INTRODUCTION

Intellectual disability (ID) (intellectual developmental disorder) is a disorder with onset during the developmental period. It includes both intellectual and adaptive functioning deficits in various developmental domains e.g. conceptual, social and practical domains **(APA, 2013)**.

Estimates of prevalence of intellectual disability range between 1–3%, with a male to female ratio of 1.6:1 **(Marrus and Hall, 2017).**

According to the Diagnostic and Statistical Manual fifth edition (DSM-5), the following criteria should be met to fulfill the diagnosis of Intellectual disability; defective intellectual functions such as reasoning, problem solving, planning, abstract thinking and academic learning. This is confirmed by both clinical evaluation and individualized standard intelligence testing. In addition to defect in adaptive function that causes failure to meet developmental and social standards for personal independence and social responsibility. Severity is specified as mild, moderate, severe, or profound based on the level of impairment in adaptive functioning and not IQ scores because it is adaptive functioning that determines the level of support required **(Cervantes et al., 2019)**.

There are many approaches for classification of intellectual disability. These approaches show a complex interaction throughout the history of ID and have had a diverse influence on

its classification. (DSM-5) and International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) adhere to the neurodevelopmental–clinical model **(Salvador and Martinez, 2018).**

Genetic disorders has prenatal onset. They are characterized by mutation in the genetic material, which may have been inherited from the parents. They include chromosomal aberrations. Down syndrome is the best-known example of prenatal genetic disorder. Monogenic causes include autosomal dominant, autosomal recessive and X-Linked disorders **(Li et al., 2018).**

Intellectual disability occurs in every nation on earth, but the understanding and perceptions of it have changed especially during the last years. More developed countries with their long-established educational, health and social care systems present a more comprehensive social context for persons with intellectual disability. Yet despite the economic and social disparities across the nations, people with intellectual disabilities and their families still encounter stigma and discrimination from their societies. Thus, the lessons learnt of tackling stigma in countries with long history of dealing with this problem may be applicable as well in other countries with less experience **(Scior, 2016).**

The prognosis of ID is variable and depends on many factors including the aetiology, associated medical conditions, environmental and social factors **(Dasteh Goli et al., 2016).**

All young children who are at risk or who have been identified with intellectual disabilities should have access to high-quality, affordable developmental services in their natural environments. These services should build on the strengths of the child and family, address their needs and be responsive to their culture and personal priorities. Moreover, it should be delivered through research-based practice **(Tassé et al., 2016).**

Contemporary systems of early intervention are designed to provide a comprehensive and integrated array of resources and supports to families whose children are experiencing or are at risk for a wide range of delays in development during the early childhood period. The overarching objective of these systems is to help create an environment that fosters children's development as optimally as possible and to establish a trajectory that will ultimately enable them to carry out their goals within family, community, and cultural contexts. Such community-based early intervention systems are complex and diverse. These systems often including preventive intervention programs for children at risk for delays **(Guralnick and Bruder, 2019)**.

The Portage Guide to Early Intervention is based on the concepts of family-training and individualized intervention. Its effects were reviewed indicating generally favorable reports by parents and professionals **(Liu, 2018).**

AIM OF THE WORK

This is an intervention study. The aim of the study is to assess the impact of early intervention program on children with intellectually disability due to genetic etiology.

Chapter 1

INTELLECTUAL DISABILITY

Intellectual disability (ID) is a specific type of developmental disability, a larger category that more broadly addresses conditions in which there may be impairments across domains such as physical, language, learning, and behavior. Intellectual disability is characterized by impairments in general intellectual abilities as well as in adaptive functioning across conceptual, social, and practical domains that occur during the developmental period (**Crnic et al., 2017).**

The introduction of "Intellectual Disability" in DSM-5 was preceded by Rosa's Law; 2010 federal statute requesting that "intellectual disability" should replace "mental retardation" in health, legal and educational policy (**Natasha Marrus and Lacey 2017).**

According to theDSM-5, the following criteria should be met to fulfill the diagnosis of Intellectual disability:

- Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized standardized intelligence test.

- Deficits in adaptive function which leads to in inability to meet developmental and sociocultural standards.

- Onset of intellectual and adaptive deficits during the developmental period **(APA, 2013)**.

Individuals with ID need support to overcome adaptive deficits which limit their abilities to participate independently in different environmental contexts. Severity of ID is classified as mild, moderate, severe, or profound based on the level of impairment in adaptive functioning and not IQ tests. IQ cut-offs no longer define severity; intellectual disability is classified by level of adaptive functioning within a range of IQ scores. The adaptive functioning is the most important factor that determines the level of support which the individual needs **(Boat et al, 2015).**

Classification of severity of intellectual disability

Two different systems for classification of intellectual disability are used in the United States one is that of the American Association of Intellectual and Developmental Disabilities (AAIDD) and the second is of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), which is published by the American Psychiatric Association (APA). Both systems classify severity of ID according to the levels of support required to achieve the individual's optimal personal functioning **(Papazoglou et al., 2014)**.

The DSM-5 definition of ID has a more comprehensive view of the individual than was encouraged under the fourth edition, DSM-IV. The DSM-IV definition included impairment of general mental abilities which affect how an individual functions in conceptual, social, and daily life activities. DSM-5 abandoned specific IQ test scores as a diagnostic criterion, although it retained the general functioning notion two or more standard deviations below that of the general population. DSM-5 placed more emphasis on adaptive functioning and the performance of daily life skills, in contrast to DSM-IV, which has stipulated impairments in two or more skill areas. The DSM-5 criteria included impairment in one or more superordinate skill domains e.g. conceptual, social, and practical **(Boat et al., 2015)** (Table 1).

AAIDD publishes a framework for assessment of the severity of ID, the Supports Intensity Scale (SIS), which focuses on types and intensities of supports required to enable an individual to lead a normal and independent life rather than defining the severity in terms of deficits. The SIS evaluates the support needed by an individual across 49 life activities, divided into the following six categories: home living, community living, life-long learning, employment, health and safety, and social activities **(Hagiwara et al., 2019).**

Table (1): Different approaches for classification of severity of Intellectual disability **(Boat et al., 2015)**

Severity Category	Approximate Percent Distribution of Cases by Severity	DSM-IV Criteria (severity levels were based only on IQ categories)	DSM-5 Criteria (severity classified on the basis of daily skills)	AAIDD Criteria (classified based on intensity of support needed)	SSI Listings Criteria (The SSI listings indicate different standards for meeting or equaling listing level severity)
Mild	85%	Approximate IQ range 50–69	Can live independently with minimum levels of support.	Intermittent support during transitions.	IQ of 60 through 70 *and* a physical or other mental impairment imposing an additional and significant limitation of function
Moderate	10%	Approximate IQ range 36–49	Independent living may be achieved with moderate levels of support.	Limited support needed in daily situations.	A valid verbal, performance, or full-scale IQ of 59 or less
Severe	3.5%	Approximate IQ range 20–35	Requires daily assistance with self-care activities and safety supervision.	Extensive support needed for daily activities.	A valid verbal, performance, or full-scale IQ of 59 or less
Profound	1.5%	IQ <20	Requires 24-hour care.	Pervasive support in daily life.	A valid verbal, performance, or full-scale IQ of 59 or less

SSI: Supplemental Security Income

Intellectual disability has been classified in ICD-10 as mild, moderate, severe and profound. This approach is helpful to differentiate mild to moderate ID from severe to profound ID **(World Health Organization, 2010)**.

Mild Intellectual Disability

Those who suffer from mild ID are slower in every field of conceptual development, social and daily living skills. Those individuals are able to learn a practical life skill that allows them to function in daily life activities with minimal levels of support **(Maughan et al., 1999).**

Moderate Intellectual Disability

Individuals with Moderate ID are slow in acquiring intellectual developmental milestones; their capability to learn and think logically is impaired but they are able to communicate and take care of themselves with some support, with appropriate supervision, they are able to perform unskilled or semiskilled work **(satter, 2002).**

Severe Intellectual Disability

Individuals with severe ID manifest major delays in development. Developmental milestones during early life are slower than matched normal children. They often have the ability to understand speech despite this they have limited communication skills. Although they are able to learn simple

daily routine activities and to engage in simple self-care, individuals with severe ID require supervision in social settings and often need family care. Through considerable practice and time, they may acquire basic self-help skills but still need support at school, home and in community **(Harris & Greenspan, 2016).**

Profound Intellectual Disability

Individuals with profound intellectual disability often have congenital syndromes. They have very limited abilities to communicate and often manifest physical limitations. These individuals are not able to live independently and they require close supervision and assistance with self-care activities. Their abilities to express emotions is limited and poorly understood. Seizures, physical disabilities, and decreased life expectancy are common **(Adams & Oliver, 2011)**.

Etiology of Intellectual Disability

The etiology of ID is heterogeneous including both genetic and environmental causes. Genetic factors play a major part in intellectual ID; however, genetic investigations have been complicated for a long time by the extreme clinical and genetic heterogeneity **(Vissers et al., 2016)**.

Genetic disorders are caused by mutations in the genetic material of the affected individual including chromosomal aberrations. In addition to single gene disorders which includes

autosomal dominant, autosomal recessive and X-Linked disorders **(Li et al., 2018).**

Down syndrome (trisomy 21) is the most common genetic cause of ID. It occurs approximately once every 700 live birth. Fragile X syndrome is the most common inherited cause of ID and it affects approximately 1 per 5,000 males **(del Hoyo et al., 2018)**.

There are many environmental factors which can affect the development of a fetus such as exposure to toxic substances (e.g. prenatal exposure to lead, mercury), nutritional deficiencies (e.g., prenatal iodine deficiency), brain radiation, brain infections, traumatic brain injuries, and maternal infections (e.g., rubella, cytomegalovirus). All these factors can lead to ID. Additionally, prenatal and postnatal complications such as complications of prematurity, hypoxemia and periventricular hemorrhage which may cause brain injury resulting in ID **(Nemerimana et al., 2018).**

Integration of central nervous system determines the level of maturation of developmental domains in addition to other environmental and psychological effects. Psychological factor has a very important impact on the development of children which was proved by studies conducted on institutions. It has been found that the development of children was severely affected by emotional deprivation even when good physical care was provided **(Hanan Abu El Nasr et al., 2016)**.

Some classification systems for intellectual disability were based on the timing of the insult to the Central Nervous System (CNS). The successive classification systems which were developed by the American Association on Intellectual and Developmental Disabilities (AAIDD) also followed the concept of timing approach **(Michelson et al., 2011)**.

Based on the symptomatic presentation of the patients, intellectual disability is divided into two categories: syndromic and non-syndromic Intellectual Disability **(Tomac et al., 2017).** In non-syndromic ID the only pathological manifestation is cognitive deficit and there are no phenotypic abnormalities and no associated anomalies of organ systems. It is a genetically heterogeneous disorder, with more than 200 candidate genes. Despite the increasing number of novel mutations detected, a relatively few number of mutated genes have been identified. A large number of patients with rare disorders still go without an etiological diagnosis **(lee et al., 2018).** Syndromic ID is related to phenotypic dysmorphism eg.craniofacial, skeletal, growth changes, neuromuscular abnormalities or metabolic disorders **(Tomac et al., 2017).**

To determine the etiological diagnosis of people with intellectual disability a systemic approach is needed. Reaching the accurate diagnosis for individuals with ID has a great value. This includes potential treatment options, providing information to family as well as the medical team about likely associated clinical problems, complications and prognosis. In

this way families are able to access special education and social care services. In addition to providing proper genetic counseling to parents about risk of recurrence and options for prenatal diagnosis and pre-implantation genetic diagnosis (PGD). A diagnosis can help families to get in contact with other families with the same condition and they can participate in research trails (**Pradeep and Mohnish, 2017**).

A comprehensive history focusing on prenatal history and birth, family history with three generation pedigree construction, and history of onset and course of the delays in different developmental domains is required. Neurological comorbidities, such as seizures, motor symptoms and regression of developmental milestones should be determined (**McPherson, 2006).**

Physical examination includes complete neurological examination, measurement of head circumference, and looking for dysmorphic features to aid the clinical diagnosis of genetic disorders. A careful evaluation of intellectual and adaptive functioning using neurological and psychological assessments is mandatory for proper assessment. When a genetic disorder or inborn error of metabolism is suspected, it is recommended to refer the patient to genetic department to assure accurate investigations and diagnosis. When microcephaly, seizures or any abnormal neurological signs are present the patient is requested for brain MRI. These potential diagnostic procedures highlight the importance of accurate evaluations and

neuropsychological investigations for proper diagnosis and management. Management of ID requires early diagnosis and intervention, including access to health care and appropriate supports. Children with ID have increased risk of other associated medical conditions, including visual and hearing impairments, cardiac or other congenital anomalies. Such comorbidities have an impact on overall function and quality of life. Moreover they can increase challenging behaviors **(Pivalizza and Seema, 2016).**

All findings should be documented and photographs obtained with informed consent for further clinical discussions. The parents should be reassured that confidentiality will be maintained at all times. Baseline investigations are requested, including blood and urine analysis. Further investigations depend on the differential diagnosis. Chromosomal microarray can be considered the first-line diagnostic genetic test in all individuals with ID (**Moeschler and Shevell, 2014**).

Testing for Fragile X syndrome is an issue of debate. Some question the cost-benefit ratio of routine Fragile X syndrome testing in ID patients. Others believe it is a useful diagnostic test (**NHS, U., 2017**).

Clinical exome sequencing can be considered a key diagnostic test for children with ID of genetic etiology. Whole exom sequencing (WES) and whole genome

sequencing (WGS) are revolutionizing the diagnostic process in the investigation of ID (**Brittain, et al., 2017**).

Differential Diagnosis

The differential diagnosis for ID includes other neurodevelopmental disorders among them the following disorders:

Autism spectrum disorder (ASD), which is characterized by impairment in social communication, defective language in addition to stereotype behaviors. The occurrence of language delay should promote investigation of other delays, so that ID is not missed in the diagnosis. Certain types of epilepsy may be manifested with delays and regression in particular developmental domains, such as language (**Moeschler and Shevell, 2014**).

Figure (1) illustrates clinical practical outlines for assessment and management of ID.