Handbook of PEDIATRIC Neuropsychology

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65 Sex Chromosome Aneuploidies

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OVERVIEW OF SEX CHROMOSOME ANEUPLOIDIES

Approximately 1 in 400 births has a combination of sex chromosomes that differs from the typical male karyotype of 46,XY or typical female karyotype of 46,XX. Sex chromosome aneuploidy conditions are a group of genetic disorders characterized by an atypical number of X and/or Y chromosomes, and are also known as sex chromosome abnormalities, sex chromosome anomalies, or X&Y chromosome variations. Examples of the most common sex chromosome aneuploidy conditions in males include 47,XXY (Klinefelter syndrome [KS]) and 47,XYY. In females, sex chromosome aneuploidies include 45,X (Turner syndrome [TS]) and 47,XXX (Trisomy X). Less common variations occur with the addition of more than one extra sex chromosome (i.e., 48,XXYY or 49,XXXXX), and the physical and neuropsychological features become more significant as additional chromosomes are added. Table 65.1 includes a complete list of the sex chromosome aneuploidy conditions and their prevalence.

The absence or addition of sex chromosomes leads to syndromes with characteristic physical and medical findings, as well as associated characteristic profiles of developmental and neuropsychological findings. The physical features of sex chromosome aneuploidies are generally much less distinct and more variable than other chromosomal aneuploidy conditions such as Down syndrome, leading to lower rates of diagnosis and lower public awareness and recognition of these conditions. The neuropsychological features of the most common sex chromosome aneuploidy conditions (including TS, XXY/KS, XYY, Triple X) are also less severe, and cognitive abilities in the intellectual disability range are rare. However, individuals with sex chromosome aneuploidies are at higher risk for developmental delays, learning disabilities, executive dysfunction, and adaptive functioning deficits. An understanding of the neuropsychological profiles associated with sex chromosome aneuploidy conditions is very important in the evaluation and treatment of individuals with these syndromes.

Table 65.1 ■ List of Sex Chromosome Aneuploidy Conditions

Karyotype	Also Known as	Estimated Prevalence
Males		
47,XXY	Klinefelter syndrome	1:650
47,XYY	–	1:1,000
48,XXXY	–	1:20,000
48,XXYY	–	1:18,000
48,XYYY	–	?
49,XXXXY	–	1:85,000
49,XXXYY	–	?
49,XYYYY	–	?
Females		
45,X	Turner syndrome	1:2,500
47,XXX	Triple X, Triplo-X, Trisomy X	1:1,000
48,XXXX	Tetrasomy X	1:50,000
49,XXXXX	Pentasomy X	1:250,000

The first large studies on the developmental and psychological features of these conditions were performed from the 1970s to 1990s when newborns at many sites around the world were screened at birth, and individuals with sex chromosome aneuploidy were identified and followed until young adulthood. The design of these studies allowed for long-term evaluation of subjects ascertained at birth, and results form the basis of our knowledge of the neuropsychological profiles. Additional research in the 2000s has supplemented and expanded these original findings. The most significant distinction is in comparison of neuropsychological profiles between TS/45,X where there is a missing X chromosome and the conditions with extra X and Y chromosomes (XXY, XYY, XXX). TS is associated with deficits in visuo–perceptual abilities and relative strengths in verbal skills, while the conditions with extra X and/or Y chromosomes share language-based deficits and relative strengths in nonverbal abilities.

The medical and psychological features in sex chromosome aneuploidy conditions are hypothesized to result from differences in the expression levels of genes on the sex chromosomes. In cells with more than one X chromosome, such as typical 46,XX cells in females or males with 47,XXY, the second X chromosome undergoes a process called X-inactivation in order to maintain a balance of gene expression in the cells. However, approximately 10–20% of genes on the second X chromosome escape X-inactivation and these genes are expressed by

both X chromosomes. In TS (45,X), genes that escape X-inactivation are then expressed at a lower level compared to typical 46,XX females, while in 47,XXY or 47,XXX they are expressed at a higher level. A good example to illustrate this principle is the *SHOX* gene and its relationship to height in sex chromosome aneuploidy conditions. Short stature is a characteristic feature of TS, while XXY/KS and Triple X syndrome are associated with tall stature. The *SHOX* gene is located on the X and Y chromosomes, escapes X-inactivation, and is known to be involved in bone growth of long bones that contribute to final adult stature. Females with TS only express *SHOX* from one X chromosome, and this decreased expression of *SHOX* in TS leads to short stature. In contrast, in 47,XXY and 47,XXX, *SHOX* is expressed from all three sex chromosomes contributing to tall stature in these conditions. Thus, differences in the levels of gene expression from genes on the sex chromosomes lead to characteristic features of the syndromes. These gene dosage effects are also hypothesized to be involved in the psychological phenotypes of sex chromosome aneuploidy; however, the specific genes involved in neuropsychological features of these conditions have not yet been identified.

SEX CHROMOSOME ANEUPLOIDY IN MALES

KLINEFELTER SYNDROME (47,XXY)

Background and History of Klinefelter Syndrome

Klinefelter syndrome was first described in 1942 by Dr. Harry Klinefelter and colleagues in an endocrinology clinic at Massachusetts General Hospital in Boston, Massachusetts. The first description was a series of nine postpubertal males with tall stature, sparse facial and body hair, small testes, testosterone deficiency, and no sperm production (Klinefelter, Reifenstein, & Albright, 1942). In 1956, Bradbury et al. identified an extra sex chromatin body in buccal cells of patients with Klinefelter syndrome (Bradbury, Bunge, & Boccabella, 1956), and in 1959 Jacobs and Strong confirmed that Klinefelter syndrome was due to a chromosome constitution of 47,XXY (Jacobs & Strong, 1959). Some reports suggest that prepubertal males with XXY should not be classified as having Klinefelter syndrome until after more distinct physical differences develop after puberty, however most medical professionals use the terms XXY and KS interchangeably for individuals of all ages.

Etiology of Klinefelter Syndrome

Males with Klinefelter syndrome have a chromosome constitution of 47,XXY, instead of the typical 46,XY. Newborn screening studies have shown the incidence of 47,XXY to be 1:600–1:800 male births. Klinefelter syndrome occurs as a result of failure of sex chromosome division (termed nondisjunction) during formation of the sperm or egg, or in the early cell divisions after fertilization. The additional X chromosome has been shown to be paternal in origin in approximately 50% of cases and maternal in origin in approximately 50% of cases (Jacobs et al., 1988; Lorda-Sanchez, 1992). In approximately 16% of cases the nondisjunction occurs after fertilization, which can lead to mosaicism, where an individual has a combination of both 46,XY and 47,XXY cells (Thomas & Hassold, 2003). Mosaicism accounts for approximately 10% of males with Klinefelter syndrome, and typically leads to milder physical and psychological findings (Paduch, Fine, Bolyakov, & Kiper, 2008). It is postulated that the physical and psychological features associated with 47,XXY result from overexpression of genes from the extra X chromosome; however, the specific genes leading to psychological features have yet to be identified.

The diagnosis of Klinefelter syndrome is made by a chromosome analysis (also called a karyotype) that shows the extra X chromosome. Approximately 10% of cases are diagnosed by amniocentesis in the prenatal period, while the remaining identified cases are diagnosed in the postnatal period due to developmental delays or learning problems in childhood, pubertal delays in adolescence, or infertility in adulthood. However, it is estimated that 64% of males with Klinefelter syndrome remain undiagnosed in their lifetime (Abramsky & Chapple, 1997).

Physical and Medical Features of Klinefelter Syndrome

In early childhood, physical and medical features of Klinefelter syndrome are often subtle or absent, but can include early developmental delay (speech and/or motor development), and physical features such as hypotonia (low muscle tone), hypertelorism (widely spaced eyes), clinodactyly (curvature of the fifth finger), hyperextensible joints, and/or flat feet. Tall stature can begin in childhood and often becomes more significant in adolescence, with adult stature approximately 3 inches taller than expected given family history. The most characteristic medical features of Klinefelter syndrome emerge during adolescence or young adulthood, where testosterone deficiency leads to slow or incomplete pubertal development in most cases. Physical findings of microorchidism (small testicles) are almost universal, and approximately 25% develop gynecomastia (male breast enlargement) that is usually mild and difficult to identify without a medical examination. Testosterone replacement therapy is needed for most individuals starting in adolescence to support physical pubertal changes, muscular development, bone density, physical endurance, and sexual functioning. The role of testosterone therapy on psychological and social–emotional aspects of Klinefelter syndrome is also important and is an area of current investigation. Other medical problems including osteoporosis, intention tremor, autoimmune diseases, thyroid problems, and Type II diabetes are more common in adolescents and adults with

Klinefelter syndrome compared with the general population. While infertility has long been considered a characteristic of Klinefelter syndrome, advances in assisted reproductive techniques now allow a subset of males with Klinefelter syndrome to father biological children.

Neuropsychological and Neuroanatomical Basis and Implications in Klinefelter Syndrome

There is significant variability in the neuropsychological features associated with Klinefelter syndrome. Many individuals have essentially no discernible concerns and may complete high school, higher education, and professional training with no apparent learning or neuropsychological concerns. However, others may have more significant deficits that usually follow a characteristic neuropsychological profile, and these individuals are most likely to present for psychological or educational evaluation in clinical practice. Studies of cognitive abilities have shown that the full-scale IQ for individuals with Klinefelter syndrome can range from low to above average, and the distribution of cognitive scores follows a standard curve similar to the general population. However, relative to the population and sibling cohorts, overall mean cognitive abilities are generally found to be 5–10 points lower (Graham, Bashir, Stark, Silbert, & Walzer, 1988; Ratcliffe, Masera, Pan, & McKie, 1994; Rovet, Netley, Keenan, Bailey, & Stewart, 1996). Findings and methods differ resulting in variance across studies; however, the most universal and robust observation is the presence of language-based deficits. These deficits in verbal abilities tend to account for the downward shift in cognitive scores for males with Klinefelter syndrome that is statistically significant compared with population means and predicted IQ based on family of origin.

Specific delays are seen in speech development, verbal comprehension, verbal conceptual abilities, higher level language processing, complex grammatical construction, word retrieval, and open-ended narrative construction (Graham et al., 1988). Overall, formal language-based learning disabilities such as dyslexia occur in 50–80%, but are not universal, and incidence varies between studies (Bender et al., 1983; Bender, Puck, Salbenblatt, & Robinson, 1986b; Graham et al., 1988; Pennington, Bender, Puck, Salbenblatt, & Robinson, 1982). Prospective studies of children with Klinefelter syndrome identified in the newborn period showed that approximately 80% required special education supports at some point for language-based or reading deficits (Bender et al., 1983). Language deficits are generally more significant in earlier development than in adulthood (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009). Nonverbal, visual perceptual abilities are a relative intellectual strength in most individuals with Klinefelter syndrome.

Neuropsychological studies in Klinefelter syndrome are limited; however, results show fairly consistent deficits in some areas of executive function. Attention deficits have been broadly reported with rates of attention deficit hyperactivity disorder (ADHD) ranging from 36% to 63% depending on the study (Bruining, Swaab, Kas, & van Engeland, 2009; Tartaglia, Ayari, Hutaff-Lee, & Boada, pending review). Across studies, inattentive symptoms including distractibility, short attention span, and poor organization cause more impairment than hyperactivity and impulsivity. Inattention during specifically verbal tasks may also be closely related to verbal processing difficulties (Rovet et al., 1996).

Other neuropsychological impairments cluster around verbal processing skill deficits and are further illustrated by lowered scores on specific subtests of vocabulary, information, and semantic fluency in addition to deficits in auditory memory, verbal retrieval, verbal fluency, processing speed, word retrieval, and confrontational naming (Bender et al., 1983; Bender, Linden, & Robinson, 1989, 1993; Geschwind et al., 1998). Verbal conceptual abilities are diminished by specific deficits in language comprehension and expression (Rovet, Netley, Bailey, Keenan, & Stewart, 1995; Rovet et al., 1996) and underlying deficits related to use and understanding of syntactic information in the judgment of sentence veracity (Netley & Rovet, 1982). General auditory processing delays are noted for both verbal and nonverbal material with more difficulty as the timed nature of tasks increases demands (Graham et al., 1988; Rovet & Netley, 1983). These findings are not universal, however, and a recent large study reports results showing more typical abilities in word retrieval on both phonetic and semantic fluency tasks and no expressive or receptive vocabulary concerns (Ross et al., 2008). This study did find the difficulties seen in higher-order language skills reported by others.

Several studies reporting on behavioral features of Klinefelter syndrome describe elevated rates of anxiety and depressive symptoms (Bender, Harmon, Linden, & Robinson, 1995). Behavioral presentations can include irritability, meltdowns, social withdrawal, perseverative questioning, separation anxiety, or expressions of low self-esteem (Visootsak & Graham, 2009). While there is great variability in personality traits, additional characteristics such as shyness, emotional sensitivity, immaturity relative to peers, social difficulties, and decreased self-assertiveness were elevated on both clinical observation and through parent and self-report measures (Bender et al., 1995). Language deficits that result in poor self-expression and frustration are likely contributory factors, and language-based learning difficulties together with social difficulties contribute significantly to comorbid conditions and overall outcome in adolescents (Bancroft, Axworthy, & Ratcliffe, 1982).

When studies are conducted with recruitment from clinical settings or support groups, increased rates of autism spectrum disorders and psychotic symptoms including paranoia, delusional thinking, or hallucinations are found, but the ascertainment bias in these studies cannot be ignored (Bruining et al., 2009; DeLisi et al., 2005; van Rijn, Aleman, Swaab, & Kahn, 2006;

Van Rijn, Swaab, Aleman, & Kahn, 2008). Van Rijn et al. (2008) describe social cognitive deficits, social distress, and elevated rates of autism spectrum disorders in males with Klinefelter syndrome. Studies that have examined the cognitive profile of the subset with more significant psychological involvement have shown that symptom severity and the number of comorbidities negatively correlates with cognitive abilities (Bruining et al., 2009; Tartaglia, Davis, Hansen, & Hagerman, 2006; Van Rijn et al., 2008). There is a small but increased risk of hospitalization with disorders on the psychosis spectrum in males with Klinefelter syndrome (Bojesen, Juul, Birkebaek, & Gravholt, 2006). Overall, social deficits, mood disorders, and psychotic disorders occur at higher rates than in the general population, and the risk for these conditions must be considered for all individuals with Klinefelter syndrome presenting with behavioral or emotional concerns.

Increased rates of left-handedness and anomalous cerebral dominance have been noted in Klinefelter syndrome, and the possible link with language-based learning disabilities has been suggested (Geschwind et al., 1998; Ross et al., 2008). The effect of genetic and hormonal factors on neuropsychological phenomena such as cerebral dominance and laterality has become a subject of interest for research. Fine and gross motor skills can also be affected, with specific deficits in upper limb coordination, motor speed, and motor dexterity (Salbenblatt, Meyers, Bender, Linden, & Robinson, 1987). Intention tremor presenting in late childhood or adolescence may also affect fine motor skills and graphomotor function in a significant number of individuals.

In support of neuropsychological findings, magnetic resonance imaging (MRI) and neuroimaging studies have found significant structural brain differences that are consistent with the intellectual and behavioral profiles of males with Klinefelter syndrome. Smaller left temporal lobe volume and larger lateral ventricular volumes correlate with the deficits in verbal and language function (Itti et al., 2006). Reduced caudate volume is consistent with delays in language production and oral motor deficits, and executive dysfunction may relate to gray and white matter findings in frontal and temporal lobes. Mood and emotional modulation are other common concerns in Klinefelter syndrome, and reduced volumes in the insula, hippocampus, and medial limbic system may be associated with these symptoms (Giedd et al., 2006; Patwardhan et al., 2002). Considerations for neuropsychological assessment and interventions in KS are addressed below.

XYY SYNDROME

Background and History of XYY Syndrome

XYY syndrome was first described in 1961 by Avery Sandberg at Rosewell Park Memorial Institute in Buffalo, NY. This initial case was an incidental finding in a 44-year-old male who was being karyotyped due to his daughter's diagnosis of Down syndrome (Sandberg, Koepf, Ishihara, & Hauschka, 1961). Subsequent reports in the 1960s ascertained cases from mental health or correctional facilities, leading to postulations that the extra Y chromosome was causing more intense male traits such as aggression and predisposing males to criminality. Later reevaluation of these studies in the context of more reliable data about the high prevalence of XYY in the general population (1:1,000 males) and the broad spectrum of involvement led to the recognition that the XYY genotype does not predict criminal behaviors. Contemporary professionals now recognize that perpetuating this association is imprudent and insensitive.

Etiology of XYY Syndrome

XYY syndrome occurs as a result of nondisjunction of the Y chromosomes during formation of the sperm, or in the early cell divisions after fertilization. Mosaicism with an XY cell line occurs in approximately 5% of cases. The diagnosis of XYY is made by chromosome analysis (karyotype). Newborn studies have shown the incidence of XYY to be 1:1,000 male births; however, it is estimated that only 15–20% of males with XYY syndrome are diagnosed within their lifetime (Abramsky & Chapple, 1997). Of those cases that are identified, approximately 30% are diagnosed in the prenatal period. For the remaining males with XYY diagnosed after birth, approximately half are identified in childhood or adolescence due to developmental delays or behavioral difficulties, and the other half for a variety of reasons including a small subset due to fertility problems (5%).

Physical and Medical Features of XYY Syndrome

Tall stature is the most consistent physical feature associated with XYY, and adult males with XYY are approximately 4–5 inches taller than expected given family history (Ratcliffe, Butler, & Jones, 1990). Other associated findings are nonspecific and similar to those seen in Klinefelter syndrome, including early developmental delay (speech and/or motor development) and physical features of hypotonia (low muscle tone), clinodactyly (curvature of the fifth finger), and hyperextensible joints. Motor tics, tremor, and a slightly increased rate of seizure disorders have also been reported, and deficits in motor skills and coordination are common (Ratcliffe, 1999; Salbenblatt et al., 1987). An important distinction from Klinefelter syndrome is that XYY is not usually associated with testosterone deficiency or small testicles, and testosterone levels are in the normal range in most cases. Myths that the extra Y chromosome leads to higher than expected levels of testosterone are incorrect. Most males with XYY have normal fertility and little risk of fathering children with sex chromosome aneuploidy; however,

fertility problems occur in a small subset and genetic counseling is recommended for males with XYY desiring to father children.

Neuropsychological and Neuroanatomical Basis and Implications in XYY Syndrome

Males with XYY have IQ scores that are generally within the average range, but there is modest downward skewing of about 10–15 points in comparison to siblings and SES-matched controls (Bender, Puck, Salbenblatt, & Robinson, 1986a). Clinically significant speech delays with generally solid nonverbal, visual–motor capabilities are reported in many studies, and the language-based learning disabilities and need for special education supports seen among other sex chromosome aneuploidy conditions are also found in 50–70% of boys with XYY (Geerts, Steyaert, & Fryns, 2003; Ratcliffe et al., 1990).

Attentional problems can occur in up to 80% of males with XYY (Walzer, Bashir, & Silbert, 1990) and are often accompanied by problems with hyperactivity and impulsivity that are more significant when compared with males with Klinefelter syndrome who often lack externalizing behavior problems. Rates of clinical diagnoses of ADHD varies from 15% to 75% between studies (Geerts et al., 2003; Tartaglia et al., pending review). Both prospective and cross-sectional studies describe clinical impairments in attention span and hyperactive/impulsive behaviors in males with XYY who do not have significant cognitive impairments. Social skills deficits may be present, and autism spectrum disorders occur in 19–35% in studies of patients recruited from support groups and clinics (Geerts et al., 2003; Tartaglia et al., 2006). Behavioral and psychiatric disorders are also more common in XYY than in the general population, with increased risks for anxiety, depression, bipolar, conduct, and psychotic disorders. Again, the variability of these features is highlighted, and some males with XYY have very few or no behavioral or psychological impairments. With regard to brain imaging studies only one study with 10 subjects has been reported, and there were no significant brain volumetric differences found in XYY compared to controls (Warwick et al., 1999). Considerations for neuropsychological assessment and interventions in XYY are addressed below.

48,XXYY, 48,XXXY, AND 49,XXXXY SYNDROMES

While the trisomy conditions of 47,XXY/Klinefelter and 47,XYY syndromes are common, the rarer tetrasomy (48,XXYY, 48,XXXY) and pentasomy (49,XXXXY) conditions deserve mention due to the more significant cognitive, behavioral, and medical involvement. These conditions are sometimes considered "variants" of Klinefelter syndrome since the presence of one or more extra X chromosomes leads to similar physical features of tall stature and shared medical problems of testosterone deficiency and impaired fertility. However, a distinction from classic 47,XXY Klinefelter syndrome is noteworthy due to the association of more significant medical, neuropsychological, and behavioral concerns. While there is similar phenotypic variability within the syndromes, males with these conditions are generally more affected than those with 47,XXY. As the numbers of X and Y chromosomes increase, so do associated medical problems such as seizures, congenital heart malformations, genitourinary abnormalities, and musculoskeletal abnormalities such as elbow dysplasia, scoliosis, and flat feet. Neuroimaging studies show increased ventricular sizes and periventricular white matter abnormalities in a large percentage of patients with both 48,XXYY and 49,XXXXY (Hoffman, Vossough, Ficicioglu, & Visootsak, 2008; Tartaglia et al., 2008).

The severity of intellectual and language disabilities also increases with additional X and Y chromosomes, and there are more significant effects on language impairment relative to nonverbal abilities. Studies suggest that there is a decrease in IQ of 10–15 points with each added X chromosome (Visootsak & Graham, 2006). Since there are many individuals with 47,XXY Klinefelter syndrome who do not have psychological disorders and are independent, successful boys and men, the association with Klinefelter syndrome can be misleading and sometimes detrimental for these conditions in most cases where services and supports are needed. For 48,XXYY, a large study of 95 males showed a mean full-scale IQ of 77, with a range of 54–102, and more significant impairments in verbal IQ (Tartaglia et al., 2008). Visual-perceptual and nonverbal skills are an area of relative strength in most males with XXYY. Similar sample sizes are not available for 48,XXXY or 49,XXXXY; however, ranges of full-scale IQs of 40–70 for 48,XXXY and full-scale IQs of 20–60 for 49,XXXXY have been reported (Linden, Bender, & Robinson, 1995). Full-scale IQ scores do not usually capture overall abilities in the tetrasomy or pentasomy conditions, since there is usually a significant discrepancy between verbal and nonverbal cognitive scores (Tartaglia et al., 2008).

Adaptive living skills usually fall close to the verbal IQ level or below, and are generally within the range of disability for most patients with XXYY, XXXY, and XXXXY (Tartaglia et al., 2008). Increased rates of attention deficits are present (Tartaglia et al., 2006). Although described as interested in prosocial interactions, disorders of mood regulation and autism spectrum disorders are also more prevalent but range in presentation (Tartaglia et al., pending review; Visootsak & Graham, 2006). Irritability and temper tantrums are often associated with poor tolerance for frustration, anxiety, and mood instability. Considerations for neuropsychological assessment and intervention are similar to those described for XXY and XYY below; however, further adjustments and considerations for more significant verbal and cognitive deficits should be made.

SPECIAL CONSIDERATIONS FOR NEUROPSYCHOLOGICAL ASSESSMENT FOR MALES WITH SEX CHROMOSOME ANEUPLOIDY (XXY, XYY, XXYY, XXXY, XXXXY)

Male children and adults with sex chromosome aneuploidy may present with a broad spectrum of clinical concerns, ranging from individuals with subtle clinical manifestations to those with significant disabilities. Thus, considerations for assessment vary depending on the individual, though specific features of the syndromes are important to consider during neuropsychological assessment in order to obtain optimal results. Adolescents may be taller than their cohorts, and desks and chairs should fit appropriately. Many males with sex chromosome aneuploidy have poor endurance and fatigue easily, and lengthy or afternoon testing sessions may be particularly challenging. Postural support concerns related to hypotonia can contribute to fatigue, particularly in tall or large individuals.

Language-based deficits should be considered during the assessment, and lengthy verbal or multiple-step directions can be problematic. Slowing the pace of verbal directions and checking for understanding is recommended. Frequent motor breaks can be beneficial. When assessment standardization conventions allow, tasks with intensive verbal demands should be alternated with nonverbal tasks to help improve cooperation and minimize fatigue.

A comprehensive evaluation for language-based learning disabilities should be considered in all individuals due to the high prevalence in this population. Likewise, speech/language concerns often require further evaluation with a speech pathologist. Speech pathologists should be aware of the association with dyspraxia and include assessment in this area (Samango-Sprouse & Rogol, 2002). In this respect, expressive speech delays and a variety of difficulties with the production of speech may require nonverbal testing alternatives, particularly if a comprehensive evaluation of strengths and weaknesses is the goal of assessment. For more affected individuals, appropriate measures for mild to moderate intellectual disability should be provided. While the verbal demands of many situations may account for attention difficulties, elevated rates of attention deficits often require shorter testing sessions to maintain optimum effort. Deficits in executive function often play a role in clinical concerns and appropriate assessment batteries should be considered. Similarly, executive function concerns may impact the examinee's ability to appropriately maintain and shift sets during various test procedures. Examiners should remain alert to the role structure and scaffolding may play in assessment.

Emotional and mood regulation are important considerations for males with sex chromosome aneuploidy. Irritability, anxiety, and emotional sensitivity (Bender et al., 1995) are factors that contribute to the need for a good working rapport and appropriate supports. Comprehensive evaluations should include thoughtful emotional assessment. A number of studies have noted emotional sensitivity and immaturity in children with sex chromosome aneuploidies, and it is important to remain alert for misattribution of height as an indicator of emotional maturity.

Social skill deficits in males with sex chromosome aneuploidy can interfere with the implicit social conventions of individual assessments, and specific examination of social skills may be a consideration. An increased risk for autism spectrum disorders is present, and should be included in the evaluation of a child or adolescent with social–emotional difficulties. Establishing the diagnosis of an autism spectrum disorder is important for individuals who meet the criteria to allow eligibility for many programs and supports that have been developed for children and adults with autism spectrum disorders targeting social deficits.

Finally, evaluation of adaptive functioning is critical, since adaptive skills are often significantly lower than overall cognitive scores due to the combination of verbal deficits, executive dysfunction, and social–emotional difficulties. Thus, these scores are a more realistic indicator of daily functioning than IQ scores, and educational goals and interventions should include consideration of all aspects of adaptive functioning. Documentation of persistent adaptive deficits is also often necessary to support the need for educational or community-based services, since cognitive deficits in the intellectual disability range are not universal.

EVIDENCE-BASED INTERVENTIONS FOR MALES WITH SEX CHROMOSOME ANEUPLOIDY (XXY, XYY, XXYY, XXXY, XXXXY)

There is a paucity of research on interventions in males with sex chromosome aneuploidy, especially interventions addressing neuropsychological or emotional deficits. One comprehensive set of clinical care guidelines has been developed by a group of experts for males with Klinefelter syndrome (Simpson, Swerdloff, Samango-Sprouse, & Rogol, 2004), while recommendations for the other syndromes are scattered throughout studies and review papers (Tartaglia et al., 2008; Visootsak, Rosner, Dykens, Tartaglia, & Graham, 2007). In summary, recommendations include developmental screening for infants and young children, and evaluation for speech/language disorders or learning disorders as indicated throughout the lifespan. Interventions including speech therapy, physical therapy, and occupational therapy are recommended when indicated, with additional consideration for strategies targeting apraxia of speech which can be associated with sex chromosome aneuploidy in young children. Interventions for reading or learning disabilities do not differ from those recommended in the general population, and evidence-based methods should be utilized instead of commercialized programs that lack

effectiveness in unbiased research. Intellectual disability should be documented if present to support qualification for community-based services.

Similar to learning disabilities, treatments for emotional and behavioral disorders require individualized interventions, and evidence-based therapies should be utilized. Consideration of the comorbidities including language deficits, learning disabilities, and emotional disorders is critical in the assessment and treatment process. ADHD symptoms respond to behavioral and medication treatments at the same rate as studies in other populations with neurogenetic disorders (Tartaglia et al., pending review). Other medication treatments for mood disorders including anxiety, depression, bipolar and psychotic symptoms are recommended as needed. As with other developmental disabilities, sensitivity to psychopharmacologic medications may be present, and smaller doses of medications are recommended as a starting point. Psychological treatments for mood and behavioral disorders should also utilize evidence-based strategies such as cognitive–behavioral therapy; however, these strategies need to be adjusted for the individual's receptive and expressive language abilities and should include visual–perceptual strategies when possible. Standard group or individual therapy settings that are highly verbal/language-based are likely to be overwhelming and ineffective for many patients. For those with social deficits and autism spectrum disorders, practical interventions to help develop social skills, social/pragmatic language abilities, and social reciprocity should be sought and applied when needed.

Testosterone therapy is a standard medical intervention for most patients with Klinefelter syndrome/XXY, XXYY, XXXY, and XXXXY starting in adolescence or young adulthood. Well-accepted benefits of testosterone therapy including muscular development, physical endurance, pubertal development and sexual function can indirectly lead to improvements in mood and self-esteem. The direct effects of testosterone therapy on psychological features of these conditions are currently being studied; however, previous descriptive literature has shown improvements in attention span, energy level, and overall mood in adult males with Klinefelter syndrome (Nielsen, Pelsen, & Sorensen, 1988). Since males with XXYY, XXXY, and XXXXY can have more significant intellectual impairments or behavioral disorders, questions often arise about the role of testosterone for these patients. Current literature supports that, if used appropriately, testosterone therapy does not increase aggressive behaviors, and potential benefits to energy level, mood, and attention span are similar to XXY (Tartaglia et al., 2008). Thus, psychologists should be aware of current testosterone treatment, and recommendations should be made to seek further medical endocrinologic care to optimize testosterone therapy. Males with XYY do not typically require testosterone replacement therapy.

Current research is focusing on deconstructing the language-based learning disabilities, executive dysfunction, and social cognitive processing of males with sex chromosome aneuploidy in order to develop evidence-based interventions (Van Rijn, Aleman, De Sonneville, & Swaab, 2009; van Rijn et al., 2007). Referral to national advocacy and support organizations is recommended.

SEX CHROMOSOME ANEUPLOIDY IN FEMALES

TURNER SYNDROME

Background and History of TS

TS was first described in 1938 by Dr. Henry Turner, an endocrinologist in Oklahoma, who reported a female with short stature and lack of pubertal development, a congenital webbed neck, and a widened carrying angle of the arms (cubitus valgus; Turner, 1938). Individuals with these features had also been reported in Europe by Dr. Ulrich and Dr. Bonnevie, so this syndrome is also referred to as Ulrich–Turner syndrome and Bonnevie–Ulrich–Turner syndrome. In 1959, the first karyotype was reported on a 14-year-old female by Dr. Charles Ford in Harwell of Oxfordshire and Guys Hospital in London, revealing the chromosome constitution 45,X (Ford, Jones, Polani, De Almeida, & Briggs, 1959).

Etiology of TS

Newborn screening studies have shown that TS occurs in approximately 1:2,500 live female births. Prenatal chromosome studies have demonstrated that approximately 98–99% of TS conceptions are lost as spontaneous abortions (miscarriages). Approximately 50% of females with TS have a chromosome constitution of 45,X instead of the 46,XX in typical females. The remaining cases of TS show chromosomal mosaicism or structural abnormalities of the second X chromosome. In a study by Birkeback et al. (2002) in 410 females with TS, 49% had 45,X; 23% had mosaicism with a structural abnormality of the second X; 19% had 45,X/46,XX mosaicism; and 9% had 46,XX and a structural abnormality of the second X (Birkebaek, Cruger, Hansen, Nielsen, & Bruun-Petersen, 2002). In the cases with a 45,X cell line, TS occurs due to a nondisjunction event, resulting in a failure of X chromosome division during formation of the egg or soon after fertilization. In 80% of 45,X females, the missing X chromosome is paternal in origin (Jacobs et al., 1997). The recurrence risk for parents of a child with TS is <1%. While most adult females with TS are infertile, fertility is present in some women with mosaicism and genetic counseling is warranted.

Physical and Medical Features of TS

Physical features of TS include short stature, webbed neck with low posterior hairline, downward slanting palpebral fissures, epicanthal folds, broad chest, and poor

nail growth. Congenital heart and/or kidney malformations are present in approximately 30–50%. Hearing loss, strabismus, and hypothyroidism are other common medical problems. Ovarian tissue is often absent or minimal, leading to a lack of estrogen production needed for typical pubertal development and infertility. Medical treatments in TS include interventions related to growth and endocrine/pubertal abnormalities. Growth hormone treatments are typically started in childhood and improve final adult height. Estrogen/progesterone replacement therapy is necessary in most girls for breast/pubertal development and bone density. Approximately 20–30% of patients undergo pubertal changes spontaneously; however, these cases are usually associated with mosaicism, and hormone replacement is still often needed at some point during the lifespan. Mild motor developmental delays can be seen in some girls with TS (Bender, Puck, Salbenblatt, & Robinson, 1984) and motor deficits can persist through childhood and adolescence, especially on tasks with spatial components (Ross, McCauley, & Roeltgen, 1996).

Neuropsychological and Neuroanatomical Basis and Implications in TS

As early as the 1980s, neuropsychological studies of TS revealed a distinct profile of stronger verbal and weaker visual–spatial abilities (Pennington et al., 1985). Since then, much of the neuropsychological research in TS has been focused on understanding which specific skill deficits give rise to this pattern. Consensus is found across studies that most girls with TS have only mild decreases in IQ when compared with the general population. The mean IQ in one of the largest studies of girls with TS was 94.6, contrasted with a mean IQ of 103.9 in the control group (Rovet, 1995). Multiple other studies show mean full-scale scores ranging from 92 to 102, with scores following a normal distribution. These overall scores, however, obscure the pattern found across several studies in which girls with TS reliably perform better on verbal than nonverbal tasks, sometimes with one or more standard deviations of difference between their verbal and nonverbal scores. Studies show deficits in nonverbal tasks including visual memory, spatial reasoning, mental rotations, visual discrimination, visual sequencing, and visual–motor coordination. Verbal conceptual abilities are preserved in most cases, and typically represent areas of relative strength for girls with TS (Rovet, 1993).

This cognitive profile is also associated with weaknesses in math skills, which occur in the majority of girls with TS. Impairments in math skills to the degree of meeting criteria for a specific mathematics learning disability occur in 45–55%. Research deconstructing the math learning disability is ongoing, with conflicting results as to whether spatial deficits are correlated with math achievement (Mazzocco, 2009). Executive function deficits and slow response times for math problems seem to play a role. Most studies show that the ability to memorize early math facts is relatively preserved.

This pattern of spatial, math, and other deficits is commonly described as a nonverbal learning disability (NVLD; Rovet, 1995), and TS is commonly associated with this diagnosis. NVLD can be associated with social and attentional deficits, which can also be found in girls with TS. While the NVLD profile generally applies to the common neuropsychological phenotype in TS, it is important to note that there is considerable variability among girls with TS, and a subset have stronger nonverbal than verbal skills or deficits in higher-order and pragmatic language skills that should not be overlooked. Also, some aspects of nonverbal functioning have been shown to be intact in girls with TS (Pennington et al., 1985; Russell et al., 2006). Thus, broad application of the NVLD diagnosis to all girls with TS should be avoided before careful, individualized assessment (Russell et al., 2006). Also, with development, the verbal–performance split may become less dramatic, perhaps due to the positive influence of estrogen on verbal skills at adolescence (McEwen, Alves, Bulloch, & Weiland, 1997).

An intriguing series of studies has investigated the role of the executive functions in mediating the cognitive deficits described in girls with TS. The executive functions include attention and goal-directed behavior, including the ability to plan, check, monitor, and adjust strategy based on feedback. Attentional problems are common in TS, and may offer a partial explanation for the difficulties in mathematics and social immaturity. Studies described by Rovet (1990) showed that WISC-III Third Factor scores (arithmetic, digit span, and coding) were a good predictor of math achievement, suggesting that working memory and other executive functions may partially mediate the math difficulties experienced by girls and women with TS (Bender, Linden, & Robinson, 1990). When verbal tasks required significant executive function, deficits were apparent on these skills as well, despite typical strengths in verbal skills (Bender et al., 1990; Rovet, 1993). A recent study showed a clinical diagnosis of ADHD in 25% of girls with TS (Russell et al., 2006).

Early motor deficits are common, and girls with TS mosaicism perform better as a group than girls with the nonmosaic form of TS. Late walking, hypotonia, and deficits in sensory–motor integration are described, leading to ongoing motor problems throughout childhood, decreased sense of athletic ability, and poor physical self-image for some girls with TS (Hagerman, 1999; Ross, McCauley, Roeltgen, Long et al., 1996). Tasks that require a combination of motor and spatial skills are often most significantly impacted, which might include some sports as well as many building and drawing tasks of early childhood.

When looking at social–emotional development in TS, studies vary in the type and severity of associated problems. Many studies show few emotional or behavioral problems, and Bender even suggests enhanced ability to tolerate stress (Bender, Linden, & Robinson, 1994).

Others show an increased risk for low self-esteem and emotional disorders including anxiety and depression in childhood and adulthood (Cardoso et al., 2004; McCauley, Feuillan, Kushner, & Ross, 2001). When more subtle areas of general psychosocial adaptation and development are considered, there is agreement that girls with TS struggle with social skills deficits. A general immaturity of social skills is described, which does not appear to be entirely attributable to short stature or physical differences. Studies that followed the same girls longitudinally suggest a progression from high levels of activity and distractibility with decreased expression of affect in younger girls to a more anxious, depressed, and withdrawn presentation in older girls (Bender et al., 1994). Despite studies attempting to control for short stature, the impact of stature and other physical differences, along with the possible confound of varying hormonal experiences for adolescents with TS (treated, untreated, mosaic, nonmosaic) further confounds the picture. Coping with knowledge of one's probable infertility is an additional, lifelong stressor. Family support may be complicated by circumstances surrounding diagnosis, and may be enhanced by involvement with other girls and women with TS who are coping well, such as through the Turner Syndrome Society.

Neuroimaging studies in girls with TS show various results, with the most consistent finding being decreased volumes of the parietal and occipital cortices (Brown et al., 2004; Reiss, Mazzocco, Greenlaw, Freund, & Ross, 1995). Volumetric MRI studies also report differences in amygdala and hippocampal volume (Kesler et al., 2004), and cerebellar volume (Brown et al., 2004). Functional MRI studies suggest impairments in the fronto–parietal circuitry (Hart, Davenport, Hooper, & Belger, 2006). Agenesis or anatomical differences affecting the corpus callosum are also mentioned (Fryer, Kwon, Eliez, & Reiss, 2003), especially in girls with TS who have the ring chromosome pattern (Abd et al., 1997). Neuroanatomical studies are confounded, like neuropsychological studies, by differing genetic presentations in TS girls (mosaic, nonmosaic) and by estrogen status. Neuropathology studies on autopsy specimens in TS are limited. One study demonstrated specific right-hemisphere pathology; others have shown diffuse or no abnormalities (Hagerman, 1999).

Special Considerations for Neuropsychological Assessment in TS

In testing girls with TS, the examiner may wish to remember their short stature, and provide adjustments to testing table and chairs to accommodate their physical needs. Because math and spatial tasks are typically more difficult, and because anxiety may be present, it may be wise to begin with more verbal tasks to establish rapport. Difficult tasks can then be alternated, perhaps with a final task chosen for its probable success. Attentional problems should be accommodated through the use of shorter testing sessions interspersed with frequent breaks. Anxiety can be monitored especially when administering timed tasks, and time demands can be removed when necessary for the girl's comfort. Any accommodations the examiner makes to compensate for the girl's executive function deficits should be carefully noted, as these are likely to be helpful classroom modifications.

Evidence-Based Interventions in TS

Evidence-based guidelines for the treatment of TS are published every 2–3 years by the Turner Syndrome Consensus Study Group (Bondy, 2007), and these include recommendations for medical screenings and interventions. Current treatment recommendations include the initiation of growth hormone therapy in childhood. This treatment increases final adult height by 6–11 cm, resulting in an average adult height in the lower percentiles of typical adult females for most cases. Ovarian failure in TS leads to decreased estrogen production needed to support pubertal development, and also results in decreased levels of androgen that are also usually present at low levels in typical females. Thus, in early adolescence, estrogen therapy is recommended to induce physical pubertal changes and to support bone mineralization. Around 30% of girls with TS will have some spontaneous pubertal changes and may not require additional estrogen until later adolescence or adulthood when ovarian function decreases. Low doses of androgen treatment are also used in conjunction with growth hormone for some girls starting at 9–10 years of age to further enhance growth.

While most of the neuropsychological features in TS are thought to be due to genetic mechanisms affecting neurodevelopment, studies have investigated whether some of these features may be partially due to either estrogen or androgen deficits. One placebo-controlled study showed that treatment with estrogen therapy led to improvements in processing speed and motor skills compared to placebo (Ross, Roeltgen, Feuillan, Kushner, & Cutler, 1998). Another recent study showed that treatment with an oral androgen (oxandrolone) for 4 years improved features of math disability (Ross et al., 2009). Growth hormone treatments themselves are not thought to have a direct effect on neuropsychological functioning; however, the increased stature often leads to improvements in self-image and self-esteem.

Other medical problems associated with TS, including high rates of ear infections and a risk for sensorineural hearing loss, may also affect learning and mood. Thus, audiology evaluations are important. Additionally, thyroid disorders can also develop, and both hypothyroidism and hyperthyroidism can affect overall mood, energy level, and cognition. Since some girls with TS can have a relatively mild phenotype, it is important to encourage all patients to follow up with their physicians to ensure that comprehensive medical screenings and treatments are in place.

Approximately 25% of girls with TS have ADHD (Russell et al., 2006), and anecdotal reports suggest that they respond similarly to the general population to ADHD medications (Hagerman, 1999). However, consultation with cardiology should be completed prior to starting stimulant medications due to the elevated rates of cardiac abnormalities associated with TS. The potential side effects of stimulant medication on appetite and growth should also be considered when determining medical treatments. There are no specific studies of ADHD medications in TS available as yet. Little research is available to document response in girls with TS to various treatments for anxiety or social skills deficits. For these concerns, evidence-based treatments developed for the general population should be used, keeping in mind modifications that may need to be made due to spatial and higher-order language deficits.

For the educational problems and math learning disability, current research deconstructing these problems hopes to identify core areas of deficit with the development of targeted treatments. Because the pattern of strengths and weaknesses often parallels that found in NVLD, techniques designed to use language strengths to compensate for spatial weaknesses can be effective (Thompson, 1997). Linguistically based social skills techniques such as the Hidden Curriculum may be successful as well (Myles, Trautman, & Schelvan, 2004). However, emphasis on a complete assessment of each individual to identify areas of strength and weakness is critical prior to generalizing the NVLD diagnosis in all girls with TS.

TRIPLE X SYNDROME

Background and History

The addition of an extra X chromosome in females is known by many names, including Triple X, Trisomy X, Triplo-X, and 47,XXX. Triple X syndrome was first described in 1959 by Dr. Patricia Jacobs and her colleagues at Western General Hospital in Edinburgh, Scotland. The initial case reported was a 35-year-old female who was 5′ 9″ tall, weighed 128 lb, had a history of premature ovarian failure at 19 years of age, and a karyotype of 47,XXX.

Etiology

Newborn screening studies have shown that 47,XXX occurs in approximately 1:1,000 females births. However, it is estimated that only 10% of females with Triple X are diagnosed in their lifetime. Females with Triple X syndrome have a chromosome constitution of 47,XXX, instead of the typical 46,XX. Triple X syndrome occurs due to a nondisjunction event, resulting in a failure of X chromosome division during oogenesis (formation of the egg) or soon after fertilization. The majority of Triple X cases result from nondisjunction during oogenesis, with paternal errors accounting for only about 10% of 47,XXX females (May et al., 1990). There is a maternal age effect causing Triple X to be more common in mothers with advanced maternal age, increasing from 1:2,500 live births at maternal age 33 years to 1:450 at 43 years (Hook, 1992). Triple X syndrome is not usually inherited. Thus, the recurrence risk for parents with one child with Triple X is less than 1%. Similarly, the risk of offspring with X chromosome aneuploidy in a woman with Triple X syndrome is also less than 1%. Genetic counseling is recommended for all women with Triple X, however, to discuss risks.

Physical and Medical Features of Triple X Syndrome

Physical and medical features of Triple X are generally mild in most cases. The most common features include tall stature, epicanthal folds, widely spaced eyes (hypertelorism), joint hyperextensibility, flat feet, and curvature of the fifth finger (clinodactyly). There is an increased risk of kidney and genitourinary system malformations, and an increased risk of premature ovarian failure. Nonspecific abdominal and musculoskeletal complaints are common. Neurological findings can include hypotonia, developmental delays, intention tremor, and motor skills deficits (Salbenblatt, Meyers, Bender, Linden, & Robinson, 1989). Seizure disorders occur in approximately 15% of diagnosed cases (Roubertie, Humbertclaude, Leydet, Lefort, & Echenne, 2006).

Neuropsychological and Neuroanatomical Basis and Implications in Triple X Syndrome

Much like the other sex chromosome aneuploidy conditions described above, the neuropsychological impact of Triple X is variable. Prospective studies of girls with Triple X identified at birth have found somewhat more significant effects on overall intellectual functioning in comparison to XXY and XYY. Mean full-scale cognitive scores are approximately 15–20 points lower than controls, with mean verbal IQ scores in the below-average range, and relatively stronger nonverbal abilities (Bender et al., 1986a; Netley, 1986; Robinson, Bender, Linden, & Salbenblatt, 1990). Studies in groups of girls with Triple X identified in the prenatal period who have a higher socioeconomic status have suggested better intellectual functioning with adult abilities commensurate with biological siblings and family (Robinson, Bender, & Linden, 1992).

Prospective studies of newborns with Trisomy X identified developmental delays in up to 80%, with expressive language often most significantly affected (Linden, Bender, Harmon, Mrazek, & Robinson, 1988; Otter, Schrander-Stumpel, & Curfs, 2010). These early language delays correlate with later learning disabilities at school age (Ratcliffe et al., 1990). Academic difficulties are very common, with language-based difficulties playing a significant role in the school years. A subset of girls has more global learning disabilities that also include math deficits. One neuropsychological study in girls and

adolescents with Triple X showed decreased semantic fluency, poor reading comprehension, impaired general reading skills, decreased conceptual abilities and low problem-solving skills (Bender, Linden, & Harmon, 2001). Studies of motor skills have shown higher rates of sensory integration disorder, delayed early motor milestones, fine and gross motor difficulties, and relatively poor overall strength and coordination (Linden et al., 1988; Salbenblatt et al., 1989).

Attentional problems are also a common concern in Triple X syndrome, and ADHD has been described in 38% of girls with Triple X (Tartaglia et al., pending review). These girls present with symptoms of inattention, distractibility, and poor organization, and significant features of hyperactivity are uncommon. Other psychological and behavioral features including shyness, anxiety disorders (social anxiety, selective mutism, separation anxiety), dysthymia, depression, adjustment disorders, poor self-esteem, conduct disorder, and psychosis are among the broadly diagnosed psychiatric disorders found in Triple X. Adolescence was identified as a particularly difficult period for girls with Triple X due to the cognitive deficits, increased interpersonal sensitivity, anxiety, and various psychological difficulties combining to adversely impact overall adjustment (Bender et al., 1995; Harmon, Bender, Linden, & Robinson, 1998; Linden et al., 1988). Studies have shown that girls with Triple X who had higher cognitive abilities or who came from families of higher socioeconomic status and/or increased parental education were less likely to have severe adjustment or emotional problems in adolescence. This may be due to an increased ability for these families to access resources for treatment and interventions leading to improved outcomes, in addition to the influence of multiple other autosomal genes involved in neurodevelopment inherited from their parents (Rovet et al., 1995).

Neuroimaging studies have identified reduced total brain volumes when compared with controls in girls with Triple X (Warwick et al., 1999). Amygdala size has also been found to be modestly reduced (Patwardhan et al., 2002).

Special Considerations for Neuropsychological Assessment in Triple X Syndrome

Children and adults with Triple X show significant variability in their cognitive presentations, so an evaluator must be prepared for a range of abilities that could include subtle neuropsychological findings to significant disabilities. As described above for males, adolescent females with Triple X may be taller than their peers, and desks and chairs may need to be adjusted for testing. Many girls have poor physical endurance and fatigability, so long testing sessions may be challenging. Postural support concerns related to hypotonia can contribute to fatigue, particularly in tall or large individuals. Frequent motor breaks can be beneficial. Examiners should also remain alert for motor concerns that require further referral.

Consideration of language-based delays and significant expressive language deficits are important for girls with Triple X syndrome. Likewise, thorough learning and language evaluations are indicated. Speech-language evaluation is recommended for all girls, with a consideration of the association with apraxia of speech seen in the sex chromosome aneuploidy conditions in early childhood. During the assessment process, slowing the pace of verbal directions and checking for understanding is recommended. Lengthy verbal or multiple-step directions can sometimes be problematic. When assessment standardization conventions allow, tasks with intensive verbal demands should be alternated with nonverbal tasks to help improve cooperation and minimize fatigue.

A thorough neuropsychological assessment for this group should include assessment for psychiatric conditions, particularly mood disorders with an emphasis on anxiety symptoms, as well as possible thought disorders. Since many of these girls tend to be immature, shy, or hesitant, it is important to take rapport building into greater consideration. Given elevated rates of depression and dysthymia seen in some girls, appropriate risk assessment should be considered. Social skills, personal adjustment, and ability to self-advocate are also important areas of assessment.

Adaptive functioning assessment is important, since adaptive skills are often lower than overall cognitive scores due to the combination of verbal deficits, executive dysfunction, and social–emotional difficulties. These scores are a more realistic indicator of daily functioning than IQ scores, and educational goals and interventions should include consideration of the different areas of adaptive functioning. Documentation of adaptive deficits is often needed to support qualification for educational or community-based services, since cognitive deficits in the intellectual disability range are not universal.

History should include questions regarding staring spells or atypical movements, since seizure disorders can be present in up to 15% of girls with Trisomy X and sometimes are unrecognized since they may present as partial or absence seizures. Medical evaluation for possible thyroid disorders or reproductive hormone abnormalities in adolescence or adulthood should be considered since these can be associated with Triple X and can affect psychological functioning.

Evidence-Based Interventions for Triple X Syndrome

Research studies directly assessing interventions in females with Triple X have not yet been published. Some recent review articles propose guidelines for evaluation and interventions based on literature review and clinical experience (Otter et al., 2010; Tartaglia, Howell, Sutherland, Wilson, & Wilson, 2010). These emphasize developmental screening in infants and children, including cognitive, speech/language, and motor skills evaluations. Therapies including speech, physical, and occupational therapy

should be initiated if definite delays are identified, but should also be strongly considered in cases where girls fall in the below-average range, where steady progress is not evident, or when there is a clear discrepancy compared to a sibling's developmental course. During school age, assessment for learning disabilities, executive dysfunction, and ADHD is recommended. Interventions for learning disabilities do not differ from those recommended for the general population, and evidence-based methods are recommended. ADHD symptoms can be treated with behavioral supports and standard ADHD medications, usually initiated at conservative doses due to neurodevelopmental differences.

Emotional assessment is also important due to increased psychiatric comorbidities, and these should be completed periodically through childhood and adolescence and into young adulthood. The tall stature of most girls with Triple X paired with social–emotional immaturity and cognitive impairments can lead to further difficulties. Psychological therapies need to be practical rather than theoretical, and adjusted for cognitive impairments, expressive and receptive language deficits, and emotional maturity. Interventions teaching safety and self-advocacy should also be considered. Evaluation for psychopharmacologic medications is recommended if behaviors or emotional difficulties are affecting daily living, educational progress, or social development. Selective serotonin reuptake inhibitor medications can be very helpful for treatment of social anxiety and dysthymic symptoms in young children and adolescents. Other medications for mood stabilization or antipsychotic effects can be utilized if needed. Referral to national advocacy and support organizations is recommended (see below).

TETRASOMY X AND PENTASOMY X SYNDROMES

Tetrasomy X (48, XXXX) and Pentasomy X (49, XXXXX) are both very rare, occurring in 1:50,000 to 1:250,000 females respectively. Current literature consists of multiple case studies ascertained for clinical presentations of developmental delays or dysmorphic features. Prenatally diagnosed cases have not been described to date. In all cases reported, the additional X chromosomes are maternal in origin and result from successive nondisjunction during meiosis.

Medical findings include increased rates of dysmorphic features, specifically hypertelorism (wide set eyes), epicanthal folds, clinodactyly, and plagiocephaly (asymmetric shape of the head), as well as congenital malformations (radioulnar synostosis, congenital heart malformations, hip dysplasia, cleft palate) due to the gene dosage effects of the extra X chromosomes (Linden et al., 1995). Important neurologic findings include hypotonia, developmental delays, intention tremor, tic disorders, and increased rates of seizure disorders. For females with Tetrasomy X and Pentasomy X, research is limited; however, due to many reported cases of pubertal delays or ovarian failure, endocrinology evaluation is recommended to determine if hormonal replacement therapies are needed.

Cognitive and neuropsychological impairments are generally more significant than the sex chromosome trisomies. Cognitive abilities in both Tetrasomy X and Pentasomy X include full-scale scores that range from the 30s to the 70s, with Tetrasomy usually less affected than Pentasomy. The neuropsychological profile is similar to Triple X; however, the discrepancy between verbal and nonverbal abilities can be more significant, with verbal abilities almost always in the intellectual disability range. Speech–language deficits, speech apraxia, ADHD symptoms, autism spectrum disorders, and behavioral–emotional disorders can cause significant impairment. About 50% of the reported cases of Tetrasomy X show features of dysregulated mood or tantrums (Linden et al., 1995). Interventions including speech–language, occupational, and physical therapies, school-based interventions for academic problems, and community services for individuals with developmental disabilities are recommended. Psychopharmacological and psychotherapeutic interventions adapted for cognitive abilities are recommended to address behavioral and emotional difficulties.

ADVOCACY AND SUPPORT ORGANIZATIONS FOR SEX CHROMOSOME ANEUPLOIDY

All individuals with sex chromosome aneuploidy and their families should be connected with advocacy organizations to receive further education and support as listed below. The organizations offer updated information, educational materials, family conferences, research studies, and opportunities to connect with other families and professionals with expertise in the conditions. They are also very helpful for professionals as they usually have strong libraries of literature and guidelines. They also present the conditions from the perspective of the family/patient, allowing a more accurate and personal portrayal of the spectrum of involvement and the important issues than standard medical literature.

- *Klinefelter Syndrome & Associates (AKA Knowledge Support & Action)*: Serves XXY/Klinefelter syndrome, XYY, Triple X, rare variations: *www.genetic.org*
- *The XXYY Project*: Serves males with XXYY syndrome: *www.xxyysyndrome.org*
- *American Association for Klinefelter Syndrome Information and Support (AAKSIS)*: Serves males with XXY/Klinefelter syndrome and variations: *www.aaksis.org*
- *Turner Syndrome Society of the United States*: Serves females with Turner syndrome: *www.turner-syndrome-us.org*
- *Tetrasomy and Pentasomy X Support Group (TPSG)*: Serves females with Tetrasomy or Pentasomy X: *www.tetrasomy.com*

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