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Longitudinal trajectories of aberrant behavior in fragile X syndrome

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ABSTRACT

The Aberrant Behavior Checklist-Community (ABC-C; Aman et al., 1995) has been increasingly adopted as a primary tool for measuring behavioral change in clinical trials for individuals with fragile X syndrome (FXS). To our knowledge, however, no study has documented the longitudinal trajectory of aberrant behaviors in individuals with FXS using the ABC-C. As part of a larger longitudinal study, we examined scores obtained on the ABC-C subscales for 124 children and adolescents (64 males, 60 females) with FXS who had two or more assessments (average interval between assessments was approximately 4 years). Concomitant changes in age-equivalent scores on the Vineland Adaptive Behavior Scales (VABS) were also examined. As expected for an X-linked genetic disorder, males with FXS obtained significantly higher scores on all subscales of the ABC-C and significantly lower age-equivalent scores on the VABS than females with FXS. In both males and females with FXS, scores on the Irritability/Agitation and Hyperactivity/Noncompliance subscales of the ABC-C decreased significantly with age, with little to no change occurring over time on the Lethargy/Social Withdrawal, Stereotypic Behavior, and Inappropriate Speech subscales. The decrease in scores on the Hyperactivity/Noncompliance domain was significantly greater for males than for females. In both males and females, age-equivalent scores on the VABS increased significantly over this developmental period. These results establish a basis upon which to evaluate long-term outcomes from intervention-based research. However, longitudinal direct observational studies are needed to establish whether the severity of problem behavior actually decreases over time in this population.

1. Introduction

Children with intellectual disabilities (ID) show a greater tendency to engage in problem behavior than individuals without ID (de Ruiter, Dekker, Verhulst, & Koot, 2007; Dekker, Koot, van der Ende, & Verhulst, 2002; Dykens, 2000; Emerson, 2003) and there is evidence in the literature that the prevalence of problem behavior among individuals with certain genetic

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conditions associated with ID is higher than in individuals with idiopathic ID (Arron, Oliver, Moss, Berg, & Burbidge, 2011; Bodfish & Lewis, 2002; Powis & Oliver, 2014). For example, individuals with fragile X syndrome (FXS) – the most common known form of inherited intellectual disability, affecting approximately 1 in 4000 individuals worldwide (Turner, Webb, Wake, & Robinson, 1996) – have been reported to engage in significantly higher levels of problem behaviors such as hyperactivity, stereotypy, self-injury, and inappropriate speech than age-, and IQ-matched controls (Baumgardner, Reiss, Freund, & Abrams, 1995; Lachiewicz, Spiridigliozzi, Gullion, Ransford & Rao, 1994; Sansone et al., 2012; Sudhalter, Cohen, Silverman, & Wolf-Schein, 1990). In addition to ID, researchers have documented a distinct behavioral phenotype associated with FXS (Reiss & Freund, 1992; Smith, Barker, Seltzer, Abbeduto, & Greenberg, 2012; Wolff et al., 2012), of which the core features include social anxiety, withdrawal and eye-gaze aversion (Hall, DeBernardis, & Reiss, 2006), elevated rates of self-injurious behavior (Hall, Lightbody, & Reiss, 2008; Symons, Clark, Hatton, Skinner, & Bailey, 2003), and hyperactivity and attention deficit (Hatton et al., 2002; Thurman, McDuffie, Hagerman, & Abbeduto, 2014). Due to varied methods of measurement and analysis, and age-ranges sampled, however, the persistence of problem behavior in this population from childhood to adulthood is not well understood (Bailey et al., 2012; Fisch et al., 1999; Hatton et al., 2002; Sansone et al., 2012; Wheeler et al., 2014).

FXS is caused by a mutation to the *FMR1* gene on the long arm of the X chromosome; located at the Xq27.3 "fragile" locus and consisting of abnormal multiple CGG replications. Expansions of approximately 55–200 repeats are associated with the fragile X "premutation" for which individuals are considered carriers and show few or no symptoms of the disorder, whereas larger expansions (>200 CGG repeats) are associated with the "full mutation" (Oberle et al., 1991). Consequently, the full mutation produces abnormal DNA hypermethylation of cytosines in the *FMR1* promoter region, transcriptional silencing of the *FMR1* gene and thwarted production of the gene's product, the fragile X mental retardation protein (FMRP; Verkerk et al., 1991). Although the syndrome affects males *and* females, males with FXS have only one X chromosome and significantly lower FMRP and are, therefore, more affected by the disorder.

A significant advance in our understanding of FXS was brought forth with the isolation of the *Fmr1* gene in a knockout (KO) mouse model of FXS, designed to characterize the structure and function of FMRP and dendritic abnormalities found in humans with FXS. The KO model has led to the discovery that loss of FMRP – which typically functions as a repressor of translation of specific messenger ribonucleic acid (mRNA) – allows for translation of mRNA near synapses, activation of metabotropic glutamate receptors (mGluRs), and subsequently increased long-term depression of transmission at hippocampal synapses (Bear, Huber, & Warren, 2004). An emerging theory therefore implicates mGluR antagonists in the potential alleviation of impairments in the FXS phenotype, and by extension, the aberrant behavior associated with FXS (Choi et al., 2011; Meredith, de Jong, & Mansvelder, 2011). As such, investigators have been charged with identifying suitable measures of behavioral outcome in clinical trials testing the theory. Following extensive research establishing concurrent and construct validity, inter-rater and test-retest reliability (Aman, Singh, Stewart, & Field, 1985b), and a gradual, but increasing adoption of the tool in clinical trials, the Aberrant Behavior Checklist-Community (ABC-C; Aman, Singh, Stewart, & Field, 1985a; Aman, Singh, Stewart, & Field, 1985) has garnered much attention for its potential sensitivity in measuring treatment response and detecting changes in behavior (cf., Aman, 2012; McCracken et al., 2002; Research Units on Pediatric Psychopharmacology Autism Network, 2005; Schroeder, Rojahn, & Reese, 1997; Shedlack, Hennen, Magee, & Cheron, 2005). Furthermore, recommendations recently published by a working group of FXS experts identified the ABC-C as one of the few measures available that came closest to meeting optimal criteria for use in clinical trials (Berry-Kravis et al., 2013).

However, there is a paucity of longitudinal investigations using the ABC-C. In one study conducted by Anderson, Maye, and Lord (2011), longitudinal analyses of scores obtained on the ABC-C were conducted with three diagnostic groups: autism, broader autism spectrum disorder (ASD), and nonspectrum developmental disabilities (DD). Caregivers were asked to rate their child on the ABC-C at age 9 and then every four months via mailed questionnaires and those with a minimum of two assessment points were included in the sample. Trajectories were presented on three of the five ABC-C subscales, i.e., Hyperactivity/Noncompliance, Irritability/Agitation, and Lethargy/Social Withdrawal. Results showed that individuals with autism displayed higher levels of aberrant behavior than individuals with ASD and DD, with decreasing trends observed over time on the Irritability/Agitation and Hyperactivity/Noncompliance subscales across all groups. However, a different pattern emerged on the Lethargy/Social withdrawal subscale. Individuals in both the autism and ASD groups showed an increasing trend in Lethargy/Social withdrawal with age (especially those in the ASD group), indicating a need for services addressing social withdrawal beyond early intervention and into early adulthood in this population (Anderson et al., 2011).

Although there have been studies that have begun to map the trajectory of development in FXS (Bailey, Hatton, & Skinner, 1998; Dykens et al., 1989; Fisch et al., 1999; Hagerman et al., 1989; Klaiman et al., in press), to our knowledge, none have measured the trajectory of aberrant behavior using longitudinal methods in a large sample of individuals with FXS using the ABC-C. Considering that pharmaceutical trials are already underway, the time is ripe for an investigation of the developmental trajectory of aberrant behavior in this population, both for specification purposes and to establish a basis upon which to evaluate long-term outcomes from intervention-based research. Revealing the developmental course of aberrant behavior in individuals with genetic disorders – particularly by utilizing longitudinal methods – is vital to understanding the specific needs and therapeutic standards that apply to the disorder.