

American Journal on Intellectual and Developmental Disabilities

On Terms: Intellectual Disability and 'Condition', 'Disorder', 'Syndrome', 'Disease', and 'Disability'

--Manuscript Draft--

Manuscript Number:	AJIDD-D-22-00030
Article Type:	Perspectives
Keywords:	nomenclature; intellectual disability; syndrome, disorder, disease condition
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Abstract:	<p>Individuals living with intellectual disability can have multiple co-occurring medical conditions including associated genetic diagnoses. The number of genetic etiologies associated with ID is growing, with some quite new and rare, and others more common and associated with what is often considered a syndrome. In the context of genetic etiologies and associated medical comorbidities, appropriate use of descriptive terminology warrants clarification. Using accurate nomenclature is essential for descriptions, especially as terms are used across both research and clinical reports. Here we discuss several terms that may be confused with each other, including 'condition', 'disorder', 'syndrome', 'disease', and 'disability'. Our goal is to shed light on the meanings of the five descriptors and their appropriate use in the ID population, especially in relation to those who have a genetic diagnosis.</p>

Abstract

Individuals living with intellectual disability can have multiple co-occurring medical conditions including associated genetic diagnoses. The number of genetic etiologies associated with ID is growing, with some quite new and rare, and others more common and associated with what is often considered a syndrome. In the context of genetic etiologies and associated medical comorbidities, appropriate use of descriptive terminology warrants clarification. Using accurate nomenclature is essential for descriptions, especially as terms are used across both research and clinical reports. Here we discuss several terms that may be confused with each other, including ‘condition’, ‘disorder’, ‘syndrome’, ‘disease’, and ‘disability’. Our goal is to shed light on the meanings of the five descriptors and their appropriate use in the ID population, especially in relation to those who have a genetic diagnosis.

On Terms: What's in a Name? Intellectual Disability and 'Condition', 'Disorder', 'Syndrome', 'Disease', and 'Disability'

The field of intellectual and developmental disabilities (IDD) is at an important and exciting juncture: increasing numbers of individuals diagnosed with intellectual disability (ID) are receiving a genetic diagnosis (Stefanski et al., 2021; Vissers, Gilissen, & Veltman, 2015), representing a much-needed step toward the oft-stated goal of precision medicine for health and mental health conditions for each and every individual. Specifically, associations of neurodevelopmental disorders such as ID with distinct genetic causes allow for genome-first approaches to understanding prognosis and more importantly, potential treatments, for specific subgroups of individuals (Arnett, Wang, Eichler, & Bernier, 2021). Precision medicine, however, requires precise clinical terminology, and a pervasive challenge in the ID community is appropriate use of four key medical terms – 'condition', 'disorder', 'syndrome', and 'disease' - as well as the legal term 'disability'.

Individuals with ID can face a complex set of symptoms and challenges (developmental, behavioral, psychiatric, neurological, systemic, genetic, social, and educational), often described with variable and interchangeable use of the five terms. For example, an individual with ID may also have a diagnosis of attention deficit hyperactivity disorder (ADHD), which manifests with impulsive outbursts and increased distractibility; anxiety leading to irritability and perseveration; epilepsy requiring anti-seizure drugs; poor growth necessitating a G-tube; an underlying chromosomal copy number variant; and an assortment of educational accommodations and curriculum modifications needed to optimize learning at school by supporting the child's ability to access the curriculum. In fact, most children with ID will have one or more such co-occurring health and behavior support problems. For some, they may occur at different points in

development; for others, several issues may go together and relate to an underlying etiology (including a genetic condition). For many providers, it is not inherently clear which of the descriptions represent diseases vs. disorders vs. syndromes vs. conditions vs. disabilities, even though these terms have distinct meanings and applications. Accurate nomenclature is essential for the ID population, because it impacts our understanding of both the research literature and an individual's clinical condition.

Our goal is to shed light on the meanings of the five descriptors and their appropriate use in the ID population, especially in relation to those who have a genetic diagnosis. We incorporate a family perspective starting with the question of how does a genetic diagnosis fit with the family's understanding of their affected child's neurodevelopmental concerns? As Figure 1 illustrates, families encounter multiple ways their child receives classifications and diagnoses, often separately, in disparate systems, including the educational system and the medical system. It is worthwhile to note that our use of the term ID itself reflects the definition of both the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the American Association on Intellectual and Developmental Disabilities, and is interchangeable with the International Classification of Disease (ICD-11) term, Disorder of Intellectual Development (Schalock, Luckasson, & Tasse, 2021). While we refer the readers elsewhere for a review of issues facing the field of IDD generally (Schalock, Luckasson, & Tassé, 2021), here we focus on describing ID with respect to how it presents in the context of other factors (Table 1) which warrant appropriate use of terminology.

Terms & Definitions

Condition

Of the terms, condition is the vaguest. A condition is defined as a “state of health” (Network), and this state of health can be considered normal/healthy, or it can be considered to reflect illness/pathology. Thus, pregnancy in an individual with (or without) ID can be considered a condition. In addition, specific disorders, diseases, syndromes, or disabilities (defined below) in an individual with ID can also be considered conditions; in this case, the term condition is sometimes considered a less stigmatizing term than the other ones used here (disorder, disease, syndrome, and disability). We included the term condition because one may argue that a child with a genetic abnormality in one of the hundreds of genes that been associated with ID (Vissers et al., 2015) has a condition associated with this gene, but the condition may not (yet) meet criteria for a syndrome, disorder, or disease.

Disorder

Disorder may be the simplest term to define and operationalize. Nasrallah (2009) defines disorder as “irregularity, disturbance, or interruption of normal functions” (p. 14). In other words, a disorder is a condition which involves disruption to a person’s functioning. Usually, there is not associated structural change in the body (in contrast to the term disease, defined below). Disorders may or may not be associated with various specific signs and symptoms. The disruption can affect physical and/or mental function domains. For mental disorders specifically, the DSM-5 definition characterizes them as a “...clinically significant disturbance in an individual’s cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying the mental functioning” (American Psychiatric Association, 2013, p. 20).

There are several examples of disorders in the fields of Neurodevelopmental Disability (NDD) and psychiatry. ID itself is considered a disorder (Intellectual Developmental Disorder; American Psychiatric Association, 2013), as it is defined as a functional impairment in cognitive abilities and not by the presence of any structural changes in the brain. An individual with ID can have other co-occurring NDDs, such as autism spectrum disorder (ASD) and a superimposed communication disorder. In the field of psychiatry, the DSM-5 utilizes this term in its title (American Psychiatric Association, 2013) and includes several different disorders throughout the manual, such as bipolar disorder and obsessive-compulsive disorder (OCD). Just as an individual with ID can have ASD, an individual with ID can have bipolar disorder or OCD. Similarly, the ICD-11 aligns with the DSM-5 in its use of disorders in F codes on mental, behavioral and neurodevelopmental disorders (World Health Organization, 2019).

Syndrome

Of the five terms discussed, syndrome may be the most relevant to conditions related to ID, but also possibly so broad that interpretations seem to vary quite a bit. Nasrallah (2009) includes that a syndrome is based on “a number of symptoms occurring together...” (p.14), and more specifically, it has also been defined as “a recognizable complex of symptoms and physical findings which indicate a specific condition for which a direct cause is not necessarily understood.” (Calvo, Karras, Phillips, Kimball, & Wolf, 2003, p. 802). Syndromes can be non-genetic or genetic. For example, congenital zika syndrome (in an individual with ID or otherwise) is considered a syndrome, because it represents a constellation of characteristics signs and symptoms (exposure to zika virus in utero, characteristic microcephaly, and neonatal hypertonia, among others); moreover, the pathophysiology in relation neurological dysfunction is

not well understood. Down syndrome (DS) and fragile X syndrome (FXS) are but two examples from among the thousands of genetic syndromes that can occur in an individual with ID.

In the context of specific genetic syndromes, the set of symptoms occurring together can be phenotypic or molecular, which is the subject of active controversy in the NDD field. There is debate about whether genetic syndromes should be identified and labeled based on their symptom or 'syndromic' phenotypic presentation (including dysmorphology as well as behavioral and medical phenotypes), or whether genetic syndromes should be characterized and therefore named based on their molecular/etiological underpinnings. A large part of the complexity comes from genetics-first approaches in the field (Simons VIP Consortium, 2012), reflecting emphasis on studying and considering syndromes based on their genetic association, rather than phenotypic expression. Although it may be relatively straightforward to label and define genetic syndromes by the gene(s) involved, this may not be the most helpful in terms of understanding the condition based on the primacy of its phenotypic expression(s) (Rasmussen & Hamosh, 2020).

A historical but important note here is that many relatively more prevalent genetic syndromes associated with ID were actually identified and known for a long time prior to the identification of the gene(s) involved. These include DS (Patterson & Costa, 2005), FXS (Reches, 2019), Rett Syndrome (RTT) (Percy, 2014), Cornelia de Lange Syndrome (CdLS) (De Lange, 1933), and velocardiofacial syndrome (VCFS) (Shprintzen, Goldberg, Young, & Wolford, 1981). The examples are important because they include several different types of genetic abnormalities, including chromosomal alterations (DS, VCFS) and single gene variants (FXS, RTT, CdLS, VCFS). RTT (Srivastava et al., 2018) and CdLS (Kline et al., 2018) are associated with variants in multiple genes. VCFS is quite heterogeneous in phenotypic

expression, as well as varied in size of chromosomal deletion that may be present (Morrow, McDonald-McGinn, Emanuel, Vermeesch, & Scambler, 2018). While there are many more complex variations on such genotype-phenotype relationships (see Biesecker et al., 2021 for a more more nuanced discussion of this topic), the important point here is that the term syndrome may be a moving target and not all genetic variants (especially when they are first identified and associated with a phenotype) are automatically recognized as a syndrome.

Disease

A disease is a condition which not only disrupts an individual's functioning, but also causes structural changes in the body. Diseases are usually associated with a set of characteristic signs/symptoms. Accordingly, in the ICD-11, the section defining ID and other NDDs is titled with the word 'disorder', while the other sections of the ICD-11 are titled with the prefix 'diseases' (e.g., diseases of the circulatory system, diseases of the respiratory system, and diseases of the nervous system), presumably reflecting that these are associated with structural changes in organ systems. One example of a disease affecting the nervous system is Alzheimer's disease. Alzheimer's disease leads to disrupted cognitive and memory functioning, volume loss in the brain evident on neuroimaging, and characteristic symptoms like memory loss, confusion, language difficulties, and shortened attention span. An individual with ID (a disorder) can have Alzheimer's disease (a disease).

In a disease, pathophysiological cause is presumed to be known, at least for the majority of cases, and this is underscored in the general medical literature (Calvo et al., 2003). While there are certainly known diseases that involve psychiatric symptoms and changes in mental status (e.g. Alzheimer's Disease, Huntington's Disease), mental disorders in the DSM-5 appropriately fall under disorders and not diseases, because even if causation appears to be

known for subgroups of those with the disorder (as is the case for some cases of ID; e.g. ID associated with meningitis, Batten Disease), there is not a known cause for the mental disorder itself.

Disability

While arguably the formerly described terms (condition, disorder, syndrome, disease) may be considered under the umbrella of medical terms, the term disability is often used in a formal legal and also broader social context (see Linden, 2017 with respect to social context of use which is beyond our scope here). Specifically in many Western countries including the United States, there are laws regarding disability. According to the Americans with Disabilities Act, disability is defined as “a physical or mental impairment that substantially limits one or more major life activity.” <https://adata.org/faq/what-definition-disability-under-ada>.

What may be confusing about the term disability, then, is its use in the full label of ‘intellectual disability’. In this instance, one may say that the term disability is being used more specifically to refer to impairment. However, it is important to keep the term’s context of use clear, given its importance in legal and financial realms, as state-funded medical insurance programs and social security systems may require use of this term.

Summary and Suggested Recommendations

Given variations in existing nomenclature, how should professionals working with people with ID use these terms? We first argue that professionals do in fact need to be precise in their terminology, as the implications for what each term means with respect to what is known about the causes and potential for treatment clearly may have effects on how individuals and their families approach care and services. Our second recommendation includes the notion that in addition to precision, use of descriptions that provides a more complete picture of an individual’s

profile will be most helpful. The DSM-5 provides suggestions for incorporating multiple diagnoses and specifiers to create a fuller description of an individual in its section on ASD, including to “record [that the] autism spectrum disorder [is] associated with (name of condition, disorder, or factor)” (American Psychiatric Association, 2013). The ID criteria do not outline the use of specifiers as clearly as is done for ASD, in which the criteria state that the ASD may be “associated with a known medical, or genetic condition or environmental factor” (p.32), adding that an additional code to identify the associated medical or genetic condition should be used when possible. However, the section on ID does state, “a genetic syndrome linked to intellectual disability should be noted as a concurrent diagnosis with the intellectual disability” (p.40).

In the DSM-5 it is assumed that individuals with ID who also have genetic diagnoses should have the genetic diagnoses identified and described in the context of the ID diagnosis. Thus, for clearly identifiable and recognizable syndromes, such as DS and FXS, that also have their own billing codes in the ICD (World Health Organization, 2019), it seems fairly clear that when reporting an ID diagnosis, both the ID and the syndrome should be reported together to help more fully describe the individual. What is less clear, however, is what to do when an individual has a pathogenic variant or variant of uncertain significance in a known disease gene or a gene not previously (or more recently) linked to human disease. This is in fact the case for the growing number of copy number variants, to some extent, and single gene variants, to a larger extent, that are increasingly being identified and eventually associated with ID among other NDDs (Mitchell, 2015; Vissers et al., 2015). This brings us back to the proposal to use a term and phrase such as “X has a variant in gene Y, and thus has a *genetic condition that may be associated with neurodevelopmental disorders*, which in this case includes intellectual disability.” In our opinion, we think that condition is the appropriate term to use, given that the

identification of the genetic variant is clearly not a disease or disorder, and also may not (at least at that point) be considered a syndrome.

Conclusions

In summary, our purpose was to delineate the terms that are of potential significance when characterizing and labeling the presentations of people with ID, both with or without identified genetic or other potentially etiologic conditions. It is important to describe an individual's condition as fully as possible, including primary (neurodevelopmental) diagnoses as well as diagnoses that may relate to the etiology of a neurodevelopmental disorder. To do so, we recommend use of the most appropriate diagnostic category, but this is not always clear, and is especially the case when a gene (and variant of that gene) first becomes associated with neurodevelopmental disorders. While some of these associations may move on to become syndromes, and even diseases, there needs to be terminology that the field agrees on to describe associations at any stage in the process of understanding the genotype-phenotype relationship.

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Table 1. Features associated with four medical terms (condition, syndrome, disorder, and disease)

	Condition	Disorder	Syndrome	Disease
Pathological?	+/-	+	+	+
Functional impact?	+/-	+	+	+
Structural changes?	+/-	+/-	+/-	+
Specific set of symptoms?	+/-	+/-	+	+
Pathophysiologic cause known	+/-	+/-	+/-	+

Figure 1. Possible genetic, educational, and medical classifications of an individual living with intellectual disability.

