



Neurodevelopmental Disorders: The Past, Present and the Future

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Abstract

Neurodevelopmental disorders are a group of complex multifactorial disorders with significant overlapping of symptoms that arise during the developmental period. This article looks into changing perspectives and evolving knowledge of these disorders as well as their future directions. These disorders can not only affect individuals but society as a whole. Accumulated knowledge of these disorders slowly began to change the perception of the disorders as well as how individuals experiencing these conditions are treated by society.

Keywords: Neurodevelopmental Disorders; Low Birth Weight; Autism; Intellectual Disability; Gene Therapy; Stem Cell Treatment; Nutraceuticals Mitochondrial Dysfunction

Abbreviations

ADHD: Attention Deficit Hyperactive Disorder; CT scan: Computed Tomography Scans; DSM: Diagnostic and Statistical Manual; EEG: Electro Encephalogram; ICD: International Classification of Diseases; IUGR: Intra Uterine Growth Retardation; IVIG: Intra Venous Immunoglobulin; LBW: Low Birth Weight; MRI: Magnetic Resonance Imaging; NDD: Neuro Developmental Disorder; PKU: Phenyl Ketone Urea.

What are Neuro developmental disorders?

Neuro developmental disorders (NDD) are a group of disorders that arise during the developmental period of an individual, before adulthood. This happens due to improper development of the central nervous system, as a result of interplay between various environmental or genetic factors. Mullin et al in 2013, described NDDs as “multifaceted conditions characterized by impairment in cognition, communication, behaviour and/or motor skills resulting from abnormal brain development” [1].

In ICD 11 NDDs are defined as - “behavioural and cognitive disorders that arise during the developmental period, that involves significant difficulties in the acquisition and execution of specific intellectual, motor, language or social functions. Although behavioural and cognitive deficits are present in many mental and behavioural disorders that can arise during the developmental period (e.g. Schizophrenia, bipolar disorder) only disorders whose core features are Neurodevelopmental, are included in this group. The presumptive etiology for Neuro developmental disorders is complex and in many individual cases is unknown” [2].

The DSM 5, published in 2013, included the new category of Neuro developmental disorders in place of the older classification of “Disorders usually first diagnosed in infancy, childhood or adolescence” [3,4]. Disorders like Pervasive developmental disorder (intellectual disability), ADHD, speech and communication disorders, Tourette's syndrome are included under NDD. Although some disorders e.g. schizophrenia also have neurodevelopmental factors as etiology, it is kept in a different category from the Neurodevelopmental disorders in both the DSM5 and ICD 11 [2-4].

The classifications of NDD have been done based on their clinical presentations, and there are many suggestions to change the classifications of NDD based on Research domain Criteria (RDoC) framework [1,5,6]. There is a significant overlap of symptoms between the various NDDs, and they share common characteristics e.g. autism and ADHD, hence using the term NDD helps to acknowledge the similarities and overlap of symptoms between these disorders [6,7].

In this article we are going to discuss how our perspective towards the NDDs have changed from the past to the present and what we can expect in the future.

Evidences from the past

From Mental retardation to Mentally handicapped, Mental deficiency, Feeble minded, Idiots, Fools, and Morons, people with intellectual disabilities/NDDs were given various terms throughout the years. These names were based on a “defectology” model, where the people with severe limitations in their intellectual, socio-cultural or behavioural areas fall behind the neurotypical individuals during the developmental period; in other words, these individuals were identified based on their weaknesses [8]. They were discriminated against and lived through oppression during the ancient period. In Ancient Greece, babies born with disabilities were thrown down from the top of the mountain and were not given a chance to live; the birth of a disabled child was considered a curse and punishment to the parents by God. According to literatures, women were forbidden from getting pregnant, if there was a little chance of having a deformed child; Aristotle recommended infanticide and abortion and Plato suggested women over forty should have an abortion. In ancient Sparta, there was a legal responsibility to abandon deformed and sickly infants [9].

With introduction of more organized religions people started having somewhat different perspective towards these vulnerable people and there developed a more protective role, although they were still marginalized.

In the mid thirteenth century the British Royal Court started assessing mental competency of people who are “idiots” or “Idiota” (Latin) especially after receiving requests from the general public, after they inherit certain land or property. And, if found to be an “Idiota”, the acquired land or properties of those people were

taken by the King, for the period of their lives [10]. People with NDD were mostly cared for by their family members or the society in Europe, until the period industrialization began in the 18th century. With societal changes, there were new challenges to the people with intellectual disabilities. The concept of institutions for the intellectually disabled/mentally and physically challenged people became popular and many such institutions and asylums started to develop in various places during that period. Although initially the concept was to give support to the disabled people, soon these institutions became overcrowded and became breeding grounds for various forms of abuse, especially the publicly funded institutions. There was also another idea known as “Eugenic” that grew out of Charles Darwin’s theory of survival of the fittest and was first introduced by Darwin’s cousin Sir Arthur Galton in 1880. Numerous methods evolved to discourage procreation of less desired groups of people including intellectually disabled. This concept was widely accepted in the industrialized countries that promoted discouragement of procreation by separating male and female inmates in the asylums. Sterilization programs were established for people with disabilities where forced sterilization were done [11].

Since the mid nineteenth hundreds, some of these institutions started to close down. With advancement of knowledge of mental illness and disabilities, people’s perception towards mental illness and disabilities started to change. As a result, programs for training these individuals, to make them a part of the society slowly developed. People with disabilities and their families became more aware of their human rights which also contributed to these changes. People with disabilities were allowed to be a part of the school system and get special education and training [11].

Present knowledge and concept

The most powerful knowledge that changed the perception of the professionals in the 21st century is the knowledge of neuroplasticity. Until a few decades ago, scientists and doctors thought that the brain stops growing once a person reaches adulthood. Those that are born with some form of neurodevelopmental disorders were considered untreatable. So there was a sense of helplessness in treating people with neurodevelopmental disorders. However, this concept became obsolete with increasing knowledge of neuroscience. There is better understanding of the etiology,

pathophysiology, diagnosis and treatment. It is proven now that people with neurodevelopmental disorders can improve and develop skills with a multidisciplinary team approach.

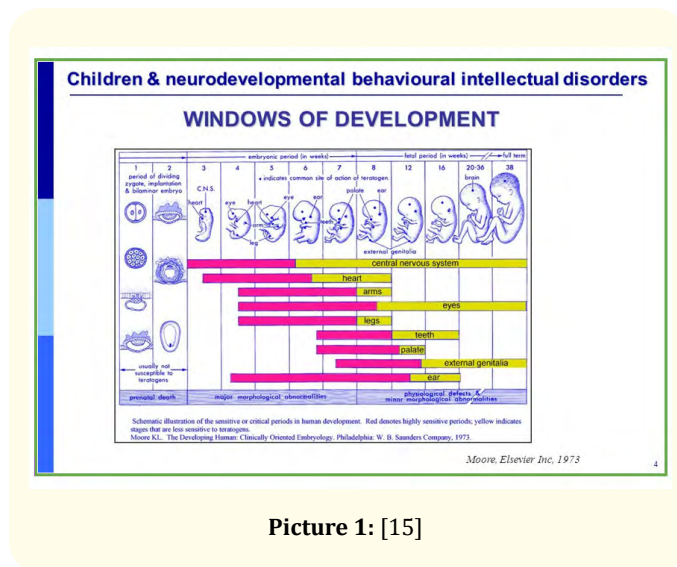
Following is the broad classification of NDD in DSM 5 [3]:

- Intellectual Disabilities
- Communication disorders (e.g. Speech, language d/o)
- Autism spectrum disorder
- Attention-deficit/hyperactivity disorder
- Specific learning disorder
- Motor disorders (e.g. tic and Tourette’s d/o)
- Other specified neurodevelopmental disorder
- Unspecified neurodevelopmental disorder.

What causes NDD?

NDD is an umbrella term that includes many diseases with heterogeneous presentations but the common factor in all these diseases is that they develop as a result of improper development of the nervous system and occurs during the developmental period of a child before their adulthood.

The early developmental period is very sensitive to intrinsic and extrinsic factors which can cause developmental delay (Picture 1).



Picture 1: [15]

The most critical periods during the development of a child are [12]

- Preconception period
- Prenatal period
- Postnatal period

Factors that can influence neurodevelopment in the preconception period are mostly Genetic factors and Other Parental factors like parental age, maternal health etc.

More than 700 genetic factors have been identified to play a role in the development of Intellectual disability or related disorders [13]. Disorders like Down’s syndrome, Angelman syndrome, Fragile X are due to single gene mutation, whereas Autism, Epilepsy are complex disorders involving multiple genetic factors [14].

The factors that interfere during the gestational and perinatal periods can be intrinsic (feto- maternal factors) or extrinsic (e.g. infections, inflammations, toxins, trauma). These factors often trigger gene expression by different processes [17] (Table 1).

Table 1: [16].

Processes triggering gene environmental interactions, giving rise to expression of certain genes	
1	CNS Excitation
2	Gut Microbiome abnormality
3	CNS inflammation
4	Immune dysfunction
5	Mitochondrial disorders
6	Oxidative stress
7	Abnormal DNA methylation
8	Dysregulation of free fatty acids.

Current diagnosis and treatment

Despite significant progress in the field of neuroscience, there is still a significant gap between the knowledge of NDD research and its implication in the clinical field. There are also concerns about only moderate amounts of connection between the research findings and current interventions [18].

Diagnosis of NDD can be done by prenatal assessment and clinical assessments at various stages after birth [19-21].

Table 2: Effects of Environmental Toxins during various stages of development [12,17].

Neuronal proliferation	Alcohol, mercury, Chlorpyrifos
Neuronal migration	X-ray, alcohol, mercury
Differentiation of neuroblast	Alcohol, nicotine, lead, mercury
Gliogenesis and myelination	Alcohol, Lead, Hormonal abnormality, Thyroid hormone
Synaptogenesis	Alcohol, lead, Mercury, Polychlorinated biphenyls (PCBs), Triethyltin, Parathion, Permethrin, Some serotonin blockers.
Apoptosis	Alcohol, Lead, Mercury, Chlorpyrifos
Neurotransmission	Alcohol, mercury, pesticides, Cholinesterase inhibitors, Aluminum

Current interventions

- Prenatal screening in high risk cases (e.g. maternal serum test, high resolution ultrasound, amniocentesis, chorionic villi sampling) - helps with early detection of developmental deficits giving the parent’s choice for informed decision making for further management [19,21,22].
- Neonatal screening- Screening for birth defects, physical deformity, features of FASD, cleft lip/palate, micro or macrocephaly, IUGR/LBW [19,22]
- Audiology- to rule out congenital deafness [19]
- Ophthalmologic/optometric examination- Rule out any visual problems/associated NDD [19]
- Suspected seizure- EEG [19]
- Blood tests within 48 hours of birth, that can detect up to 50 diseases including Phenylketonuria (PKU), Congenital hypothyroidism; early treatment of which can prevent intellectual disability in later life [19,22,23]
- Imaging Techniques- MRI/CT scan to rule out any structural abnormalities, can detect upto 30% of non-specific developmental abnormalities [20]
- Developmental milestones monitoring- Symptoms of Autism can be diagnosed as early as 18 months by screening developmental milestones [19,22]

- 2 tiered “TIDE protocol” is designed to identify treatable IDs in high risk patients [23]
- The first tire test applied to all unexplained IDs could identify up to 60% of treatable IDs.
- The second tire had targeted metabolic work up that identified specific Inborn Errors of Metabolisms in 40% cases, requiring specific testing [23]
- Genetic screening-
 - Genetic counselling- Done to parents with known genetic conditions, pregnant mothers of age 35 and older due increased risk of genetic disorders as well as diagnosed expectant parents [19,22]
 - Prenatal diagnosis can be made by various prenatal screening techniques mentioned above. After diagnosing a genetic disorder, genetic counselling to the couple helps to decide on next step. Treatment of genetic disorder by intra uterine genetic intervention is still in research stage [19,22]
 - Genetic testing is done mostly for diagnostic clarification of specific NDD after birth [22]
 - Chromosomal microarray analysis is used as a first line genetic testing in children with genetic disorders with suspected specific genetic disorders like Fragile X syndrome or whose symptoms are not specific or well delineated [24,25]
- Evaluation of Lead/mercury/Iron and other toxins in suspected cases.
- Multidisciplinary team involvement- The NDD should involve a multidisciplinary team for diagnosis and management. Ideally, a multidisciplinary team that includes - neurologists, psychiatrists, developmental paediatricians, neuropsychologists, education specialists, behaviour specialists, occupational therapists, physical therapists, speech and language therapists and social workers is needed, who can monitor the child regularly and work collaboratively.
- Treatment of Inborn errors of metabolism - Diseases due to enzyme deficiency/inborn errors of metabolism show the most favourable outcome if diagnosed at birth and treated early with enzyme replacement [23]

- Treatment of Autism-The core features of Autism are impaired social interactions, delayed language development, narrow area of interest & repetitive behaviours, with or without intellectual disability and behavioural problems. But there are significant differences in presentation of each autistic individual and a treatment of “one size fits all” is not applicable in treating patients with Autism.
- LADDERS model for treatment of Autism-(Learning And Developmental Disabilities Evaluation and Rehabilitation Services) is a multidisciplinary program started in late 1980's for diagnosis and management of Autism and other neurodevelopmental disorder patients. These centres provide evaluations by various professionals and treatment resources with collaborative approach [28]
- Pharmacotherapy- According to the underlying cause and symptoms, e.g.- neuroleptic medications are often used for behaviour management.
- Alternative Medicine/Dietary measures- various supplements/drugs are being used and studied to improve symptoms of NDD [16]
 - For immune/inflammation as a cause-
 - Melatonin, Vitamin D- some benefit
 - IVIG, Corticosteroid, Hyperbaric oxygen- not much evidence.
 - For Mitochondrial dysfunction- CoQ10, Carnitine, L-Carnosine – insufficient evidence
 - For Oxidative stress- Methyl B12 [29], NAC has shown moderate benefit
 - Lowering Glutamate excitation- D Cycloserine with some evidence
 - Omega3 supplements, Vit. B6/Magnesium, Vit. A, Folic acid, Vit. C, Iron supplement, Oxytocin, Zinc/copper are given to some NDD patients, with possible benefits, although there is not extensive research yet.
 - Microbiome- Probiotics and pancreatic digestive enzymes – some promise.

Conclusion and Future Direction

NDD is an umbrella term for a heterogeneous group of disorders as a result of abnormal neurological development; it is

multifactorial, with a wide range of symptoms depending on the part of the nervous system involved.

RDoC Framework

The knowledge and understanding of the NDD have expanded over last decade or so, and we know more about the intrinsic factors influencing the development of the NDD. With newer understanding of development, a neurodevelopmental model for classification of psychiatric disorders – “Research Domain Criteria” (RDoC) framework has been developed by National Institute of Mental Health. This classification system will be very helpful for future diagnosis and treatment [5].

Neural Stem cell treatment

Several researchers have been speculating possible neuroplasticity using neural stem cells and this appears to be promising. Also, possible associated dangers need to be clarified [5,30,31].

Gene therapy

Has been promising area of research and shown success with animal models. Single gene involvement disorders – Fragile X syndrome, Rett syndrome and Angelman syndrome studies initially showed some progress, but there are still a lot of obstacles to cross [32,33].

Electrophysiological treatments

Deep brain stimulation and Trans Magnetic Stimulation are also possible treatment for NDD and are being studied and is an interesting area for further research [5,34].

Neuro feedback training

Review articles give mixed results of neuro feedback training; however more research may be done to find out if these relatively easy/no invasive techniques are helpful possibly in combination with medication or other therapy [35,36].

Supplements and nutraceuticals

This is another area of emerging research that is mentioned earlier under current interventions. Study of metabolomics (sulphoraphane) and supplements are other promising areas to study [37].

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