Psychiatric comorbidities in common genetic disorders with physical disability

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The burden of genetic disorders associated with physical disabilities and psychiatric disorders is connected to increasing healthcare expenses and demands on the patients and their caregivers. Psychiatric comorbidities such as anxiety and mood disorders affect a large number of children and adolescents with genetic disorders, leading to poor quality of life and impaired psychological adjustment. Research on this population is scarce compared with studies on the comorbidity of psychiatric problems with physical illnesses (e.g., endocrine disorders and neurological problems). The aim of this review is to focus on the most prevalent genetic disorders that cause physical disability and are most commonly associated with psychiatric disorders in children and adolescents. These include Duchenne muscular dystrophy, neurofibromatosis, myotonic dystrophy, hemophilia, Turner syndrome, Klinefelter's syndrome, tuberous sclerosis complex, fragile X syndrome and velo-cardio-facial syndrome.

Pediatric HEALTH

As definitions of health have developed to acknowledge not only the clinical disease but also its impact, physical disability and psychiatric morbidity have been attracting more attention as an area of research due to the major implications they have on quality of life [1].

A physical disability is defined as the lack of ability or restricted ability to perform activities requiring physical effort or mobility due to an impairment, and a dependence on others in order to perform activities of daily living (ADL) and instrumental activities of daily living [101].

The burden of physical disability is associated with escalating healthcare expenses, increasing healthcare demand, higher rates of comorbid conditions and higher rates of morbidity and mortality [2–4]. Mental health problems in children and adolescents with various chronic physical illnesses have been reported in various studies in the literature. Compared with the physically healthy population, approximately 20–30% of children and adolescents with physical illnesses and disabilities are also diagnosed with one or more psychiatric disorders [5]. While a larger number of studies have focused on the comorbidity of psychiatric problems with various physical illnesses (neurological, cardiovascular, gastro-intestinal disorders and endocrine disorders), less research to an extent has documented the general prevalence rate of psychiatric disorders in children and adolescents with genetic disorders that lead to a physical disability and illness.

Studies have found that children with certain genetic disorders implicating a physical disability suffer from various mental health illnesses such as pervasive developmental disorders, anxiety disorders, mood disorders and intellectual disabilities [6,7]. The presence of both physical and psychological ailments in this population suggests a diminished quality of life and impaired psychological adjustment [8].

For the purpose of this review, we focus on genetic disorders that most commonly cause physical or medical problems and psychiatric comorbidities according to a literature search by the authors [9–11]. These disabilities include: Klinefelter syndrome (KS), Turner syndrome (TS), neurofibromatosis type 1 (NF1), Duchenne muscular dystrophy (DMD), hemophilia, tuberous sclerosis complex (TSC), myotonic dystrophy type 1 (DM1), fragile X syndrome (FXS), and velo-cardio-facial syndrome (VCFS; 22q11.2 deletion syndrome). This by no means is an exhaustive list and excludes rarer entities such as Rett syndrome and the mucopolysaccharideses type III and rarer disorders such as Sanfilippo type A and B patients, and the newly emerging genetic causes of syndromic autism.

Methods

The search yielded a large number of abstracts, which were screened according to their relevance. The literature search was restricted to articles dating back to 1981 until the present day.

The following genetic disorders were used as keywords: 'Duchenne Muscular Dystrophy', 'Neurofibromatosis', 'Myotonic Dystrophy', 'Hemophilia', 'Turner Syndrome', 'Klinefelter Syndrome', 'Tuberous Sclerosis Complex',

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Keywords

• Duchenne muscular dystrophy • fragile X syndrome • hemophilia • Klinefelter's syndrome • myotonic dystrophy • neurofibromatosis type 1 • physical disability • psychiatric disorder • tuberous sclerosis complex • Turner syndrome • velo-cardio-facial syndrome

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'Fragile X Syndrome' and 'Velo-cardio-facial Syndrome'. These keywords were used in combination with the following: 'Psychiatric', 'Psychological', 'Mental Illness', 'Depression', 'Anxiety', 'Attention Deficit Hyperactivity Disorder', 'Pervasive Developmental Disorders', 'Children' and 'Adolescents'.

The search engines used were PsychNet, PubMed, Medline, Scopus and Google Scholar.

Klinefelter syndrome

Klinefelter syndrome is characterized by a male who is usually recognized by his tallness, normal appearing genitalia with small firm testes, sterility and abnormally low testosterone blood levels. It is generally owing to the 47 XXY genotype (i.e., one extra X chromosome in each cell). Its estimated frequency is approximately one in 500 live male births [12,13].

In the 1960s and 1970s, systematic screenings in psychiatric hospitals detected 1.3% KS among hospitalized boys (i.e., ten-times more than in the general population) and 0.6–1% KS among hospitalized men. Therefore, psychiatrists should consider a KS diagnosis when they examine boys or men who present typical physical traits of KS (i.e., tallness and underdeveloped testes) associated with psychiatric or school problems [12].

Patients with KS may present with social, language and cognitive deficits and are likely to develop symptoms of axis I disorders such as autism and schizophrenia [14]. Imaging studies have revealed reduced brain volumes localized in the insula, temporal gyri and amygdala, and enlargement of the ventricles; these changes are consistent with language deficits observed in patients with XXY syndrome [14]. In addition, the involvement of the X chromosome may explain the high male:female ratio seen in autism spectrum disorder (ASD) [14]. It is still unclear how many subjects with KS develop variants of autistic features, but they often present with nonspecific symptoms of shyness and social awkwardness [13] with a history of immature behavior, including difficulties separating from their attachment figures. However, they do not seem to present with restricted interests, which is one of the core features of autism. While they fall within the autism spectrum, they do not meet the full criteria for autistic disorder based on the onset, severity and range of symptoms [14]. In addition, overexpressed genes on the X chromosome have been associated with higher incidence of late speech development, significant difference between performance IQ and verbal IQ, with verbal IQ below normal and delayed emotional development and problems at school [10,12].

A number of hypotheses have been suggested to explain psychiatric symptoms associated with KS but none can explain their specificity. These include low levels of androgens during fetal and child development, personality disorder associated with hypogonadism and delay of mitosis of cells with an extra X chromosome. Androgen replacement therapy, especially during puberty, has been proven to generally improve physical well-being and mood, as well as concentration and level of functioning [13]. If KS goes undiagnosed, these men are at a higher risk of developing psychiatric disorders [13].

Turner syndrome

Turner syndrome is a genetic disorder that affects development in girls. The cause is a missing or incomplete X chromosome and is the most common sex chromosome abnormality, affecting one in every 2500 live females at birth. They are at risk for health difficulties such as high blood pressure, kidney problems, diabetes, cataracts, osteoporosis and thyroid problems. The essential physical features are short stature and ovarian dysgenesis, with subsequent infertility. Other typical features of TS are a short 'webbed' neck with folds of skin from the top of the shoulders to the sides of the neck, a low hairline in the back, low-set ears, swollen hands and feet, and a typical profile on neuropsychological testing [15,16].

In a study by Kiliç *et al.*, self-esteem, depressive symptoms and anxiety symptoms in girls with TS were compared with those in girls with familial short stature and healthy controls [17]. Studies looking at the impact of their physical features show that girls with TS manifest nonspecific psychiatric symptoms such as lower self-esteem and higher state anxiety levels than healthy controls and are at risk of psychological problems. It is therefore important that girls with TS are monitored psychologically for social, educational and psychotherapeutic interventions with the aim to address their self-esteem and avert emotional difficulties [17].

Social adjustment is another consequence of physical features in girls with TS which make them different from their peers. In 2001, McCauley *et al.* conducted a study on girls with TS who consistently displayed nonspecific problems of social functioning, reflected by poor social competence, immaturity and less social activity [15]. On a scale rating social

problems, early adolescence appeared to be a vulnerable time for girls with TS since it is a time of extreme body image comparison with others. In addition, these social impairments may be secondary to neuropsychological deficits, which impact their ability to generate problem solving strategies, and to generalize learning from one situation to another. In a study comparing TS women with a paternally derived X versus women with a maternally derived X, the former had better social adjustment, with superior verbal and executive function skills [18]. This implies that there is a significant genetic implication of social cognition that is not reflected in the maternally derived X chromosome [18]. Nonspecific mental health problems of anxiety and depression were also agreed upon by parents. Subjects express their anxiety through shyness, a fixation on keeping things ordered and lack of flexibility in their routines [19]. Interestingly, girls with TS did not support a higher rate of self-reported anxiety symptoms when compared with their mothers' clinical interviews. This could possibly illustrate that they were responding in a socially acceptable manner, thus minimizing their difficulties [15].

In addition to nonspecific and sub-threshold psychiatric symptoms, girls with TS are at higher risk for developing axis I disorders, such as attention-deficit hyperactivity disorder (ADHD) compared with the general population [20]. According to Firth *et al.*, weaknesses in core cognitive skills, including difficulties with distraction, planning, and short-term and working memory contribute to patterns of behavior present in ADHD. These deficits may in turn play a role in social immaturity and problems with their peers [18].

In addition, a case report of a 36-year-old woman, with a 15-year psychiatric history and a TS diagnosis at age 14 years, revealed a possible association between bipolar disorder (BD) and TS. Only one other case with both of these disorders was described in the literature [20]. Several studies have suggested X chromosome linkage for BD, and this report may be further evidence that BD could be linked to the X chromosome in a subset of patients [20].

Despite some contradictory findings in the literature, it is generally agreed upon that individuals with TS and their families should also receive psychological support through social, educational and psychotherapeutic interventions, in addition to medical treatment [15,17].

Neurofibromatosis type 1

Neurofibromatosis type 1 is a common hereditary disease that appears in one of 2500–3000 children and may result in severe dermatological, gastrointestinal, neurological, cardiovascular and orthopedic complications. The distinguishing features of NF1 are café-au-lait patches, axillary freckling, optic gliomas, pseudoarthritis, and scoliosis or other bony dysplasia [8,21]. Other prominent findings include macrocephaly, prominent brow, short stature and pectus excavatum; these occur in 10–45% of patients with NF1 [22], all of which may result in severe physical deformities. When present, physical symptoms of the disease may begin at birth, but are more likely to be established by the age of 10 years. Complications are likely to increase with age, especially at puberty and during pregnancy possibly due to hormonal changes [23].

Neurofibromatosis type 1 has been associated with numerous psychiatric and behavioral disorders. The most commonly documented in the literature are cognitive deficits resulting in learning disabilities and an increased risk of mental retardation [21,24], depression, anxiety, obsessive compulsiveness, sleep disturbances [25,26], ADHD [27], ASD [28], suicidal attempts and psychosis [21].

Cognitive impairments in children with NF1 are manifested by a slightly lower IQ score ranging from 89 to 98 [24]. Learning disabilities are also common in 30–65% of these children [29]. They often meet the criteria for enrollment in special education curricula because of deficits in written expression, mathematics and reading [30]. Another problem impacting their academic performance is poor attention and hyperactivity. The prevalence of ADHD among an NF1 group reached 49% in one study [27]. Deficits in executive functioning common in NF1 patients are often associated with ADHD [31,32]. Many cognitive skills such as planning, organization, focused attention and problem solving may be impaired [24]. Few studies have addressed the direct relationship between ADHD and executive function in this population, and further investigation into this topic is required [23]. Treatment of children with NF1 and ADHD with medications such as methylphenidate has been associated with improvement in sustained attention as measured by the Test of Variables of Attention (TOVA) [27].

Children with NF1 often exhibit other nonspecific deficits such as poor social skills, and a higher rate of internalizing disorders compared with externalizing disorders as manifested by

higher rates of anxiety and depression in these children [24,25]. In addition, Johnson *et al.* reported in their study that 45% of the children had sleep disturbances such as parasomnias, sleep walking and sleep terrors [26]. Marui *et al.* investigated the association between NF1 and autism; their findings suggest that the *NF1* locus may play a role in autism; however, these results still need further exploration and replication [28].

Duchenne muscular dystrophy

Duchenne muscular dystrophy is a common X-linked recessive genetic disorder that occurs in one out of 3300 male births, and results in progressive and fatal muscular degeneration. It is usually diagnosed between the ages of 3 and 5 years when children present with symptoms of delayed motor milestones, proximal muscle weakness, and in some cases, delayed language skills [33–35]. Boys with DMD have difficulty walking, running or jumping, fall more frequently and find it difficult to rise up without the use of their hands. By the age of 12 years, most boys will need a wheelchair to ambulate [33].

Duchenne muscular dystrophy has been associated with mental retardation, learning disabilities, ASD [35,36], ADHD and obsessive–compulsive disorder (OCD) [33,37].

Prevalence estimates of mental retardation among children with DMD have been reported to range between 20 and 50% [36] compared with 9% in the healthy population. Cotton *et al.* reported that 34.8% of their total population (n = 1224) had full-scale IQ scores falling below 70, indicating mild-to-moderate mental retardation [36]. They also found that children with DMD scored lower on verbal (80.4) and performance (85.4) IQ tests than the normal population (100). These results imply that verbal intelligence is more severely impaired in this group of children [37,38]; however, Cotton *et al.* found that verbal skills tend to improve with age [34,38]. These deficits have been linked to the lack of dystrophin protein in the cerebral cortex and cerebellum of patients with DMD [34,39]. Furthermore, Hinton *et al.* demonstrated that among a group of 46 boys with DMD, poor facial affect recognition is consistently observed and is also highly associated with social behavioral problems as reported by parents and confirmed by the Child Behavioral Check List (CBCL) [40]. Although these phenotypic aspects are not sufficient for a diagnosis of autism, ASDs have been reported to co-occur in higher rates than expected (ranging from 3.8 to 5.4%) among boys with DMD. A susceptibility to pervasive developmental disorders (PDD) has also been repeated [5,35,37].

Attention-deficit hyperactivity disorder and OCD among children and adults with DMD were found to be almost twice that of the general population [37]. Findings report a nonprecedent prevalence rate of 12% 'parent-reported diagnoses of ADHD' and 4.8% frequency rate of OCD in a sample of 351 males with DMD. Furthermore, comorbidity of ADHD, OCD and autism was not uncommon among this sample, as 55 males were diagnosed with one or more of the above disorders. A neurobiological association between DMD and these psychiatric disorders is also in need of further investigation [37].

Fragile X syndrome

Fragile X syndrome is the most prevalent heritable neurodevelopmental disorder that results in impairment in adaptive, cognitive and behavioral functioning. It is responsible for 1–5% of all cases of mental retardation or severe learning problems [10,41]. FXS is caused by the "mutation of a cytosine–guanine–guanine (CGG) repeat expansion mutation on the *FMR1* gene, located on the long arm of the X chromosome" [10]. Prevalence is approximately one in 4000 live births for boys and one in 6000–8000 for girls [10]. Individuals who have a partial mutation are known as carriers because they are at an increased risk of causing a full mutation in their offspring. Prevalence of the partial mutation is high, affecting one in 130–250 women and one in 250–810 men [10,11,41]. Recent findings have shown that individuals with the partial mutation are also at risk of many problems, such as developmental disabilities, psychiatric disorders and others.

Physical features of the syndrome are highly irregular and variable, and may not be apparent until late childhood, if at all. Therefore, these features should not be relied upon for diagnosis. These features include prominent ears and jaw, an elongated face, strabismus, dental malocclusion, a highly arched palate, small joint laxity, kyphoscoliosis, pectus excavatum (deformity of the anterior wall of the chest), flat feet, macrocephaly and postpubertal macro-orchidism [11,41]. Older adolescents and adults may develop cardiac mitral valve prolapse, hypertension and dilation of the aortic root [10,11].

The distinctive profile of aberrant behavior observed in boys with FXS involves hyperactivity and distractibility, gaze aversion, hand flapping, irritability, social cognitive deficits and striking

speech impairments (i.e., typically rapid speech, with poor intelligibility, tangentiality and perseveration) [11,41]. A number of studies demonstrate that more than 20% of boys or a quarter to half of all individuals with FXS technically meet the specific criteria of DSM IV [11,41].

However, not all research agrees with the above findings. Some believe that individuals with FXS do not meet the specific criteria of autism. In 2010, Hall conducted a study on individuals with FXS, aged 5–25 years. His results indicated that there were significant differences between the symptomatology profile of FXS and idiopathic autism. Indeed, individuals with FXS showed less impairment in communication and social interaction than individuals with autism, consequently not meeting the DSM IV criteria. Therefore, it was concluded that individuals with FXS need not be subjected to conventional autism interventions [42].

Most boys with FXS have an IQ score within the range of mild-to-severe intellectual disability [10,11]. They specifically struggle with abstract thinking, sequential cognitive processing, short-term memory, math and visuomotor processing [42]. Regarding girls with FXS, a third to a half have IQs in the range of intellectual disability. They mainly have marked difficulties with visuospatial processing, executive functioning, mathematical skills and attention [10].

Recent findings combining molecular biology and sets of cognitive, behavioral and adaptive measures shed light on the role of the *FMR1* gene in brain development and neurobehavioral phenotype among individuals with FXS [41]. This could help in the development of more targeted and thus effective interventions for individuals with FXS [42], especially if diagnosis can be made early on [11,42].

Hemophilia

Hemophilia is an inherited and chronic bleeding disorder. The annual incidence of hemophilia A is one case per 5000 male births. The incidence of hemophilia B is much rarer, estimated to be approximately one in 30,000 male births [101]. It is usually diagnosed by a known family history or after presentation with bleeding. Severe hemophilia is characterized by spontaneous bleeding into the joints and muscles. These occur due to mild injuries, which often go unnoticed or unremembered but produce chronic and sometimes severe pain. In the long term, this pain and the orthopedic deformity that may result from repeated bleeds in the same joint are the primary physical manifestations of the disorder. Immobility of the person, loss of function or his/her dependency to a wheelchair may result as well as absenteeism from school or work [43,44]. In addition, the mental health aspects of the disorder are an important component of management of the disease and have recently gained recognition.

Ghanizadeh *et al.* studied the prevalence of major depressive disorders and separation anxiety disorders in 83 children and adolescents with hemophilia [43]. Findings showed that the rate of major depressive disorders was 6.0%, with approximately 2.4% of the patients suffering from at least five symptoms of major depression and 3.6% from more than five symptoms. Recurrent thoughts of death and suicidal ideation were also highly common. Approximately 36% of the subjects had wished to die at least once in the last 6 months and 6% had suicidal ideation. In addition, criteria for separation anxiety were met by approximately 4.8% of them and 12% met at least two symptoms of separation anxiety diagnostic criteria [43]. Therefore, Ghanizadeh *et al.* (2009) concluded that depressive and separation anxiety symptoms were frequent in children and adolescents with hemophilia but only a limited number of them were diagnosed with major depressive disorder or separation anxiety disorder [43].

22Q11.2 deletion syndrome (velo-cardio-facial syndrome)

22Q11.2 deletion syndrome, also known as VCFS, is the most common genetic microdeletion syndrome among humans with a population prevalence of one in 2000 to one in 6000 live births [45]. It is caused by a deletion of approximately 3 million base pairs in almost 90% of the cases [46]. Clinical presentation may vary widely as it involves multiple organ systems [47]. More than 180 clinical features of the disorder have been reported [48]. These include congenital heart disease; palatal abnormalities; ocular, cranial and limb anomalies; facial dimorphism such as a long face or nose, hooded eyes and short ears; short stature, long tapering fingers; and hypotonia [46,48,49].

Velo-cardio-facial syndrome is also commonly associated with a number of psychiatric disorders and a distinct cognitive phenotype [45]. The cognitive phenotype of children with VCFS is characterized by an IQ score falling in the borderline to mild range of intellectual disability (70–75), with boys being more affected than girls [50]. Most difficulties lie in the areas of mathematics, reading comprehension and visual–spatial

perception [51]. These difficulties lead to lower nonverbal IQ scores than verbal IQ scores [50]. Many studies have looked at the relationship between these cognitive dysfunctions and the brain structure in individuals with VCFS. Reduced parietal lobe volumes [52,53], cerebellar reduction [54], hippocampal reduction and the size of the amygdala [55] are suggested to be possible biological substrates leading to cognitive difficulties. Antshel *et al.* also hypothesized that the low activity of the (*Met*) allele in VCFS may predispose to cognitive dysfunction [45].

In addition, high prevalence of comorbid psychiatric disorders in VCFS has played an important role in leading to its diagnosis as other clinical features may not manifest until later in life [10,48]. Comorbid psychiatric disorders that have been most commonly reported in VCFS are ADHD, anxiety disorders (simple phobias, separation anxiety, generalized anxiety disorder and OCD), major depressive disorder, psychotic disorders, schizophrenia, oppositional defiant disorder and ASDs [10,11,45–47,56]. Evidence suggests that these psychiatric disorders are not primarily due to the effect of borderline intellectual functioning in these individuals [10,57].

Attention-deficit hyperactivity disorder has the highest prevalence among the other psychiatric disorders in VCFS with rates ranging between 25 and 46% [10,46]. High rates of ADHD have been reported in numerous neuro-genetic syndromes, which makes it unlikely that ADHD is a specific behavioral phenotype of VCFS [56]. Nonetheless, more research is needed to target the anatomical etiology of ADHD in children with VCFS and whether ADHD may be a risk factor to later onset of schizophrenia, depression and BD in this population [45,46].

Furthermore, highly common among children with VCFS are anxiety disorders (30–40%) [45]; especially specific phobias, separation anxiety disorder, generalized anxiety disorder and OCD [47,56,58]. Among the latter, OCD was found to be the strongest predictor of later onset of a psychotic disorder [59] and the most comorbid with ADHD [57]. OCD, ADHD and the presence of both in children with VCFS have been significantly correlated with the high frequency of the *COMTL* allele in this population [57].

Rates of major depressive disorder in VCFS range between 12 and 30% [45,58]. In a recent study, Antshel *et al.* report a much higher rate of 64% in their VCFS sample [45] compared with an earlier study reporting 40% of adolescents diagnosed with depression [59]. In their sample, Antshel and colleagues also found that performance on the Wechsler Intelligence Scale for Children- Third Edition (WISC III) in childhood and nonverbal task performance were strongly associated with the onset of depression during adolescence [45]. A high rate of BD (52%) was reported in one study only and was not confirmed by any other study [60–62].

Schizophrenia, schizoaffective disorder and other psychotic disorders remain the most investigated and most worrisome of the behavioral phenotypes linked to VCFS [45]. It is now evident that VCFS is the most common genetic risk factor for schizophrenia [56]. By late adolescence or early adulthood, 20–30% of individuals with VCFS will be diagnosed with schizophrenia, and conversely, 1–2% of schizophrenic patients will also have VCFS; attesting to the significant bidirectional relationship [10,63]. Haploinsufficency of the *COMT* gene and other anatomical substrates and genetic factors have been extensively studied and highly implicated with the onset of schizophrenia and psychosis in individuals with VCFS [45,64].

Tuberous sclerosis complex

Tuberous sclerosis complex is a genetic disorder with a birth incidence of one in 6000 and is caused by mutations in either of two genes, *TSC1* and *TSC2*. It is mainly characterized by hamartomatous growths. Hamartomas, which are noncancerous tumor-like growths and generally benign, can cause problems owing to their location. When located on the skin, especially the face or neck, they can be extremely disfiguring, as in the case of a man with a hamartoma the size of a small orange on his eyelid [65,66]. Furthermore, TSC can emerge in a number of different forms and severity [65,66]. Even within a same family, one individual may have few physical characteristics, normal intelligence and no epilepsy, while a sibling may have marked physical problems, autism and severe disruptive behavior [65,66]. Prather *et al.* outlined in a review evidence regarding specific cognitive and behavioral problems in children with TSC [67]. These included global intellectual abilities, behavioral problems, psychiatric diagnoses, learning disorders and certain neuropsychological deficits for which individuals with TSC are at particular increased risk [67].

Research has shown that global intellectual impairment is a strong predictor of behavioral problems and psychiatric disorders, and individuals with TSC are no exception. Between 60 and 70% of children with TSC with global intellectual impairment are likely to present

with one or more behavioral problems. Only 20–30% of children with TSC with normal intellectual functioning can have such behavioral difficulties. Essentially, the mere presence of TSC should be considered as a significant predictor for behavioral difficulties [67].

Children with TSC are also at higher risk of developmental disorders, in particular, the specific diagnoses of autism and ADHD. Psychiatric comorbidities are significantly more prevalent among those with global intellectual impairment (more than 60% with intellectual impairment can present with a form of autism, in contrast to 6% without intellectual impairment). Limited data are available on other psychiatric disorders in TSC. Commonly seen are nonspecific and severe affective symptoms of anxiety or depressed mood and they are the most likely to be diagnosed during adolescence and into adulthood. These affective symptoms are possibly due to the psychological impact of having a genetic disorder, or may be a consequence of seizures associated with the primary condition or medications [67].

In summary, individuals with TSC are at a high risk of having global intellectual deficits and a number of psychopathologies. The evidence also suggests that even those with no intellectual impairment are at a significantly higher risk of behavioral, developmental and other psychiatric disorders than individuals without TSC.

Myotonic dystrophy type 1

Myotonic dystrophy type 1 is a common inherited autosomal dominant neuromuscular disease with an incidence rate of one in 8000. It is characterized by muscular weakness and myotonia, and may also cause other multisystem diseases depending on the affected organ [68]. Based on the age of onset and clinical symptoms, four classifications of the disease exist: mild form, classical or adult form, juvenile form and congenital form [69]. DM1 is also highly associated with a wide range of psychiatric disorders.

Myotonic dystrophy type 1 has been associated with learning disabilities, anxiety disorders and ADHD [70,71], sleep disorders [72], ASD [73] and depression [74].

Attention-deficit hyperactivity disorder is reported to be the most frequent psychiatric diagnosis co-occurring with DM1 with a prevalence rate ranging from 30 to 35% [68] followed by anxiety disorders ranging from 18.75 to 25% [68,71].

Several studies have also documented comorbid learning disabilities in children and adolescents with DM1 [68,70,71]. In a recent study of 55 children and adolescents with DM1, Ekstrom *et al.* showed there was a prevalence rate of moderate-to-severe learning disabilities in 83–95% of individuals [70]. Full-scale IQ for this group varies between 42 and 114 with the majority of subjects performing significantly better on verbal IQ than performance IQ. In addition, the mean IQ was reported to be borderline across studies, ranging from 69.75 to 80 [71]. The need for special education was also common among this group. A high rate of sleep-related abnormalities (66%) was linked to periodic leg movements (PLMs) and to sleep apnea syndrome (SAS) impacting children's learning and academic performance, commonly impaired in DM1 [72].

Ekstrom *et al.* investigated the prevalence of ASD in 57 children and adolescents with DM1, of whom 49% fulfilled criteria for ASD due to impairments in communication and social interaction, while 35% were diagnosed with autistic disorder. ASD symptoms were found to be frequent in more severe cases of DM1 [73].

The prevalence of mood disorders among children and adolescents with DM1 has not been ascertained, and the causes of depression in this group may be the result of genetic abnormalities and not a result of an adaptation to the disease [74]. While a 32% rate of depression has been reported in adults with DM1 [74], to date, no data are published on its prevalence in the younger population.

Future perspective

We have provided an overview of psychiatric comorbidities in children with the most common of the genetic disorders associated with physical or medical disabilities. The high prevalence of psychiatric disorders in physically disabled children and the added health burden, suggest that all children and adolescents with genetic disorders associated with physical or medical disabilities should be regularly screened by healthcare providers for psychiatric disorders with a focus on emotional, behavioral, academic and social difficulties. A referral for a psychiatric evaluation should be initiated when needed to ensure early detection of psychiatric disorders and potential interventions started when appropriate.

Most studies investigating psychiatric disorders in children with genetic disorders associated with physical disability have so far been cross-sectional in nature. Therefore, future studies

on this population should aim to focus on the longitudinal course of psychiatric comorbidities as the physical illness progresses. Future studies should also look into the potential effect of the medications on inducing and exacerbating psychiatric symptoms in these children since it is well established that many medications used to treat the medical complications associated with genetic disorders (e.g., antiepileptic drugs or AEDs) are associated with cognitive and emotional impairments.

In addition, there is a need to understand neurobiological markers of psychiatric disorders in this patient population and to determine what they share in common with the primary illness causing the physical or medical disability. We presented evidence suggesting that certain biological risk factors (genetic or neurobiological) can predispose individuals to both conditions. To further investigate this question, future studies should be designed to identify and compare neurobiological markers (neurocognitive and/or neuroimaging markers) in four groups of patients: those with the primary illness and psychiatric comorbidities; those with the primary illness and no psychiatric comorbidities; those with the psychiatric diagnoses only; and healthy controls.

Executive summary

Klinefelter's syndrome

- Boys with Klinefelter's syndrome often present with shyness, little energy and initiative, and few friends.
- They also show late speech development, verbal IQ below normal range, delayed emotional development and problems at school. They are likely to show autistic-like behaviors but not the full-blown syndrome of autism.

Turner's syndrome

- Girls with Turner's syndrome show poor social competence, immaturity, and less social activity, maybe secondary to learning difficulties and neuropsychological deficits. Attention-deficit hyperactivity disorder (ADHD) is also a common problem.

Neurofibromatosis type 1

- In youth with neurofibromatosis type 1, cognitive deficits and learning disabilities are highly common and a high prevalence of ADHD significantly impairs their academic performance.
- Internalizing disorders and sleep disturbances are other associated psychiatric problems and an association with autism is being investigated.

Duchenne muscular dystrophy

- Boys with Duchenne muscular dystrophy are likely to suffer from mild-to-moderate mental retardation and consequent learning disabilities.
- Their social and behavioral problems are suggestive of autism spectrum disorder, and may imply a susceptibility to pervasive developmental disorders.

Hemophilia

- Depressive and separation anxiety symptoms are frequent in children and adolescents with hemophilia, however, only few are diagnosed with major depressive disorder or separation anxiety disorder.

Fragile X syndrome

- The distinctive profile of aberrant behavior seen in boys with fragile X syndrome (FXS) involves hyperactivity and distractibility, gaze aversion, hand flapping, irritability, social cognitive deficits and striking speech impairments.
- IQ generally falls in the range of intellectual disability, which is generally mild to severe.

Myotonic dystrophy type

- ADHD and anxiety disorders are the most common comorbid psychiatric disorders in myotonic dystrophy type 1 (DM1).
- Moderate-to-severe learning disabilities are also widespread among this group, which implies a need for special education.

Velo-cardio-facial syndrome

- Velo-cardio-facial syndrome is one of the genetic disorders that are commonly associated with cognitive and psychiatric phenotypes, which may even often lead to its diagnosis; namely ADHD, anxiety disorders, major depression and other psychotic disorders.
- Velo-cardio-facial syndrome is also known to be the most common genetic risk factor for schizophrenia.
- Biological and anatomical substrates of the disorder are significantly associated with the high prevalence of psychiatric disorders in this group.

Future perspective

- All children with genetic disorders associated with physical disability should be screened for psychiatric disorders and referred for a psychiatric evaluation when needed.
- Identifying biomarkers of psychiatric comorbidities and determining whether they overlap with the biomarkers of the primary illness would help understand the association between the two conditions.

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