive topics. Incorporation of a robust methodology similar to that essential for SR would strengthen the quality of NR. Similarly, SR would improve by incorporating the reader friendly style of presentation of NR. Young researchers as well as practicing clinicians would benefit by following the Steps of writing a review article which can easily be remembered by the simple mnemonic **REVIEW** - **R**esearch Question/ Topic of interest selection, **E**vidence search, **V**alue assessment, **I**ntegration and synthesis of descriptive data, **E**xamining quantitative data and **W**riting the review.

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RESEARCH ARTICLE

Impact of Screentime on quality of life in children with Autism and Social communication disorder – A Comparative study

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Abstract

Background:

Autism is a neurodevelopmental disorder with impairment in social emotional and communication domains and presence of repetitive behaviours and restrictive interest. Social communication disorder is closely related to Autism and is characterized by a persistent difficulty in using verbal and nonverbal communication in a socially appropriate manner with absence of stereotypical behaviour present in autism. Excessive screen time has significant impact on the quality of life of children especially those with neurodevelopmental disorders like autism, SCD.Quality of life evaluation has a significant influence on the treatment and intervention options of ASD children. Hence, this study was conducted to compare the effect of screentime in quality of life of children with autism and SCD.

Methods:

60 children in the age group of 2-10 years diagnosed with ASD/SCD along with 60 age and sex matched normal children as controls were included in the study. After applying exclusion criteria, informed consent, detailed history including complete details of screen exposure was obtained and evaluation was done. Pediatric Quality of life inventory (PedsQL) was used to assess the quality of life of these children.Data were analysed and comparison was done using SPSS-23 statistical software.

Results:

In the study,8 girls and 20 boys were diagnosed with SCD and 10 girls and 22 boys were diagnosed with ASD.65% of children were in 2-5 years of age and 35 % were in 5-10 year age group. Children with ASD with screen time <2hrs was 59.3% and >2hrs was 40.7% and in SCD, screen time < 2 hours was 82.1% and >2 hours was 17.8%. 8(72.7%) children with severe ASD had screen time >2 hours while only 1 child with severe SCD had screen time >2 hours.The quality of life was significantly different between the control and the ASD/SCD groups with ASD group more significantly affected. Further, the difference in quality of life was statistically significant with ASD and SCD having higher screen exposure, with ASD children more affected (p value < 0.01%)

Conclusion:

Quality of life is affected in children with ASD and SCD, but more so in ASD children with screen exposure. Hence parents must strictly adhere to the screen time guidelines of Indian Academy of Pediatrics to improve the overall prognosis

and quality of life in children with autism and SCD, which in turn may have significant effect on effectiveness of therapy. While giving therapy with electronic tools in children with communication disorders, specific caution on quality of program should be considered for the ASD subgroups than in SCD.

Keywords :Autism , SCD , screen -time , quality of life , neurodevelopmental disorder .

Introduction :

Autism Spectrum Disorder (ASD) is a neuro developmental condition distinguished by difficulties with social communication and adaptive skills. The core features of ASD include deficits in the quality of communicative interactions, like difficulties with initiating, misinterpreting information and impairment in nonverbal communication and responding and maintaining conversations, impairments in sharing pleasure or joint attention, limitations in making inferences, and difficulties with developing and maintaining age-related social relationships.[1,2] Most parents worry that their children will not be able to live normally and independently.In addition, lack of public awareness about autism and the increasing numbers will bring a heavy burden on society and health systems. Since the prevalence of ASD in India is increasing(1:65) in age group of 2 -9 years,[3]the parents of autistic children need to be empowered to make their children self-reliant in life.

Autism Spectrum Disorders (ASD) and Social Communication Disorder (SCD) are closely related entities. SCD is characterized by a persistent difficulty in using verbal and nonverbal communication in a socially appropriate manner, which is not otherwise explained by other diseases such as global developmental delay, autism spectrum disorders, intellectual disability, or hearing impairment. DSM-5 defines this as a separate disorder. Initially, it was not thought to be a separate entity from ASD, while ASD does comprise of social communication issues, but it also includes restricted, repetitive stereotypical behaviour. ASD must be ruled out to diagnose SCD. So, a separate diagnosis of SCD had to be coined to warrant that the distinctive requirements of these children were fulfilled.[4]

Digital technology and screen time have become an inevitable part of childhood, with the shift of learning and socialization to virtual environments. [5]According to IAP consensus 2021, Children below 2 years age should not be exposed to any type of screen; in children 2 -5 years of age screen time should be limited to less than 1 hour per day which includes recreational screen time, and time spent on screen at home to complete educational and extra-curricular assignments. In the age group of 5 -10yrs the screen time should be limited to less than 2 hours per day. Screen exposure should be used for the purpose of social interaction, education, and learning, with recreational screen time kept to a minimal. [6]

Quality of life evaluation has a significant influence on the treatment and intervention options of ASDchildren.PedsQL-4 Generic Core Scales, which has 23 items, measure the core dimensions of health as delineated by the World Health Organization and the role (school) functioning. There are four multidimensional scores and three summary scores, which include physiological function (8 items), emotional function (5 items), social function (5 items), and role function (5 items).[7]Lack of awareness, lack of acceptance by parents in early stages and resource constraints prevent early interventions making it more complicated, affecting the QoL of these children later in life.

Television watching for greater than 2 hours per day causes obesity among preschool children. [8]Food advertisement is an important link connecting media time with unhealthy food consumption and subsequent obesity.[9] There are various proposed mechanisms of screen exposure and obesity which include decreased physical activity, increased intake of high-calorie, low-energy food, and decreased sleep.Violent daytime media exposure has also been associated with sleep problems, nightmares and night awakenings, again affecting the quality of sleep

adversely.[10]Reduced blink rate and amplitude have been consistently reported with screen use, which leads to headaches.[11]

Excessive screen time has significant impact on the quality of life of children especially in those with neurodevelopmental disorders like autism, SCD.[12]This study was conducted to study the impact of screen time on the quality of life of children with ASD and SCD and to know significant difference if any,between the quality of life of both the groups.This will in turn help us to improve the quality of life of these children,which will in turn improve their therapy outcomes.

Materials and Methods:

Sixty children enrolled in Saveetha Child development centre in the age group of 2-10years, diagnosed with either autism spectrum disorder or social communication disorder by DSM -V criteria, were included by consecutive sampling for thisprospective study conducted over a 2 year period from August 2020to july2022after getting IEC approval(002/08/2020/IEC/SMCH). 60 normal age and sex matched children were also recruited and their screen time exposure was also assessed.

Inclusion criteria: Children in 2-10 years with documented diagnosis of autism / social communication disorder by a developmental paediatrician and a clinical psychologist according to DSM-5 criteria were included in the study.

Exclusion criteria:All children with other co-morbidities like other system disorders like heart disease, autistic symptoms as part of other disorders, including neurodegenerative disorders, other psychiatric disorders like schizophrenia, depression, etc. were excluded.Children with screen time < 1 hour /day were also excluded.

Informed consent was obtained. Detailed history with emphasis on screen time was obtained. Diagnosis of ASD was done with DSM-5 and severity of ASD assessed by ISAAand Clinical Global Impressions scale(CGI), whereas severity of SCD was assessed by CGI alone. CGI was chosen as SCD as such had no severity rating scale. Pediatric Quality of life inventory (PedsQL) was used to assess the quality of life of these children. PedsQL has two scales- one for children and the other one for their parents. We used the parent-report version in this study.PedsQL-4 Generic Core Scales, which has 23 items, measure the core dimensions of health as delineated by the World Health Organization and the role (school) functioning.There are four multidimensional scores and three summary scores, which include physiological function (8 items), emotional function (5 items), social function (5 items), and role function (5 items).

AAP guidelines was used initially, followed by ratified guidelines by IAP on screen time. It was introduced to parents, focussed group discussions were held to help them understand, followed up with checking their understanding and reinforcement of following the directions at home at every encounter with parents. PedsQoL data was collected before this counselling sessions and Data were analysed using SPSS-23 and effect of screen time on quality of life of children with ASD and SCD was compared.

Results :

In the present study we had 8 girls and 20 boys with SCD and 10 girls and 22 boys with ASD in the study sample.Children in the age group of 2-10yrs were enrolled where, a majority of 65% were in 2-5 years of age and 35 % were in 5-10years.

Table 1. Screen time in ASD , SCD and Control:

Condition/ Hour of exposure	N	Percentage
ASD<2hr	19	59.3%
ASD>2 hr	13	40.7%
SCD<2 hr	23	82.1%
SCD >2 hr	5	17.8%
Control <2hrs	27	45%
Control >2hrs	33	55%

Table 1 shows screen time in ASD <2hrs as 59.3% and more than 2hrs as 40.7% and less than 2hrs in SCD as 82.1% and more than 17.8%.

Table 2. Screen time vs age group

Age group/ screen time	<2 hours	>2hours
ASD 2-5 years	19(48%)	9(23%)
ASD 5-10 years	0	4(19%)
SCD 2-5 years	8(20.5%)	3(8%)
SCD 5-10 years	15(71.4%)	2(9.5%)

19 children(48%) with ASD within age group of 2-5 years had screen time of < 2 hours, 9 children with ASD in the age group of 2-5 years had screen time more than 2 hours.

Table 3.Compare ISAA and CGI of ASD

Severity	ISAA	CGI	Significance
Mild	14	13	0.8459 (not significant)
Moderate	7	9	
Severe	11	10	

10 children had severe ASD while 9 children hadmoderate ASD and 13 children had mild ASD using CGI.

Table 4. Severity of ASD vs SCD using CGI scale

Type (N)	Mildly ill	Moderately ill	Severely ill
ASD	13	9	10
SCD	19	7	2

10 children had severe ASD while 9 children hadmoderate ASD and 13 children had mild ASD using CGI. In SCD group only 2 children had severe illness while 19 were mildly ill.

Table 5: ASDand severity vs screen time

ASD severity*/ Screen time	<2 hours	>2 hours	Signifi-cance
Severe ASD	2(6.25%)	8(25%)	0.0405*
Moderate ASD	7(21.8%)	2(6.25%)	
Mild ASD	10(31.2%)	3(9.3%)	
Severe SCD	1(3.5%)	1(3.5%)	
Moderate SCD	6(21.4%)	1(3.5%)	
Mild SCD	16(57.1%)	3(10.7%)	

8 children with severe ASD had screen time more than 2 hours while2 children withmoderate ASD had screen time >2 hours.

Table 6. PedQol of ASD vs SCD vs control in children

Type (N)	Physiological function	Emotional function	Social function	Psychological function	Overall function
ASD(32)	61.8+/-26.01	52.97 ± 26.62	45.03 ±26.92	36.69 ± 31.60	49.27 ± 24.3
SCD(28)	80.01 ± 10.07	69.89 ± 10.15	78.89 ± 19.26	71.05 ± 10.03	73.14 ± 13.1
Control(60)	90.17 ± 12.98	78.89 ± 19.26	84.89 ± 16.41	81.75 ± 17.03	83.23 ± 15.2
t	t=12.988	t =9.951	t =17.131	t=16.786	t=16.872
p	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01

There is statistical significance between the quality of life in children with ASD and SCD when compared with controls.

Table 7. Disease severity vs PedQol of life in ASD & SCD

Groups	Physiological function	Emotional function	Social function	Psychological function	Overall function
1. Severe ASD(n=10)	51/02 ± 21.79	41.75 ± 23.50	31.73 ± 21.04	23.15 ± 21.58	36.59 ± 14.89
2.Moderate ASD (n=9)	73.867 ± 10.61	62.53 ± 19.90	51.19 ± 17.29	47.54 ± 32.70	62.61 ± 39.45
3.Mild- ASD (n=13)	83.767 ± 14.94	75.81 ± 16.70	70.13 ± 19.89	68.68 ± 22.25	74.49 ± 15.05
4.severe SCD (n =2)	71.542 ± 19.53	61.52 ± 17.81	52.24 ± 14.21	49.52 ± 13.72	65.73 ± 29.43
5.Moderate SCD(n=7)	86.965 ± 13.71	70.84 ± 16.50	62.10 ± 29.70	69.78 ± 82.21	78.72± 18.42
6.Mild SCD(n=19)	90.14 ± 13.42	79.17 ± 19.47	85.29 ± 16.42	82.55 ± 16.33	85.63 ± 13.89

The quality of life in children with ASD was significantly impaired when compared to children with SCD,especially those children with severe ASD.

Discussion :

Excessive media exposure is fraught with many ill-effects,mainlycausing delay in language development. This early exposure and continuing exposure will not only result in speech & language disorders but also retard the progress of already established disorders. In our study we had 8 girls and 20 boys with SCD and 10 girls and 22 boys with ASD.Children in the age group of 2-10yrs (n-60) were enrolled out of which, a majority of 65% were in 2-5 yrs of age and 35 % were in 5-10yrs.19 Children(59.3%) with ASD had <2hrs screen time and 13(40.7%) had more than 2hrs screen time and in SCD ,23(82.1%)

children had screen time <2 hours and 5(17.8%) children had > 2 hours of screen time[table -1].

Out of 32 children with ASD,according to ISAA severity scale,11 children (34.3%)had severe ASD while 21 children (65.6%)had mild/ moderate ASD.Among 11 children with severe ASD ,8 children(72.7%) had screen time more than 2 hours,while only 5 children (23.8%) with severe ASD had screen time less than 2 hours. All children enrolled in the study had screen time >1hour.

According to a study conducted inThailand,it wasfound that children with autism watched TV earlier and more frequently than normally developing children.[12]This is supported by our study where out of 28 children in the age group of 2-5 years of age with ASD,19 (67.8%)children and 9(32.1%) children had screen time of less than 2 hours and more than 2 hours respectively[Table 2].According to American Academy of Paediatrics (AAP) guidelines children less than 2 years of age should not be exposed to any kind of media, in ages 2-4 years, it should be limited to less than 1 hour per day and beyond 5years it can be up to a maximum of 2 hours.[13]

In a study conducted by Healy et al. it was found that children with ASD had a longer screen time and less physical activity than normally developing children.[14]In addition, because of their lower activity rate and longer screen time, children with ASD were more commonly overweight or obese than typically developing children.[15]

Christina et al tested the Clinical Global Impression (CGI), a clinician rating scale, with a group of children with ASD with limited language who received intervention to improve social interactions and communication. Children's CGI ratings were comparable to other assessments in measuring social communication.[16] The Clinical Global Impression-Severity (CGI-S) scales are widely accepted tools that measure overall disease severity, synthesizing the clinician's impression of the global state of an individual. CGI scales are quite often employed in clinical trials of neuropsychiatric disorders along with disease-specific rating scales. CGI scales can be adapted to reflect specific symptom domains relevant to the disorder when no disease-specific rating scales are available. In a study conducted by Kolevzon et al , CGI was used to assess the disease severity of children with angelman syndrome.[17] In our study we compared the ISAA severity scores of ASD with CGI scores ,and there was no statistically significant difference[Table 3](p value-.0.845).Hence in our study we used CGI to grade the severity in SCD[Table 4].

The increasing accessibility to smart phones and other gadgets has augmented their usage among the parents and in turn, the children are being exposed to media like mobile, iPads, tablets T.V, computer directly and indirectly at a very early age. This usage is happening not only at home but also at the day care centres, which is affecting the neurocognitive development and social communication of these children among many other ill effects.[18] It is proven that good communication skills, including both receptive and language skills at an early stage is important for good adult mental health later on and psychosocial adjustment; hence, children should be protected from exposure to media at early age to prevent communication delay.[19] According to a recent study conducted in 101 children with ASD, the longer the screen time, more severe was the symptoms of ASD (especially sensory symptoms), and more obvious was the developmental delay in ASD children with a longer screen time and younger age, especially in the language domain. [20]Parental concerns over learning issues, bullying, coping with stress and achievement were significant in both groups ASD and SCD.[21]

Not only the language domain, but also the other domains are affected by screen time. A longer screen time restricts the development of physical activities and gross motor ability and limits the development of toy operation ability, which is related to fine motor ability, adaptive

behaviors and cognitive levels. According to a study conducted by Dadson et al, the screen time affected fine motor ability and visual-motor integration in children. Playing with toys and using object substitution in play can offset these effects to some degree. [22] The recommendation by Canadian Society for Exercise Physiology is that for the normal development of motor skills and cognitive skills, young infants and toddlers should minimize the time spent sitting and watching screen for a long time.[23]A study done previously also shows that screen time was negatively associated with social skills throughout early childhood.[24]

In both ASD and SCD groups, screen time was found to be affecting severity of the condition,especially in children with ASD.8 children with severe ASD had screen time>2 hours while 2 children with moderate ASD had screen time >2 hours.In case of SCD children, only 1 child who was classified as severely ill by CGI had screen time more than 2 hours where as3 children with mild illness had screen time of more than 2 hours. [table 6]It is statistically significant with a p value <0.05.

Quality of life between the groups was analysed, which showed that the QoL of autistic children was significantly lower than that of social communication disorder in both the individual and overall domains. All domains were significantly impacted, though the effect in the physiological domain was lesser; psychological function is the most affected, bringing the overall score significantlylower.[table.7]

When compared with SCD children, ASD children, especially of severe autism, showed considerable difficulty in having a good quality of life(QoL). In mild, moderate and severe grade, QoL showed statistically significant problems. The physiological functions of body movement showed not much difference in mild-moderate variety. In all other domains, there was a significant difference in both when compared to SCD as depicted in [Table 8].

Hence it is evident that screen-time affects the quality of life in children even when effective interventions were going on in both ASD and SCD. However, its negative implications in SCD were less than in ASD and hence parents have to be more cautious with use of media especially in ASD children during education and even with therapy. Even in SCD children, the screen time should be selected, monitored and quality of program should be checked by parents to enable children get quality program at optimal time and not over exposure.Parental concerns over learning issues, bullying, coping with stress and achievement were significant in both ASD and SCDgroups.

Hence it is clear that screen time significantly affects the developmental domains of children which in turn negatively impact on the quality of life.Thus screen time has to be minimised in children especially those with NDDs like ASD ,SCD which will in turn improve the quality of life of these children hence improving their therapeutic outcome.

Conclusion:

Quality of life is significantly impaired in children with autismdue to screen time.Hence parents must strictly adhere to the screen time guidelines to improve the overall prognosis and quality of life in children with both autism and SCD.

The interventions which we consider to correct the core features in Autism should also address the core concerns of QoL.The significant impact in social, emotional and psychological domains has to be considered in all ASD children, even in high functioning, as it will affect the scholastic and overall performance.

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REVIEW ARTICLE

Newborn Screening – Indian Perspective with Issues & Challenges

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Background:

Newborn Screening (NBS) began in early 1960's by a pioneering work of Dr. Robert Guthrie, USA with discovery of detecting Phenylketonuria (PKU) from dried blood spots (DBS) on filter paper, by a simple test as bacterial inhibition assay (Guthrie, 1961). His research work led to the now well-known 'Guthrie' card procedure/ test which is nothing but blood absorbed from the baby's heel prick onto the special thick filter paper to screen PKU in the newborn.

The credit of the development of screening tests goes to Bickel and his co-workers, when they successfully made dietary control on phenylketonuria in 1954 and made a remarkable breakthrough in the management of PKU and innovations in detection techniques. The importance of early diagnosis of phenylketonuria was realised when it was observed that individuals with phenylketonuria had improvement in their clinical status. However, very soon the development of robust immunoassays for thyroxine and thyroid stimulating hormone (TSH) in the 1970s became feasible to add congenital hypothyroidism (CH) to the NBS panel. In 1963, Massachusetts in United States began universal mandatory screening for phenylketonuria and rapidly other states started establishing newborn screening programs by adding more disorders to the panel.

Newborn screening popularly now known as neonatal screening is testing newborn babies for serious developmental, genetic and metabolic disorders so that important action can be taken during the critical time before symptoms such as mental and/ or motor retardation, physical disabilities or death occurs (Dave and Das, 2010). It is the process of testing newborn babies after 48 hours of birth for treatable genetic, endocrine, metabolic, and hematologic diseases before the development of symptoms because in the newborn period, inborn errors of metabolism (IEM) can be asymptomatic and easily be misdiagnosed as sepsis or birth asphyxia. The delay in diagnosis or undiagnosed IEMs can lead to severe mental deterioration and even death. The prompt detection therefore requires vigilance and the early & pre-symptomatic measurement of biochemical markers of IEMs.

Newborn Screening is considered by many countries as a modern public healthcare program that identifies inborn errors of metabolism (IEM) affecting a child's long-term health and survival. The program is aimed at pre-symptomatic detection of possible risk of neonates & infants with life threatening genetic diseases, facilitating

proper diagnosis and intervention of their clinical conditions. By preventing morbidity or mortality of children, it ensures proper growth and development of children.

How the NBS Disorder is selected ? :

In 1968, Wilson and Jungner published their World Health Organization (WHO) report entitled "Principles and practice of screening for disease" which remains till date a significant contribution toward public health and population study literature. The WHO issued guidelines and criteria for selecting disorders in a particular nation/ geographic area which also have important ethical and legal implications.

The ten Wilson-Jungner criteria for selection of newborn screening disorder and appraising the validity of a screening program (Wilson and Jungner, 1968) are as follows:

1. The condition being screened for should be an important health problem.
2. The natural history of the condition should be well understood.
3. There should be a detectable early stage.
4. Treatment at an early stage should be of more benefit than at a later stage.
5. A suitable test should be devised for the early stage.
6. The test should be acceptable.
7. Intervals for repeating the test should be determined.
8. Adequate health service provision should be made for the extra clinical workload resulting from screening.
9. The risks, both physical and psychological, should be less than the benefits.
10. The costs should be balanced against the benefits.

American Association of Paediatrics Newborn Screening Task Force in 1999, recommended that "Maternal and Child Health Bureau of Health Resource and Services Administration" should engage in a national process involving government, professionals, and consumers to advance the recommendations of this Task Force and assist in the development and implementation of nationally recognized Newborn screening system standards and policies; outlined a process of standardization, of outcomes and guidelines for State Newborn Screening Programs, defined responsibilities for collecting and evaluating outcome data, recommended uniform panel of conditions to include in State Newborn Screening Programs (AAP, 2000). American College of Medical Genetics, Newborn Screening Expert Group also provided guidelines towards a uniform screening panel and system for newborn screening (ACMG, 2006).

There are some disorders whose screening offers clear and direct benefits to the newborn, and others in which the benefits of screening are not that obvious. The screening of few diseases that are not treatable are also included with a primary objective of getting important information for future genetic counselling of the family or prenatal diagnosis with preventive approach. All of these issues have led to significant discrepancies in the criteria used to establish the diseases to be included in screening (Castineras et al, 2019).

What is a Newborn Screening Test ? :

NBS is a simple blood or urine screening test conducted on apparently healthy babies soon after birth & is not designed to be diagnostic. Therefore, abnormal newborn screen results prompts the initiation of further confirmatory diagnostic testing, neonate evaluation, and consideration of treatment while waiting for the diagnostic test results. Hence, newborn screening is always considered as a program rather than a simple laboratory test as it involves early detection, treatment and management of the newborn who may be affected with IEMs (Dave, 2016). These disorders may individually be rare but their collective incidence is 1 in 1500–2000. Their early & pre-symptomatic detection is significant as timely intervention, treatment and therapy

by the referring doctor can lead to the reduced morbidity, mortality and associated disabilities in affected infants, thus giving baby the best chance of healthy life. Any presumptive positive result of the NBS test requires confirmation, preferably with an independent sample and test method. The prompt detection therefore requires vigilance and measurement of biochemical markers with appropriate technology.

Advances in NBS Technology:

From the first generation of PKU screening using ferric chloride reactions in neonatal diapers to Guthrie and Susi's bacterial inhibition assay, the next significant milestone in newborn screening methodology was the advent of tandem mass spectrometry (TMS) using dried blood spot (Chaceetal,1993). Other techniques include spectrophotometry, fluorometry, and immunoassays.

The rapid and multi component techniques of tandem mass spectrometry (LC/MS-MS) screens about 46 metabolic conditions simultaneously from a single blood spot. Since its first application by Tanaka in 1966 to discover isovaleric acidemia, the GC/MS urinary metabolic screening has been used worldwide to diagnose number of IEMs because of its high accuracy, sensitivity and power of analyzing multiple compounds simultaneously. Matsumoto and his research team developed a rapid, practical, non-invasive and simultaneous urinary metabolite analysis in Japan for Newborn Screening (Matsumoto & Kuhara, 1996). The author of this Review is the first to introduce the same GC/MS technology in 1998 in India for High-Risk Screening of IEMs using urine filter paper, when concept of NBS was not initiated/accepted due to various health constraint factors.

The High-risk screening differs from NBS in that the metabolic screening is conducted on critically ill sick / NICU babies. Over a period of time the hospital/Lab based data offers the incidence of common IEMs in that area or referral population. Based on the last 20 years' of our experience in high-risk neonates and children, the most common 13 IEMs are identified which are satisfying the Wilson & Jungner guidelines to select NBS disorders (Dave, 2022) in Indian population. Though individually rare, the collective incidence of IEMs in more than 7300 high-risk babies was found to be 1: 30 - 1220 (Table-1). Out of total 22% metabolic abnormality (1633 of total 7330 cases), these 13 common IEMs constituted 12.4%. It is evident that State or private hospitals can focus on these 13 metabolic conditions while considering newborn screening service. In general population, the collective incidence of IEMs is reported to be around 1:1500-2500.

Recently, screening methodologies have subsequently expanded to include DNA-based testing strategies. Targeted genetic testing has been included in newborn screening algorithms for cystic fibrosis, where an elevated immunoreactive trypsinogen measurement is followed by screening for a panel of CFTR (cystic fibrosis transmembrane conductance regulator) gene mutations. Similarly, a targeted genetic testing strategy has also been described for screening the newborns for familial conditions (e.g. familial hemophagocytic lymphohistiocytosis (FHLH) due to UNC13D inversion mutations) (King and Hammarstrom, 2017). The advent of next generation sequencing (NGS) has opened up the new era of Newborn Genomic Screening which is currently at the research level, viz. NIH Genome Screening project.

Newborn Screening (NBS) Program :

Screening programs are often run by the state or national governing bodies such as public health departments. It is done for all neonates born in their jurisdiction for a defined panel of treatable disorders. The number of diseases screened for is set by each jurisdiction, and can vary greatly.

The high-risk screening data from these areas often indicates the priority NBS disorders.

While typically using blood taken from a heel-prick, more recent newborn screening expansion has included bedside testing to detect conditions

such as hearing loss (Nelson et al, 2008) and congenital heart disease (Thangaratinam et al, 2012 ; Therrell et al, 2015). A population-based dried blood-spot screening (NDBS) received the general acceptance in early 1960s as an essential preventive public health activity. The nickname of NBS test was a 'PKU test' in general population. Since then many feedbacks from the medical & social scientists helped in how to implement NBS as a universal screening program.

The importance & outcome of population-based NBS programs has been well illustrated at Boston Children's hospital emphasising the long-term outcome of expanded newborn screening (Landau et al, 2017). Various NBS panels based on the number of disorders to be tested are available, such as NBS-2 (CH & CAH), NBS-3 (CH, CAH & G6PD), NBS-5 (NBS-3+ Galectosemia & PKU), NBS-7(NBS-5+Biotinidase Deficiency & Cystic Fibrosis).

The expanded neonatal screening using Tandem MS technology includes additional 46 conditions involving, amino, organic & fatty acid disorders. The selection of the panel depends on the existing epidemiological data or prevalence in that region and also affordability of the parents, if the NBS tests are not free or covered under national program. The informed consent of the parents is a must to undergo any NBS tests and generally remains the responsibility of the hospital.

What is NBS Referral Laboratory? :

The NBS tests are ideally conducted by the 'Referral NBS Laboratory' exclusively devoted to various NBS Panels using ELISA, Immunofluroscent Assays, or Mass Spectrometry methods having capacity of 100-1000 tests per day. The ideal NBS Laboratory at State level also conducts public awareness, education, training to medical /paramedical professionals, regional data analysis & publications. These laboratories observe strict quality management rules & NBS laboratory accreditation programs. The pre-analytical, analytical & post analytical systems must be followed for the integrity of work flow, sample collection, time & condition of collected sample, transport temperature & conditions, quality of collected sample etc. by a well certified & accredited NBS laboratory.

Being a screening test, the high false positive rate is accepted with a goal of not escaping a single positive case from the program. The less than 0.3% false positive rate & positive predictive value of > 20 is considered as an ideal target by the NBS Laboratory (Jalan & Kudalkar, 2021). The confirmatory diagnostic test in presumptive positive cases with further advice to the patient's family & coordination with the clinician for appropriate dietary & therapeutic intervention should be immediately provided by the same NBS laboratory. This is to avoid the delay in intervention &treatment.

The screened positive newborns, once confirmed with diagnostic tests are often referred to the tertiary care hospital or the expert metabolic paediatrician /neonatologist for treatment. The genetic counseling to the parents is necessary here to explain the nature of NBS condition, recurrence risk with future preventive prenatal diagnosis, importance of therapy & possibility of lifelong care in some cases (Dave, 2022).

Worldwide NBS Scenario:

Newborn Screening is considered as a modern science program, having firm roots in international countries like US, UK, Europe, Australia, Japan, etc., and is slowly entering Indian healthcare system and other developing countries like sub-Saharan Africa, South Africa and some parts of Asia.

The conditions included in newborn screening programs around the world vary greatly, based on the legal requirements for screening programs, prevalence of certain diseases within a population, political pressure, and the availability of resources for both testing and follow-up of identified patients. From a relatively simple blood or urine screening test, originally used for detecting a single congenital condition (viz. CH or CAH) to a more comprehensive and complex

mass-spectrometry screening system that can detect over 46 different disorders in one single test is used in population (Therrell, et.al., 2015). Tandem Mass Spectrometry (TMS) is widespread accepted method in developed countries, referred as expanded neonatal screening test, covering many preventable amino, organic & fatty acid disorders.

The American College of Medical Genetics published the document newborn screening toward a universal screening panel and system in 2006 with the aim of establishing a uniform screening programme across its states which consists of 29 core diseases as primary targets for screening and 25 diseases as secondary targets depending on the benefits of the disease detection (ACMG, 2006).This led to the establishment of the 'Recommended Uniform Screening Panel' (RUSP), including a large group of diseases. Until 2019, RUSP includes 35 primary targets and more than 26 secondary targets and is also considered a reference for the purpose of debate and evaluation in other countries. (RUSP, 2018).

Similarly, newborn screening for lysosomal storage diseases is also considered with an ethical and policy analysis (Ross, 2012).The screening for hemoblobinopathies, with special emphasis on sickle cell disease has also gained the priority in certain countries with high prevalence to reduce the national burden.

In Canada, newborn screening includes a considerable number of metabolic disorders, although fewer compared to the US. Some countries in Central and South America have high-quality, well-established NBS programmes, especially Costa Rica and Uruguay, where all newborns are screened by means of MS/MS. However, most screening programmes in South America include a limited number of diseases in addition to PKU, and few regions use MS/MS (Queiruga, et. al., 2011). Egypt has an established NBS programme, using MS/MS in some part of the population, and other North African countries are aiming at projects for the establishment of routine newborn screening (Shawky, et. al., 2012). The situation in Sub-Saharan Africa and South Africa is quite different, with very few reports on NBS programs.

In Europe in the past 50 years, a screening for PKU with addition of screening for biotinidase deficiency and classic galactosemia is established through the European Commission funded project to analyse newborn screening policies and practices with a goal of setting the foundations to develop guidelines (Burgard, et. al., 2012). There are still differences between different countries, as in France where only routine screening of PKU is done. The situation is quite different in Southeast Europe, as screening is not done there to detect any metabolic disorders (Groselj, et. al., 2014). In Italy, a law was passed in 2016 to do routine NBS programme consisting of 40 conditions (Castineraset al, 2019). The Middle East, Qatar or Saudi Arabia screen all newborns for a broad range of metabolic disorders; others screen only 2 diseases e.g. United Arab Emirates and Kuwait, and a third group continues to not have any form of screening program.

In many Asian developing countries, NBS is now implemented with few parameters reflecting their economy and the public health systems but many other countries with fewer resources have not instituted any NBS programmes till last decade (Padilla & Therrell, 2007). Being the developed countries, all newborns are screened in Australia and Japan for a substantial number of metabolic diseases with MS/MS (Wilcken, et. al., 2009 and Yamaguchi, 2008). In China, screening already covers 80% of newborns and includes PKU, and testing by MS/MS in some regions (Shawky, et. al., 2012).

NBS- Indian Perspective:

For the first time in 1984, screening for Congnital Hypothyroidism (CH) in 12,407 newborns was reported by M. Desai & group from Wadia Children Hospital, Mumbai using fetal cord blood with the incidence of 1:2804 (Desai et al,1987). Later, NBS was carried out for

aminoacid disorders using conventional method in Karnataka in 1987 (Ramadevi & Rao, 1988). A pilot newborn screening program using dried blood spots from heel prick was initiated by CDFD at Hyderabad in 1988 & 12,500 newborns were screened for aminoacidopathies, Congenital hypothyroidism (CH), Congenital Adrenal Hyperplasia (CAH), Glucose-6- phosphate dehydrogenase deficiency(G-6-PD),etc. The CH (1 in 1700) followed by CAH (1 in 2575) emerged as most common disorders (Ramadevi & Naushad, 2004).

There are 3 public screening programs with varying degrees of complexity (panels, geographical areas covered, and births screened per year) that have been running for more than 5 years. In 2007, the union territory (UT) of Chandigarh in India started a program to study the prevalence of three disorders (CH, CAH, and G6PD deficiency), concentrated in four urban government hospitals with about 15,000 births per year (Kaur, et al., 2010). Chandigarh's NBS program is the pioneering public NBS program in India and continues to this day with the addition of other government hospitals.

The Goa NBS Program (2008 to 2013) was initiated based on the desire of the state government to improve neonatal care in a public hospital & screened (~48,000) about 50% of the births in Goa in the five-year period (Mookken, 2020). The six disorders (CH, CAH, G6PD, galactosemia (GALT), biotinidase deficiency, and cystic fibrosis) were initially screened at NSQAP Neogen laboratory, Bengaluru followed by about 46 conditions using MS/MS method. The Goa program is the best example of a public–private partnership (PPP) model that was financially beneficial to the state government. Kerala screens more than 1,40,000 births per year in over 90 government hospitals (Maya, 2015). The program screens for CH, CAH, G6PD, and GALT for 25% of all births in Kerala per year in four laboratories spread across the state. None of the state screening laboratories participate in NSQAP. The 5 conditions were screened by a tertiary care Govt. hospital in Bengaluru, South India for 47,623 babies in 3 years (Year 2016 to 2018) giving G6PD as the most common IEM (1:414) followed by CH (1:2735) & CAH (1:4102) using the infrastructure of private Navigene Genetic Lab. Mumbai (Kommalur et al, 2020). The Galectosemia & PKU were found to be rare with incidence of 1:20513 & 1:41027 respectively, though in a smaller cohort study.

In India, we have certain geographic / tribal belts with high incidence of Sickle cell disease & Thalassemia, emphasizing the screening for Hemoglobinopathies which is also currently undertaken by National Health Mission (NHM) in various States .

As India does not have population-based genetic epidemiology studies, the exact burden & incidence of NBS disorders is not known. We simply followed the Western data. The incidence of PKU is also low in our country compared to the other countries. In 2008, ICMR had launched a pilot multi-centre NBS program to screen 100,000 babies for only 2 disorders (CH & CAH) in five cities – Mumbai, Delhi, Chennai, Hyderabad & Kolkata indicating the feasibility of NBS in India (ICMR, 2014). The collective incidence of CH was found to be 1: 1172, while Southern India showed higher incidence rate as 1: 727, possibly contributing to consanguinity & endogamous marriages. In Bangalore-based study, the incidence of CH was estimated to be 1:1042 in 19,800 babies screened (Kishore et al 2014). The incidence of CAH from Indian reports varies from 1:2600 to 1:16000 livebirths which is relatively higher than Western countries (Maiti & Chatterjee, 2011).

In 2011, National Neonatology Forum (NNF) recommended 3 NBS conditions- CH,CAH & G6PD – as the basic screening panel to implement NBS in India. In the affordable patients, it can be extended NBS panel of 46 conditions using MS/MS test. The West Bengal in 2009 & Gujrat in 2011 have approved a launch of Govt. NBS programs but these are yet to be implemented.

Issues & Challenges in Universal Implementation of NBS in India-

Currently in India, the consensus is that all babies need to be screened, but there is no coherent national strategy for implementing a universal screening program nor guidance on which disorders should be included in the screening panel. The ICMR study was a pilot study conducted on very small cohort considering high annual birth rate (about 27 million per year), though it is well accepted that NBS is the need of the hour in India (Verma & Bijarnia, 2015).

Today, there are numerous NBS laboratories, public and private, in India offering NBS tests.

Some of them offer comprehensive NBS panels, resembling the Recommended Universal Screening Panel (RUSP) in the USA (https://www.hrsa.gov/advisory-committees/heritabledisorders/rusp/index.html). Many, but not all of them participate in the Newborn Screening Quality Assurance Program (NSQAP) offered by the Centers for Disease Control and Prevention (CDC), US. (https://www.cdc.gov/labstandards/nsqap.html)

The biggest difficulties to start NBS program in

India are as follows:

- The cost of case finding (including diagnosis) is not economically balanced to possible expenditure on medical care as a whole.
- Facilities for diagnosis and treatment is not easily available at the screening site/referral NBS laboratory. In short, NBS is not under one umbrella of health services.

All the above mentioned programs use panels of disorders that are well understood by physicians in India and easily treatable. Disorders screened by MS/MS (fatty acid, organic acid and amino acid disorders) are not often the part of the screening panels due to resource constraints (significant capital costs, few experts, lack of treatment facilities, and high cost of diets).

With annual birth rate of about 27 million babies, the hearing defects (4:1000) & congenital heart defects (5:1000) are other NBS conditions requiring serious attention besides IEM screening. The high-incidence rate of consanguinity, endogamous marriages, racial & religious genetic diversity & tribal populations in selected geographical areas contribute significantly to the national burden of NBS conditions.

In our experience, it is not the technology that is preventing Indian babies from getting screened, be it newborn or high-risk screening. But lack of awareness about NBS screening and knowledge about the latest technologies among the healthcare providers, as well as our different national health priorities are the main contributing factors for the delay in implementing NBS program. As in the case of introducing iodinated salt or compulsory polio vaccination, the support & advocacy by the Govt. of India is a prime factor at the population level. Government support will go a long way in establishing national level newborn screening program in collaboration with private laboratories as a countrywide network system. Nevertheless, it is also the moral responsibility of those professionals caring for the neonates to inform & educate the parents about the newborn screening & explain them its long-term benefits & cost-effective approach of prevention of disabilities. The primary care physicians & paramedical staff like nurses, midwives need to be educated. The NBS programs will not only help in improving our IMR & NMR rates but will produce important genetic epidemiological data which is currently lacking in India.

Important questions need to be answered while implementing the NBS process in India, such as

1) What barriers does a primary care physician face in coordinating a medical evaluation and communicating with the family in an infant with a positive screening result? 2) What obstacles do families confront in the time after a newborn screening result returns positive? 3) How can coordination of follow-up care be optimized in a confirmed newborn screen result? These fundamental questions must be addressed to

optimize collaboration between primary care and specialty care physicians by public-private partnership, and to ensure the continued success of newborn screening in the 21st century.

CONCLUSION:

In brief, there is a need of a holistic comprehensive newborn screening program and not just the provision of laboratory testing services. The shortcomings of the previous program need to be addressed, and more emphasis to be placed on follow-up activities, access to experts and availability of diets. Benefits of NBS do not end only with saving life of the diagnosed case but they extend up to prenatal period of diagnosis and family genetic counseling. It is also true that the fruits of genomic science should not remain a luxury available only to the developed nations. The next technological advances like mass spectrometry, microarrays & next generation sequencing are on the horizon and fast entering into clinical practice. Yet, it should be noted that technology is only one facet of a well-functioning newborn screening program, which must have both excellent detection and follow-up services. The ethical, social & legal implications should not be overlooked. The challenge finally in India is the ultimate coverage of 100 % screening of neonates & infants which can only be achieved with a political will & financial commitment considering our socioeconomic infrastructure.

Table 1- High-Risk Screening of 7330 Babies Abnormal=1633 (22 %) & Normal= 5697 (78%)

Incidence of 13 IEMs -1: 30- 1220

Table 1: Selection of NBS Disorders based on Incidence of IEMs High- Risk Screening Data by GC/MS Comprehensive Test (2005-2022)

Sr. No	Inborn Error Of Metabolism	2005 N= 2040 Abn = 176 - 8.6%	2015 N= 3341 Abn= 291- 8.7%	2018 N= 5880 Abn = 568 -9.6%	2020 N= 6510 Abn=717 – 11%	2022 N= 7330 Abn=906 -12.4 %
1.	Methylmalonic Acidemia (MMA)	1: 55 (37)	1: 64 (52)	1: 34 (172)	1: 30 (214)	1:28 (265)
2.	Tyrosinemia / Hepatic Dys	1: 78 (26)	1: 88 (38)	1: 96 (61)	1: 72 (91)	1: 50 (146)
3.	Hyperglycinemia	1: 146 (14)	1: 119 (28)	1:189 (31)	1: 171 (38)	1: 179 (41)
4.	Glutaric Aciduria 1	1: 102 (20)	1: 90 (38)	1:95 (62)	1: 90 (73)	1: 93 (79)
5.	Galactosemia	1: 136 (15)	1:176 (19)	1:120 (49)	1: 130 (50)	1: 113 (65)

6.	Maple Syrup Urine Disease(MSUD)	1: 156 (13)	1: 239 (14)	1: 128 (46)	1: 99 (66)	1: 99 (74)
7.	Propionic Acidemia (PA)	1: 170 (12)	1: 176 (19)	1: 155 (38)	1: 105 (62)	1: 106 (69)
8.	Urea Cycle Disorder (UCD)	1: 170 (12)	1: 134 (25)	1: 168 (35)	1: 186 (35)	1: 188 (39)
9.	Fructose-1, 6-Diphosphatase Def. (FDPD)	1: 136 (15)	1: 134 (25)	1:235 (25)	1: 217 (30)	1: 159 (46)
10.	Multiple Carboxylase Def. (MCD)	1:510 (4)	1: 257 (13)	1:309 (19)	1: 260 (25)	1: 271 (27)
11.	Isovaleric Acidemia (IVA)	1: 680 (3)	1: 835 (4)	1:534 (11)	1: 591 (11)	1: 488 (15)
12.	Beta-Ketothiolase deficiency	- -	1: 304 (11)	1: 420 (14)	1: 383 (17)	1: 215 (34)
13.	Ornithine Trans-Carbamylase Def. (OTC)	1: 408 (5)	1: 668 (5)	1: 1176 (5)	1:1302 (5)	1: 1221 (6)

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Self injurious behaviours

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Definition: Self-injurious behaviour (SIB) was defined in the original study (Oliver et al., 1987) as repeated, self-inflicted, non-accidental injury producing bruising, bleeding or other temporary or permanent tissue damage, and repetitive behaviours that had the potential to do so if preventative measures were not taken. The study therefore included people whose self-injury was very clear and did not include those people who merely showed stereotyped behaviour. (1) It is included in "Conditions for further study" in DSM-V and is coded in ICD under Intentional self-harm X71-X83.

Examples of self-injurious behaviours: repeated wetting and rubbing of hands in the mouth which causes maceration of the skin, biting or picking of skin resulting in open lesions which may get infected, violent banging of head or other body parts against hard surfaces which may result in fractures, retinal detachments, intracranial hemorrhages and even leading to death. (1)

Defining self-injurious behaviour by using an observable behaviour as a criterion may lead to under-estimation of SIB in young children, thereby having implications on the early interventions and thus future outcomes. (2)

Also, this definition when used in prevalence studies, does not give importance to the form of self-injury (For example: . lip and finger biting in Lesch–Nyhan syndrome; hand biting in fragile X syndrome; skin picking in Prader–Willi syndrome).

Self injury is a major reason for intensive special education usage and hospitalisation thus increasing costs of an individual's care. (3) In addition to this, the presence of SIB increases the risk of family, educational and residential placement breakdowns, restrictive practices in primary care settings and use of psychotropic medications. (4)

Prevalence: Within the total population of people with intellectual disability estimates of the prevalence of self-injury vary from 4 to 24%. (2) Prevalence of SIB in individuals with autism is reported to be as high as 50% which is much higher than for individuals with intellectual disability. (4) The limited data available suggests that self-injury is very persistent. Taylor, Oliver, and Murphy (2011) report approximately 84% persistence over 18 years, Emerson et al. (2001) 71% over 7 years and Cooper et al. (2009), using a definition of self-injury with a high threshold, 62% over 2 years. Also, majority of studies suggest that the prevalence of self-injury increases with age into adulthood and persists for many years. (2) With such high rates of prevalence and persistence, it is very important to understand various aspects of self-injury to help in the intervention and management.

Etiology of SIBs:

Environmental and biological factors are associated with both repetitive and self-injurious behaviours. (3)

Environmental factors:

Results from earlier studies have showed that:

(a) environmental events can evoke and modify SIBs,

(b) self-injury can be reduced by manipulation of existing contingencies,

(c) self-injury can be reduced by the introduction of adaptive behaviours that displace self-injury and

(d) self-injury can be reduced by increasing the non-contingent availability of specific reinforcement. These demonstrations support the argument that self-injury can be influenced significantly, favourably and unfavourably, by the immediate environment. (2)

For example, in individuals with prolonged institutionalization, especially when living in confinement, increase in repetitive and self-stimulatory behaviours has been observed. In children with visual impairment, self-injurious behaviour in terms of applying pressure on the optic globe has been observed. In such cases, increasing the environmental stimulation can decrease the occurrence of SIBs.

High levels of environmental stimulation can lead to anxiety, frustration and stress leading to SIB. Also, children with intellectual disability and ASD have deficits in the ability to convey their experiences which also contributes to the frustration.

Operant learning influences self-injurious behaviours. (2) As with other behaviours, predictable reactions of caretakers to SIB, can reinforce the behaviours. Caretakers may reinforce the behaviour by allowing access to materials or activities that are otherwise restricted or by removing the task demands. In these situations, SIB may be viewed as a learned behaviour that serves as a form of non-verbal communication. (3)

There is also a role for behaviour dysregulation as indicated in literature. Overactivity, impulsivity and repetitive behaviours are associated with higher levels of SIBs. These are behavioural markers for impairments in behavioural inhibition. Behavioural inhibition comprises both the capacity to inhibit prepotent responses to evoking stimuli and the capacity to inhibit a response once emitted. (4)

Biological factors:

Biological factors are also important in predicting the occurrence of self-injurious behaviours. Table 1 lists the biological risk factors for SIBs.

Table 1:

RISK FACTORS	
Intellectual Disability	More severe deficit in adaptive behaviour Level of ID
Autism	Meeting criteria for autism on a standardised measure
Genetic Syndromes	Cri du Chat syndrome Cornelia de Lange syndrome Fragile X syndrome Prader–Willi syndrome Lowe syndrome Down syndrome
Physical health	One or more health problems Visual impairment
Sensory sensitivity	Tactile hypersensitivity

Syndromes in which the prevalence of self-injury is higher than expected given relevant group characteristics include: Lesch–Nyhan, Cornelia de Lange, Cri du Chat, fragile X, Prader–Willi and Smith–Magenis, etc. The current data demonstrate that the presence of specific syndromes is associated with a two to 35-fold increase in the odds of self-injury. (2)

Alterations in neurotransmitter levels in early development are thought to contribute to SIBs. For example, Dopamine deficiency in Lesch-Nyhan syndrome.

In another hypothesis, it has been suggested that SIBs release endogenous opiates that maintain the behaviour, therefore there have been trials of opiate antagonists (naltrexone) for reducing SIBs. This is thought to occur due to the dysregulation of hypothalamo-pituitary-adrenal axis, the pro-opiomelanocortin (POMC) molecule specifically. The POMC molecule, which is produced mainly in the anterior pituitary, undergoes enzyme cleavage producing a number of biologically active products including the opioid peptide β-endorphin and the peptide hormone adrenocorticotrophin (ACTH).These products of POMC are normally released together by the pituitary in response to stress, and in adults plasma levels of the two

products are normally highly correlated. Studies have suggested however that this normal "coupling" of β-endorphin and ACTH is reduced following episodes of SIB in adults with developmental disabilities, with levels of β-endorphin elevated with respect to levels of ACTH. Subsequent

studies of response to naltrexone revealed a complex pattern of results in which higher basal levels of β-endorphin relative to ACTH and elevation of β-endorphin levels following episodes of SIB were associated with different patterns of response to treatment with naltrexone. (5)

Increased rates of SIBs have been noticed in association with menstruation, physical conditions such as otitis media, fatigue, allergies, etc. These conditions may not directly have an effect on SIBs but may reduce threshold of individual's tolerance towards task demands leading to frustration and thus SIB. (3)

A number of studies in the past have indicated that pain may be directly related to self-injury. For example, children with chronic pain tend to self injure near the site of pain. Some studies showed that gastro-oesophageal reflux was related to self-injury in Cornelia de Lange syndrome, presumably as a result of pain and discomfort. It has been observed that self-injury occurs in response to pain before being subjected to social reinforcement. Self-injury along with reinforcements can then moderate pain perception and thereby increase the pain threshold leading to an increase in SIB. (2)

Self-restraint behaviours:

Self-restraint behaviours are those which restrict the movement of an individual's body parts using clothing, objects or a person's own body. There are many different topographies in self restraint behaviours which can be grouped into three major categories. First would be restricting the movement of body parts by wrapping or entangling them in inanimate objects, like in a cloth. The second category comprises behaviors in which one part of the body is used to restrain another, for example, by clasping hands together, sitting on hands. The third category consists of self-applying, or requesting application of protective equipment or restraints, or holding particular objects. The Self-Restraint Questionnaire (SRQ) which is a 23-item instrument, can be used to assess self-restraint behaviours. (5)

Stages of SIB:

According to the Guess and Carr (1991) model of the development of self-injury, in the first stage there is emergence of rhythmic repetitive behaviours. In Stage 2, these repetitive behaviours function to optimise arousal. In Stage 3, these behaviours become sensitive to environmental (social) reinforcement and are shaped into increasingly severe behaviour. While Guess and Carr's model explains the development of self-injury, it does not account for the elevated prevalence of self-injury in ASD or genetic disorders, and the associations between self-injury and painful health problems, repetitive behaviours and impaired behavioural control.

Oliver et al (2015), modified this model by

adding a fourth stage where the SIB becomes less sensitive to the environmental and social triggers and the behaviour is not under the individual's control anymore. Self-restraint behaviours become increasingly evident in this stage in an attempt to control the SIB. Stage 2 was also modified as to include behaviours that are sensitive to internal states and this accounted for the associations between pain and SIB (2)

Evaluation:

The first step in assessment of an SIB, is to describe the behaviour of concern. For example, hitting head with hand. The clinician should take a complete clinical history by reference to previous clinical notes and discussions with the caregivers. The behavior concerned will often have emerged at a relatively young age and may not have been regarded as particularly problematic until it started to result in tissue damage. The clinician should enquire regarding possibly relevant life events, including those with traumatic potential such as abuse and bereavement.

A wide variety of physical health problems may contribute to SIB and initial assessment should include enquiries about pain in any part of the body, headache, migraine, and menstrual pain and about other sources of discomfort such as fever, coughs and colds, and constipation.

Psychological examination will obviously include assessment of ID and ASD with severity levels using appropriate tools and consideration of the possibility of genetic syndromes associated with SIB including Cornelia de Lange syndrome, fragile X syndrome, Lesch-Nyhan syndrome, Rett syndrome, Smith-Magenis syndrome. Assessment should also consider the possible presence of other potentially treatable psychiatric disorders which may contribute to causation and/or persistence of SIB, including anxiety disorders, mood disorders, post-traumatic stress disorder, and psychotic disorders.

Assessment of co-morbid conditions like pain, sleep disturbances, overactivity and impulsivity should be done.

The clinician should gather descriptions of the form, interrelationships, context, consequences, and history relating to a challenging behavior, together with information on the client's communicative abilities and possible socially appropriate behaviors which might be reinforced as functional alternatives to challenging behavior. The Functional Assessment Interview (FAI) includes questions on the topography, frequency, duration, and intensity of the behaviors to be assessed, their co-occurrence, motivating operations, antecedents, and possible maintaining consequences. This helps us identify a communicative function for the SIB. (5)

Interventions:

The intervention needs to be personalised to every child based on the level of intellectual functioning, ASD, genetic factors, internal states and environmental factors. From the stages of SIB described earlier, during the first stage, i.e., when the child has rhythmic repetitive behaviours broad communication training can be done to improve functional communication. Documentation of the child's typical behaviour can also be done when the child is healthy. This will help identify "pain" in the future when there is a change in the typical behaviour.

During the second stage, i.e., when the self-injury is sensitive to internal states, appropriate pain relief measures should be taken. Appropriate medical interventions to relieve pain and painful health conditions should be ensured. Also, regular assessments of physical health and behavioural changes should be carried out.

In stage 3, i.e., when the behaviour is sensitive to environmental factors and social reinforcement, specifically designed communication strategies based on functional analysis report should be used. This is known as functional communication training. This can also be initiated in stage 2 preemptively. Environmental factors should be identified. Environmental modifications and change in caretakers response to SIB should also be targeted. Additionally, precursor behaviours need to be identified and physical health should

be monitored including prompt intervention for pain and painful health conditions.

Stage 4, i.e., when there is loss of behaviour control, restraint fading should be done. This is done by brief removal of restraint and replacement with another behaviour that can easily be faded. Compliance training is then implemented to increase the time out of the restraint. Following this, generalisation of the habit is facilitated. (2)

Drugs used in the treatment of SIB:

Drugs can be tried in SIB when a communicative function of SIB is not identified. (3)

Risperidone initially came into the market as a treatment for Schizophrenia. Risperidone acts by modulating the levels of Dopamine and Serotonin in the brain. Schroeder had a hypothesis that SIB may be caused by a depletion of dopamine and an excess of serotonin in the basal ganglia region of the brain. He thus pursued Risperidone as a treatment option for SIB. (4)

Other atypical anti-psychotics like olanzapine and ziprasidone have also been tried. However, caution must be exercised while using these medications as they have serious side-effects like dystonia, weight gain, neuroleptic malignant syndrome, hypotension, etc. (3)

Research on the use of Selective serotonin re-uptake inhibitors (SSRIs) in the past have shown equivocal results with some reductions in the rate and frequency of SIBs. (2)

The most consistent evidence in the use of medications for SIB has been seen with opiate antagonists (naltrexone). The probable mechanism of action of naltrexone in SIB has been described earlier in the article. It is possible that naltrexone and naloxone act by simply increasing the pain experienced from self-injury and hence influencing the response cost of an operant behaviour. (2)

For patients with severe refractory SIBs where a trial of behavioral and pharmacotherapy has been given, neuromodulation can be considered as a last resort. There are multiple areas found along the limbic system which when subjected to deep brain stimulation lead to an improvement in the outcome. It is believed that the neuronal circuits connecting the amygdala, the hippocampus and the periaqueductal gray, control reactive aggressiveness and this is moderated by the ventromedial frontal cortex. (6)

Prognosis of SIB:

Current literature suggests that SIB remains stable over lifetime. It remains persistent in adolescence and adulthood both among patients with and without ASD. Age-related decline in SIB is seen. This is also associated with reduction in symptomatology, stereotyped and repetitive behaviours in patients with ASD. Despite this, current studies have shown persistence of approximately 40% over a 10-year period in children with autism. Persistence of SIB is observed to be much higher in children with ID with one study quoting a persistence of 84% over an 18-year period. Persistence of SIB beyond 20 years of age is considered to be a chronic problem requiring professional intervention. These data support arguments advocating early intervention to prevent SIB from occurring and therefore persisting over time. (4)

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A case of Tuberous Sclerosis with Behavioral Problems and Poor Scholastic Performance

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ABSTRACT

Background: Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome with variable and heterogeneous expression. Prevalence is of 1 in 6,000 newborns affecting both sexes equally. TSC1 and TSC2 genes are tumor-suppressor genes, either of which when lost causes formation of hamartomas. Although there has been great progress in the identification and treatment of many of the physical features, the neuropsychiatric manifestations remain highly under identified and undertreated.

Case Presentation: An 8 years old, male, studying in second grade of an English medium school, only child of a non-consanguineous marriage, was brought with behavioral issues namely inattention and hyperactivity, reported from school and home settings with poor scholastic performance since beginning of schooling. No history of seizures was reported. Family history was not significant. There was initial speech and language delay. Other developmental domains were age appropriate. General examination revealed multiple hypomelanotic macules with normal systemic examination. His intelligence quotient (IQ) indicated low average intelligence. He could not perform corresponding to his grade in battery of psychoeducational and scholastic assessments. MRI brain had findings suggestive of TSC.

Management: Multidisciplinary holistic intervention plan with goals tailored according to child's needs were formulated and regular multidisciplinary follow-ups were planned.

Conclusion: TSC runs a progressive course and can lead to various systemic complications. Early diagnosis by clinical diagnostic criteria, timely management and regular surveillance is crucial.

Keywords: Tuberous sclerosis complex, hamartoma, poor scholastic performance, behavioral issues, hypomelanotic macules, case report

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome with variable and heterogeneous expression affecting multiple organs, with a prevalence of 1 in 6,000 newborns [1] affecting both sexes equally [2]. Spontaneous genetic mutations occur in 65% of the cases. TSC1 gene, located on chromosome 9q34 which encodes protein hamartin and TSC2 gene, located on chromosome 16p13 which encodes protein tuberin, are two identified foci for TSC. Overall in 85% of TSC cases, 31% have TSC1 mutation (hamartin gene) and 69% have TSC2 mutation (tuberin gene) [1, 2]. TSC1 and TSC2 genes are tumor-suppressor genes, which when lost cause formation of hamartomas [1, 3].

Although there has been great progress in the identification and treatment of many of the physical features of TSC, including subependymal giant cell astrocytoma (SEGA), the neuropsychiatric manifestations remain highly under identified and undertreated [4].

Case Presentation

An 8 years old, male, studying in second grade in an English medium school, only child of a non- consanguineous marriage delivered at term/ vaginally with birth weight of 1.5 kg (intra-uterine growth restriction), cried at birth with NICU stay for 12 days for low birth weight care and neonatal hyperbilirubinemia, was brought by his parents for behavioral issues in the form of inattention and hyperactivity reported from school and home settings and poor scholastic performance since beginning of schooling. There was no history of seizures. Family history was not significant.

Developmental History

1. Gross motor development: Age appropriate
2. Fine motor development: Age appropriate
3. Cognitive development: Understood complex commands
4. Social communication development: Age appropriate
5. Speech and language: Initial delay reported; Could narrate with unclear articulation
6. Academics: Concerns reported since early schooling in comprehension and writing, needed repetition of instructions
7. Behavior: Poor attention span with hyperactivity reported from home and school settings

Examination

- Anthropometry (according to IAP growth charts)
    - Weight: 23 kg (25th-50th percentile)
    - Height:122.8 cm (10th-25th percentile)
    - Body Mass Index (BMI): 15.45 kg/m^2 (50^{th} percentile)
- General examination: multiple (08) hypomelanotic macules over chest (2), abdomen (2), back (3) and right thigh (1) each measuring approximately ≥ 7 mm.
- Systemic examination: Normal

Summary of Psychoeducational Assessments

- IQ was 88 (low average intelligence)
    - Verbal IQ was 82
    - Performance IQ was 93

Table 1: IQ Assessment

Verbal Scale		Performance Scale	
Domain	IQ	Domain	IQ
Information	80	Picture completion	70
General comprehension	90	Block design	125
Arithmetic	80	Object assembly	62
Analog and similarity	90	Coding	94
Digit span	67	Mazes	113
Vocabulary	85		

Social maturity by Vineland Social Maturity Scale was adequate (Social Quotient=95)

- He could not perform corresponding to his grade in battery of reading and spelling, graded reading and listening comprehension tests, graded mathematical test and expressive language.

Table 2: Battery of Scholastic Performance Tests

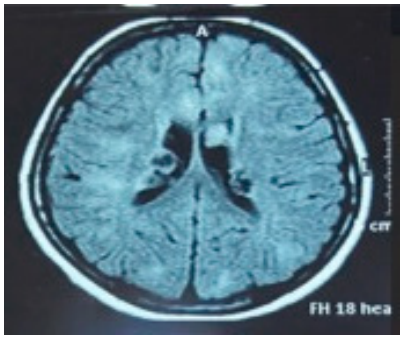
Test	Result	Inference
Schonell's Graded Word Reading Test	Reading Age (RA) = 6 years 10 months	1 year 2 months below chronological age (CA)
Schonell's Graded Word Spelling Test	Spelling Age (SA) = 5 years	3 years below CA
Graded Reading Comprehension Test	Below the level of grade I	Not grade appropriate
Graded Listening Comprehension Test	Below the level of grade I	Not grade appropriate
Expressive Language	Not grade appropriate	Not grade appropriate
Graded Math Achievement Test	Not grade appropriate	Not grade appropriate

- Conners-3 ADHD rating scale reported by parents showed moderate to severe dysfunction in domains of Inattention, Hyperactivity/Impulsivity, Learning problems, Executive functioning, Defiance/ Aggression with normal scores in peer relations.

Other Investigations

- Ophthalmological evaluation- Normal fundus examination; No evidence of retinal hamartoma
- Audiological evaluation- Pure tone audiometry was within normal limits
- Magnetic Resonance Imaging (MRI) of brain was done in view of the hypopigmented macules to look for TSC and the findings were consistent with findings suggestive of TSC.

Figure 1: MRI brain Axial T2-weighted image showing cortical tubers with subependymal nodules



- A genetic diagnostic testing was offered to the patient but they could not do it for economic reasons.

Management

Multidisciplinary intervention plan with goals were counseled to parents constituting

1. remedial teaching for academic issues
2. speech and language therapy for misarticulation
3. occupational therapy for graphomotor issues
4. behavioral therapy with the child and his parents (medication plan for ADHD/ behavioral issues had been kept for later plan)

Regular follow up with developmental pediatrician (to monitor and review goals for the intervention 3 monthly), pediatrician, neurologist and ophthalmologist (to follow up and monitor features and progression for the TSC) was advised.

Discussion

TSC was first observed by Von Recklinghausen in 1862, but the first clear description of TSC was given by Desire-Magloire Bourneville in 1880, who recognized the pathological features of white tumors or tubers and areas of sclerosis of cerebral gyri at post-mortem in patients with epilepsy and mental retardation [2, 5].

The cognitive and behavioral problems are of greatest concern to parents and caregivers.

Approximately 50% of the individuals diagnosed with TSC present with epilepsy, cognitive impairment and developmental psychopathologies including autism spectrum disorder. Those with normal intellectual abilities are also at high risk of specific neuropsychologic deficits, behavioral, learning, and other psychiatric disorders [1, 4]. Average IQ is observed in 40–50% patients with TSC [4]. The characteristic brain lesion is a cortical tuber. Subependymal nodules found along the wall of lateral ventricles which calcify latter by 2nd decade of life and project into ventricular cavity (candle-dripping appearance) which can later grow into SEGAs and can cause obstructive hydrocephalus [1].

Retinal lesions consist of hamartomas and white depigmented patches found in 50% to 80% patients [5]. Other retinal findings include retinal pigmentary disturbance ranging from hyperpigmented areas to "punched out" hypopigmented areas at the posterior pole or mid periphery. Non-retinal findings include angiofibromas of the eyelids, coloboma of the iris, lens and choroid, strabismus, poliosis of eyelashes, papilloedema and sector iris depigmentation [5].

Hypomelanotic patches over trunk and extremities are found on 90% of patients. Shagreen patch in lumbosacral region is also a hallmark of TSC. About 15-20% of TSC cases may develop small fibromas or nodules around fingernails or toenails during adolescence. Facial angifibromas develop by 4 to 6 years of age [1].

Approximately 50% children with TSC have cardiac rhabdomyomas which may cause congestive cardiac failure or arrhythmias. In children older than 10 years of age, angiomyolipomas may develop in kidneys in 75-80% cases, which by third decade may cause lumbar pain, hematuria or rarely, retroperitoneal bleeding [1].

Table 3: Diagnostic Criteria of TSC

Definite TSC diagnosed when at least two major or one major plus two minor features are present [1, 5].

Major Features of TSC	Minor Features of TSC
1. Cortical tuber	1. Cerebral white matter migration lines
2. Subependymal nodule	2. Multiple dental pits
3. Subependymal giant cell astrocytoma (SEGA)	3. Gingival fibromas
4. Facial angiofibroma or forehead plaque	4. Bone cysts
5. Ungual or periungual fibroma (non-traumatic)	5. Retinal achromatic patch
6. Hypomelanotic macules (>3)	6. Confetti skin lesions
7. Shagreen patch	7. Non-renal hamartomas
8. Multiple retinal hamartomas	8. Multiple renal cysts
9. Cardiac rhabdomyoma	9. Hamartomatous rectal polyps
10. Renal angiomyolipoma	
11. Pulmonary lymphangioleiomyomatosis	

Our patient had three major features of TSC with low average IQ, behavioral issues and academic difficulties.

Conclusion

Multiple systemic involvement renders regular follow ups and screening by developmental pediatrician, neurologist, ophthalmologist and dermatologist. A brain MRI in every 1-3 years, renal imaging in every 1-3 years and neurodevelopmental testing annually with regular follow ups to monitor progress is needed in all patients with TSC [1, 2].

The surveillance and management recommendations for TSC (2012) advise to screen and assess behavioral and neuropsychiatric symptoms under the terminology TAND, proposed to describe interrelated functional and clinical manifestations of brain dysfunction common in TSC-including aggressive behaviors, autism spectrum disorders, intellectual disabilities, psychiatric disorders, neuropsychological deficits and school and occupational difficulties [6]. These include the behavioral level (such as sleep problems or aggressive behaviors), the psychiatric level (DSM/ICD defined psychiatric disorders such as autism spectrum disorders or attention deficit hyperactivity disorder, the intellectual level [intellectual ability as defined by intelligence quotient (IQ)-type tests], the academic level (learning disorders, e.g., reading or mathematics difficulties), and the psychosocial level (e.g., self-esteem, family difficulties) [4].

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