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Motor abilities of children diagnosed with Fragile X Syndrome with and without autism

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Abstract

Background—Previous studies suggested that children diagnosed with Fragile X Syndrome (FXS) often meet criteria for autism or PDD. This study describes the fine motor abilities of children diagnosed with FXS with and without autism spectrum disorder, and compares the motor scores of those groups controlling for cognitive level.

Method—Forty-eight children, ages 12-76 months (SD=16) diagnosed with FXS were assessed with the Mullen Scales of Early Learning, and the Autism Diagnostic Observation Schedule (ADOS). Their parents were interviewed with the Autism Diagnostic Interview-Revised (ADI-R). We used a one-way analysis of variance (ANOVA) to determine if the fine motor scale of the Mullen would show group differences based on autism classifications for the sample. In addition, we used Pearson correlation coefficient to examine the relationship between the cognitive level, the autism severity and the motor abilities. Lastly, we conducted a one-way analysis of covariance (ANCOVA) to determine the difference between the motor abilities of the ASD groups controlling for cognitive level

Results—We found that 60% of the children with FXS met criteria for autism or PDD-NOS. Children with FXS with autism and PDD-NOS had lower fine motor scores than those without. However, there was no significant association between degree of motor impairment and communication and social impairments after controlling for cognitive level, indicating that cognitive level contributes to impaired motor abilities of children diagnosed with FXS and autism, more than the severity of autism symptoms.

Conclusion—children with FXS and autism are at risk for impaired motor abilities. Implications for development and intervention are discussed.

Introduction

Fragile X syndrome (FXS) is a genetic disorder associated with mental retardation and in milder forms learning disabilities and emotional problems without significant cognitive deficits (Hagerman and Hagerman 2002). FXS affects all races, with an estimated prevalence rate of approximately 1:3600 (Crawford, Meadows et al. 2002). The syndrome

results from an unstable expansion of trinucleotide (CGG) repeat in the 5' untranslated regions of the fragile X mental retardation 1 (*FMR1*) gene, leading to a deficient production of the fragile X mental retardation protein (FMRP), an essential element for brain development and functioning (Loesch, Huggins et al. 2004). A normal *FMR1* gene has 5-44 CGG repeats, while the abnormal expansion is classified into intermediate or gray zone (45-54 repeats), premutation (55-200 CGG repeats) and full mutation (more than 200 repeats) (Maddalena, Richards et al. 2001). A mix pattern of full mutation and premutation is termed mosaicism. The full mutation is associated with lower levels or absence of FMRP causing cognitive impairment and other behavioral abnormalities. Mosaicism is associated with milder cognitive impairment than the full mutation and better development of adaptive skills (Loesch, Huggins et al. 2004). The premutation can cause mild clinical involvement such as anxiety, attention deficit hyperactivity disorder (ADHD), executive function deficits, premature ovarian failure, and late onset tremor and ataxia (FXTAS)(Farzin, Perry et al. 2006), (Hagerman and Hagerman 2004). Individuals with FXS typically have physical and neurobehavioral symptoms. Physical features often include long face with prominent ears, flat feet, hyperextensible joints, high arched palate, macroorchidism, mitral valve prolapse, and strabismus. Neurobehavioral symptoms include social anxiety (shyness), gaze avoidance, repetitive behavior such as hand flapping and hand biting, sensory hypersensitivity, tactile defensiveness, delayed speech development, echolalia, and poor motor coordination (Hagerman and Hagerman 2002),(Belmonte and Bourgeron 2006)

Autism is present in several genetic disorders such as FXS, tuberous sclerosis, Rett syndrome and phenylketenuria (Dykens E.M. 1997). The prevalence rate of autism in FXS ranges between 21% to 33% (Hatton, Sideris et al. 2006), (Bailey, Mesibov et al. 1998), (Kaufmann, Cortell et al. 2004), (Rogers, Wehner et al. 2001). In addition, many individuals diagnosed with FXS without autism present some autistic-like behaviors such as eye gaze avoidance, sensory sensitivity, atypical language and repetitive behavior (Hatton, Sideris et al. 2006). Several studies reported that individuals diagnosed with FXS and autism have lower cognitive abilities (Cohen 1995), (Turk and Graham 1997), (Kaufmann, Cortell et al. 2004) lower developmental scores (Rogers, Wehner et al. 2001) as well as lower adaptive behavior levels and problem behavior (Hatton, Hooper et al. 2002); (Kau, Tierney et al. 2004) than individuals with FXS without autism.

Although there is a body of knowledge about the cognitive and behavioral abilities of individuals with FXS and autism, there is a gap in the literature regarding the motor abilities of this population. There are only two studies that examined motor functioning of individuals with FXS with and without autism. Baranek and colleagues (Baranek, Danko et al. 2005) compared the sensory-motor features of children with FXS, autism and other developmental delays during the first year of life and found unusual motor patterns such as posturing and repetitive leg movement as discriminating features of FXS at 9-12 months. Rogers and colleagues (Rogers, Wehner et al. 2001) compared toddlers with FXS and autism, FXS without autism, autism without FXS, and other developmental disabilities on the Mullen Scales of Early Learning (Mullen 1995). They found differences between the FXS and autism group and the other three groups on all the Mullen scales except the Visual Reception scale. Consistently, the FXS groups had lower scores on the motor scales.

Intact development of motor skills enables infants, toddlers and children to explore their environment and engage in meaningful physical and social interactions. Various studies in children with autism reported a deficit in the organization of the action towards a goal (Barthelemy, Adrien et al. 1994), presentation of movement disturbances during early infancy (Teitelbaum, Teitelbaum et al. 1998), significant effect of IQ on the postural deficit (Minshew, Sung et al. 2004), as well as poor motor control causing poor fine and gross motor skills. There have been no similar studies regarding children with FXS, although these

children are characterized by low tone and endurance that affect their motor development, and predispose them to have difficulties in self-care activities, play, academic skills, and social participation.

The purpose of this study is: 1) to describe the motor abilities of young children diagnosed with FXS both with and without and autism. 2) To compare the motor scores of these two groups. Our research question is: Are the motor abilities of children diagnosed with both FXS and autism different from those of children with FXS without autism. We hypothesize that children with FXS with autism will exhibit poorer performance on the Mullen motor scales than children with FXS alone, when removing the effect of their cognitive abilities, by controlling for the visual reception score of the Mullen.

Method

Participants

Our study includes 48 children (36 males and 12 females) assessed at the M.I.N.D. Institute at the University of California at Davis Medical Center between 2001 and 2007 whose parents signed a consent form approved by our institutional review board to participate in this research. All the children have the *FMR1* mutation by DNA studies as previously described and were diagnosed with FXS. Their age ranged from 12 months to 76 months. Thirty-two of them were white (66.7%), two Asian (4.2%), four East Indian (8.3%), two African-American (4.2%), four American Indian (8.3%), and four Hispanic or other race/ethnicity (8.3%) (see Table 1).

Measurements

The Mullen Scales of Early Learning (Mullen 1995) is a standardized developmental test for children from birth to 68 months. The Mullen provides normative scores for five specific scales: Gross Motor, Visual Reception, Fine Motor, Receptive Language, and Expressive Language. The Mullen was standardized on a nationally representative sample of children ages 2 days-69 months. The Mullen is highly reliable (internal consistency of .91, interscorer reliability of .91-.99), and valid instrument (concurrent validity with the Bayley .53-.59., and .65-.82 with the fine motor subtest of the Peabody).

In this study we used the T scores of the Fine Motor, and the Visual Receptive Scales. The T-scores range from 20-80 with a mean of 50, and S.D of 10. The Gross Motor Scale was not used, as it is administered from birth to 33 months, and most of the study participants were older than this age.

The Fine Motor Scale provides a measure of visual- motor ability. The items require visual discrimination, motor planning and motor control. Scores on the fine motor scale may indicate fine motor planning, fine motor control, unilateral and bilateral manipulation, visual reception and memory, and gross motor development.

Visual Receptive Scale assesses the child's performance in processing visual patterns. The items require visual organization, visual sequencing, and visual spatial awareness, including concepts of position, shape and size. Scores on the visual receptive scale may indicate the child's visual form perception, spatial organization and visual memory.

The Autism Diagnostic Observation Scales (ADOS) (Lord, Rutter et al. 1999) is a standardized play-based assessment of the child's current behavior. It utilizes "presses" to elicit behaviors from the individual being assessed. One of four modules is administered to the client, and the choice of module administered is based on the individual's expressive language level and overall developmental functioning. The scoring of the ADOS is based on

an algorithm of several of the items that are coded for the entire battery, and includes domains of Communication, Reciprocal Social Interaction, Imagination/Creativity, and Stereotyped Behaviors and Restricted Interests. The Communication and Reciprocal Social Interaction domain scores are used together for the determination of the overall ADOS classification, which includes a cut-off for Autism Spectrum and Autism.

The Autism Diagnostic Interview – Revised (ADI-R) (Lord, Rutter et al. 1994), (Rutter, Le Couteur et al. 2003) is a semi-structured parent interview used in the assessment of autism. It is administered to the primary caregiver(s) of the individual being assessed, and includes questions encompassing Abnormalities in Reciprocal Social Interaction; Abnormalities in Communication; Restricted, Repetitive, and Stereotyped Patterns of Behavior; and Abnormality of Development Evident at or Before 36 months. The interview includes questions regarding the current functioning of the individual being assessed, as well as questions about the individual at the 4-5 year age period, although the algorithm used to score and rate the individual is based primarily on coding of the 4-5 year age period. This is an important distinction between the ADI-R and the ADOS, because these ratings may be based on very different behaviors (current behaviors for the ADOS or age 4-5 for the ADI-R) depending on the current age of the child being assessed. In order to meet the criteria for autism on the ADI-R, scores must be at or above the cutoff level for each of the three domains, and there must be at least one positive indicator in the child's developmental history, such as age when symptoms were first noted by parents. Another important distinction between the ADI-R and the ADOS is that the ADI-R does not include a cutoff for PDD-NOS, whereas the ADOS does.

To be diagnosed with Autism or Autism Spectrum Disorder (ASD) the participants had to meet criteria for autism on two of the three diagnostic measures; the ADOS, the ADI-R and the autism criteria defined in the DSM-IV (American Psychiatric Association 2000). A final diagnosis was given following review of data by the clinical team. It is worth noting that the examiners were experienced clinicians who were trained to administer the tests. The examiners who administer the Mullen Scales were blinded to the autism status of the children.

Results

We found 19 children without autism (39.6%), 16 with PDD-NOS (33.3%), and 13 with autism (27.1%). See Table 1 and 2 for participant's demographics and assessments scores. We examined the relationship between fine motor abilities, visual perception, expressive and receptive language, and communication and social abilities using Spearman correlation. A significant inverse relationship between the fine motor scores and the communication and social score of the ADOS was found ($-0.42, P < .01$), such that the more significant motor impairment was associated with more significant autism symptoms. A significant relationship was found between the fine motor score and the visual reception scores ($.70, P < .01$), such that more significant fine motor impairment was also associated with poorer non-verbal cognitive performance (See Table 3). A significant positive correlation was found between the fine-motor scores and the expressive language scores ($.59, P < .01$). To examine the differences between the motor abilities of children diagnosed with FXS with and without autism, we conducted a one way analysis of variance (ANOVA), which was significant, $F(2,45)=5.64, p=.007$. Follow-up tests were performed to evaluate pairwise differences among the means, conducting Post hoc comparisons using the Tukey test. We found a significant difference between the FXS and autism group and the FXS group without autism. In addition, we found a significant difference between the FXS and PDD-NOS and the FXS groups. No significant difference was found between the motor abilities of the FXS and autism and the FXS and PDD-NOS groups. To examine the difference between the motor

abilities of these three groups controlling for cognitive level, we conducted a one-way analysis of covariance (ANCOVA) using the visual reception score of the Mullen as a covariate, because it is independent of the motor score, and represents an estimate of non-verbal intelligence. The ANCOVA was significant $F(1, 44) = 36.72$, $MSE = 13.22$, $p < .01$. To evaluate pairwise differences among these adjusted means we conducted follow-up tests. The Bonferroni procedure was used to control for Type I error. There were no significant differences in the adjusted means between the groups.

In addition, we found that 100% of children with FXS and autism, and 93% of children with FXS and PDD-NOS scored 3 SD below the mean on the fine motor scales. However, only 60% of children with FXS alone scored 3 SD below the mean on the fine motor scales, while 20% scored 2 SD below, and 20% scored 1 SD below the mean.

Discussion

The results of this study show that 60% of the children with FXS met criteria for autism or PDD-NOS. These findings are similar to that reported by Harris et al. (Harris, Goodlin-Jones et al. 2006), Rogers et al. (Rogers, Wehner et al. 2001), and Kauffman et al. (Kauffman, Cortell et al. 2004). The results partially support our hypothesis. Children with FXS with autism or PDD-NOS have lower fine motor scores than those without ASD. However, we did not find significant differences between the fine motor scores of children with FXS with ASD and those without when controlling for visual reception, indicating that visual reception contributes to fine motor abilities of children diagnosed with FXS and ASD more than severity of autism symptoms. This is consistent with the association of a lower IQ in those with autism and FXS (Rogers, Wehner et al. 2001; Kaufmann, Cortell et al. 2004).

The relationship between lower IQ or even lower fine motor skills in those with FXS and ASD compared to FXS alone might be explained by additional genetic or medical insults to the brain. These insults would introduce barriers to the motor or cognitive or social development of these children in addition to the FXS diagnosis. Such insults could include seizure disorders, particularly if chronic or severe (Garcia-Nonell, Ratera et al. submitted). Literature suggests that additional genetic problems that might affect the FXS phenotype and predispose to autism includes the lowered expression of *CYFIP1* in the FXS Prader-Willi Phenotype described by Nowicki et al. (Nowicki, Tassone et al. 2007). Also, Hessel et al. (Hessel, Tassone et al. 2007) reported that children with FXS who were homozygous for the serotonin transporter long allele had higher rates of stereotypic behavior and aggression than those homozygous for the short allele. Other genetic mutations associated with autism might interfere with the development of motor skills of children with FXS and autism. In addition, the significant correlation between the fine-motor scores and the expressive language supports previous studies (Rogers and Pennington 1991; Rogers, Hepburn et al. 2003) about motor deficits that interfere with the development of imitation abilities, and as a result limit expressive language and communication skills of children with autism. Recent study by Macedoni-Luksic (Macedoni-Luksic in press) demonstrates impairment of imitation in children diagnosed with both FXS and autism, pointing towards the importance of motor aspect of imitation abilities in these children.

Although there is no empirically validated OT intervention for children with FXS, we might apply the OT evidence based literature in autism and other developmental disabilities to treat children with FXS (Baranek 2002) (Case-Smith 1996). For example, we recommend early intervention occupational therapy (OT), caregiver's consultation, home-programs, and one-on-one therapeutic services as soon as FXS or motor deficits are apparent. Occupational therapy usually addresses deficits such as poor trunk stability, reduced muscle tone, poor endurance, tactile defensiveness, proprioceptive processing issues, and cognitive

impairments that are associated with motor skills development in children with FXS (Scharfenaker, O'Connor et al. 2002). In addition, occupational therapy combined with speech and language therapy can focus on oral-motor intervention to reduce tactile sensitivity and increase muscle tone in order to enhance language development. Such an approach is embodied in PROMPT intervention, which has demonstrated efficacy in young children with autism (see the Denver Model and the PROMPT intervention). (Rogers, Hayden et al. 2006), (Scharfenaker, O'Connor et al. 2002). It is worth noting that developing motor skills in babies and toddlers with FXS and autism might contribute to their imitation abilities, and as a result will enhance their gestures and communication skills (Dewey, Cantell et al. 2007), (Rogers, Hepburn et al. 2003).

Limitation of the study

The visual reception, and the fine-motor measurements used in this study are from the same assessment tool (Mullen), which might introduce some bias to the study results, possibly inflating the association between fine motor and visual reception abilities. This may limited the power to detect the true association between fine motor abilities and autism symptoms.

There are other cognitive aspects that are not covered by the visual reception scale, but an independent measure of cognition was not available on all study participants. Further studies are warranted to examine the association between fine motor abilities, severity of autism symptoms and cognitive level of children with FXS with and without autism using a cognitive assessment such as the Leiter International Performance Scale (Roid and Miller 1997) which does not rely on motor or language abilities.

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Table 1

Participant's characteristics

| | Frequency | Percentage | | |
|----------------------|-------------|------------|-------------|------------|
| Diagnosis | | | | |
| No Autism | 19 | 39.6 | | |
| PDD-NOS | 16 | 33.3 | | |
| Autism | 13 | 27.1 | | |
| Gender | | | | |
| Male | 36 | 75 | | |
| Female | 12 | 25 | | |
| Race | | | | |
| Caucasian | 32 | 66.7 | | |
| African American | 2 | 4.2 | | |
| East Indian | 4 | 8.3 | | |
| Asian | 2 | 4.2 | | |
| American Indian | 4 | 8.3 | | |
| Hispanic/ Other | 4 | 8.3 | | |
| Age in Months | Min. | Max | Mean | S.D |
| | 12 | 76 | 41.3 | 16 |

Table 2

Descriptive statistics for the T scores

| | Groups | Mean | SD | Min | Max |
|---------------------|-----------|-------|-------|-----|-----|
| ADOS-Com&Soc | No Autism | 4.36 | 2.14 | 0 | 9 |
| | PDD-NOS | 9.0 | 1.63 | 7 | 12 |
| | Autism | 16.3 | 1.7 | 14 | 20 |
| Fine-motor | No Autism | 29.16 | 12.57 | 20 | 59 |
| | PDD-NOS | 21.38 | 4.98 | 20 | 40 |
| | Autism | 20.15 | .55 | 20 | 22 |
| Receptive Language | No Autism | 35.4 | 10.9 | 20 | 52 |
| | PDD-NOS | 27.8 | 13.7 | 20 | 56 |
| | Autism | 24.63 | 9.88 | 20 | 52 |
| Expressive Language | No Autism | 32.3 | 10.1 | 20 | 50 |
| | PDD-NOS | 23.9 | 5.62 | 20 | 37 |
| | Autism | 23.45 | 6.68 | 20 | 41 |
| Visual Reception | No Autism | 33.95 | 12.2 | 20 | 49 |
| | PDD-NOS | 27.18 | 11.8 | 20 | 62 |
| | Autism | 20.92 | 3.32 | 20 | 32 |

Table 3

Correlation among Communication and social scores, fine-motor scores, receptive and expressive language, and visual reception scores

| | Fine Motor | Receptive Language | Expressive Language | Visual Reception |
|---------------------------|------------|--------------------|---------------------|------------------|
| ADOS-Communication&Social | -.42** | .47** | .44** | .57** |
| Mullen Fine motor | | .61** | .59** | .70** |

**
P<.01