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Brief Report: Bone Fractures in Children and Adults with Autism Spectrum Disorders

Ann M. Neumeyer,
Lurie Center for Autism, Massachusetts General Hospital and Harvard Medical School, One Maguire Road, Lexington, MA, USA

Julia A. O'Rourke,
Lurie Center for Autism, Massachusetts General Hospital and Harvard Medical School, One Maguire Road, Lexington, MA, USA

Alexandra Massa,
Lurie Center for Autism, Massachusetts General Hospital and Harvard Medical School, One Maguire Road, Lexington, MA, USA

Hang Lee,
Biostatistics Center, Massachusetts General Hospital, Boston, MA, USA

Elizabeth A. Lawson,
Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Christopher J. McDougle, and
Lurie Center for Autism, Massachusetts General Hospital and Harvard Medical School, One Maguire Road, Lexington, MA, USA

Madhusmita Misra
Pediatric Endocrine Unit, Massachusetts General Hospital for Children and Harvard Medical School, Boston, MA, USA

Abstract

Peripubertal boys with autism spectrum disorder (ASD) have lower bone mineral density (BMD) than typically developing controls. However, it is not clear whether lower BMD in ASD results in an increased fracture rate. This study examined the rate of fractures in children and adults with and without ASD using a national database of emergency room visits (Nationwide Emergency Department Sample). A higher odds ratio for hip fractures in children and young adults (3–22 years) as well as older adults (23–50 years) with ASD than those without ASD, and a higher odds ratio for forearm and spine fractures in women ages 23–50 with ASD were found. Further studies are necessary to better understand the decreased bone density in ASD and its implications for fracture development.

A. M. Neumeyer, aneumeyer@mgh.harvard.edu.

Keywords

Autism spectrum disorders; Autism; Fractures; Low bone density; Osteoporosis

Introduction

Autism spectrum disorders (ASD) are a group of behaviorally-defined disorders characterized by impaired social communication, as well as restricted or repetitive patterns of behavior, interests or activities which present in the early developmental period and cause clinically significant impairment in functioning (American Psychiatric Association 2013). The prevalence of ASD in US children has been reported to be 1 in 68 by the Center for Disease Control (CDC 2014), and even higher in other countries (Kim et al. 2011).

Low bone mineral density (BMD) and osteoporosis are typically believed to be a problem of the elderly. However, they are now being increasingly recognized and diagnosed in a younger population. The major consequence of low BMD is an increased risk for fracture, and its associated morbidity (Genant et al. 1999). Most fractures are first identified in the Emergency Department (ED).

Bone metabolism may be adversely affected in children with ASD. Hediger et al. (2008) have reported lower cortical bone thickness in 4–8 year old boys with ASD than in age matched controls, and we have previously reported lower BMD in peripubertal boys with ASD compared to controls as measured by dual energy X-ray absorptiometry (DXA) (Neumeyer et al. 2013). In this study, boys with ASD had lower BMD at the hip, femoral neck and lumbar spine than typically developing controls. BMD was even lower in boys with ASD on a gluten-free and casein-free (GFCF) diet. Self-imposed restrictive diets or “therapeutic” diets such as the GFCF diet (Hyman et al. 2012), lower exercise activity (Maiano et al. 2010; Neumeyer et al. 2013; Maiano 2011), and commonly prescribed medications such as anticonvulsants or atypical antipsychotics may contribute to low BMD in these children. Furthermore there are numerous studies showing that vitamin D levels are lower in children, adolescents and young adults with ASD (Kocovska et al. 2014; Mostafa and Al-Ayadhi 2012; Neumeyer et al. 2013). This is of concern given that the peripubertal and pubertal years are typically characterized by marked increases in bone accrual, and optimal bone accrual during childhood and adolescence is critical for optimal peak bone mass in adult life (Bachrach 2001). These factors are important determinants of future bone health and fracture risk.

It is not clear whether lower BMD in children with ASD translates to an increased fracture rate either during childhood or in adult life. The only available data regarding fractures in ASD come from a recent small retrospective case follow-up study using data from the Danish National Health Register, which reported lower fracture rates in 118 individuals with ASD versus a comparison group (Mouridsen et al. 2012). The investigators also noted that the nature of the fractures differed in the two groups. An increase in forearm fractures was more common in the ASD group than controls and fractures of the wrist and hand were more common in the control group. However, many of their case subjects were institutionalized and may have had reduced physical activity, and lower alcohol abuse,

factors associated with decreased risk of fracture. Other factors which may influence the risk of fractures, particularly forearm fractures, include falls or abuse in older or infirm patients. In a study of adults with profound developmental disabilities in a residential setting, the rate of hand and foot fractures was increased, and overall prevalence of fractures increased with increasing mobility (Glick et al. 2005).

In this study we sought to expand on the finding of decreased BMD in peripubertal boys with ASD by examining rates and types of fracture in a large sample of children and adults with ASD versus those without ASD, by querying a national database of ED visits (the National Emergency Department Sample-2010) (Wang et al. 2013; Agency for Healthcare Research and Quality 2010 over the period of a year. We hypothesized that those with a diagnosis of ASD would display higher rates of fractures at the hip and spine compared to those without a diagnosis of ASD both in children and adults.

Methods

Study Design

This study used data from the 2010 National Emergency Department Sample (NEDS) database (Agency for Healthcare Research and Quality 2010), designed to support research and policy makers. This database contains information from over 28 million ED visits at 961 hospitals approximating a 20 % stratified sample of U.S. hospital EDs. The NEDS database is weighted such that it can be used to calculate national estimates for 130 million ED visits in 2010.

This study included two populations: children and young adults (3–22 years old) and adults (23–50 years old). Because children younger than 3 years of age cannot always be reliably diagnosed with ASD, they were not included in this study (Freedman et al. 2012). Most fracture studies require large populations to be sufficiently powered. Based upon the relatively small number of patients with ASD who presented to the ED in this database, and the mandate of NEDS data use requirements, we elected to study fractures in those less than or equal to 22 and those above 22, and did not assess fracture risk in specific age ranges.

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes were used to identify patients with ASD. The NEDS database contains patients with up to 15 diagnoses related to ASD sampled from the ED or an inpatient unit for admitted patients. To identify patients with an ASD diagnosis, we searched any of the 15 diagnoses for the presence of the ICD-9-CM code for Pervasive Developmental Disorder 299.XX, which includes codes for autistic disorder (299.0), childhood disintegrative disorder (299.1), and specific and nonspecific pervasive developmental disorders (299.8 and 299.0).

The Agency for Healthcare Research and Quality (AHRQ) has developed the Clinical Classification Software (CCS) that collapses multiple ICD-9 codes into more meaningful clinical categories. The NEDS database contains up to 15 CCS diagnoses for each ED visit. We searched all 15 CCS diagnoses to identify ED visits due to hip fracture (CCS code 226), spinal cord injury (CCS code 227) or upper limb fracture (CCS code 229).

Data Analysis

Data were analyzed using the SAS 9.2 (SAS Institute, Cary, NC) software package. Analyses were conducted per AHRQ recommendations and accounted for the NEDS sampling design, weighting factor, stratification (NEDS_STRATUM variable in the NEDS dataset) and the hospital ED departments as primary sampling units. The weight adjusted number of visits represents the number of visits expected to occur in 130 million ED visits in 2010. To compare categorical variables, we utilized X^2 (SURVEYFREQ procedure in SAS) analysis and to compare continuous variables we utilized student *t* test (SURVEY-MEANS procedure in SAS). We calculated odds ratios and adjusted for age differences across groups using a survey weighted logistic regression model: ASD diagnosis and age were independent variables, and the presence of fracture was a dependent variable (SURVEYLOGISTIC procedure in SAS). Similarly, we calculated survey weighted Cox Proportional Hazards Ratios for predictors of fractures in individuals with ASD versus those without ASD adjusting for sex (SURVEYPHREG procedure in SAS). p value < 0.05 was considered to be significant.

Results

Clinical Characteristics

Tables 1 and 2 include the sex and age distribution of study subjects. Overall, children and adults with ASD were younger than those without ASD.

Fractures in Children with ASD versus Controls

In the 3–22 year old patient population, children with ASD had a higher risk of hip fracture than those without ASD [odds ratio (OR) 3.33, $p < 0.0001$], and this difference was more marked within girls than boys (Table 1). The OR for hip fracture was 8.1 in girls with ASD compared to those without ASD ($p = 0.0005$), and 2.0 in boys with ASD compared to those without ASD ($p = 0.06$). In contrast, compared to those without ASD, upper extremity fractures were less common in boys with ASD ($p < 0.0001$). The OR for upper extremity fractures did not differ in girls with ASD compared with those without ASD. The frequency of spine fractures was too low to report based on AHRQ recommendations for the NEDS database.

Overall, children without ASD in this dataset were about 2.6 years older than those with ASD. Therefore, we also analyzed our data after controlling for age using a logistic regression model, and found that our observed differences across groups persisted after controlling for age (Table 1). Finally, we employed the Cox Proportional Hazards Model to compare fractures with increasing age in children with or without ASD after controlling for sex, and observed that hip fractures remained more likely in children with ASD [hazard ratio 3.70 (1.97–6.95)] even after controlling for sex.

Based on the ICD-9 codes we used to determine our study population, 15 girls with Rett syndrome (who were co-diagnosed with ASD) and 113 children with childhood disintegrative disorder (CDD) were included in the ASD group. None of the children with Rett syndrome and ASD had any fracture. Only two children from the CDD group had upper

limb fractures and none had hip or spine fractures. Thus, children with Rett syndrome or CDD did not preferentially contribute to the higher risk of fracture seen in the ASD population.

Fractures in Adults with ASD Versus Controls

Similar to our data in children with ASD, adults with ASD 23–50 years old had a higher OR for hip fractures than adults without ASD (OR 11.7, $p < 0.0001$) (Table 2). This was observed in both men and women with ASD, although the OR was much higher in women (OR 24.8, $p < 0.0001$) than in men (OR 6.8, $p < 0.0001$). Also, similar to our data in children, adult men without ASD had a higher risk for upper extremity fractures than those with ASD, and no increase in the risk for spine fractures. In contrast, we observed that women with ASD compared with those without ASD had a higher OR for upper extremity fractures (OR 2.27, $p = 0.0038$), and also spine fractures (OR 10.61, $p = 0.0034$). Because adults without ASD were about 3.3 years older than those with ASD, we controlled for age in our analyses and as with the children, we found that differences across groups persisted after controlling for age (Table 2). Using the Cox Proportional Hazards Model to compare fractures over time in adults with or without ASD after controlling for gender, we observed that hip fractures remained more likely in adults with ASD (hazard ratio 14.67, $p = 0.0001$) even after controlling for gender.

Eight women with Rett syndrome (co-diagnosed with ASD) and 30 adults with CDD were included in the ASD group. Only one individual from each of these groups had upper limb fracture. None had hip or spine fractures. Thus, these diagnoses did not preferentially contribute to the higher risk of fracture seen in the ASD population.

Discussion

Using a large database of ED visits in the US, we report for the first time a significant increase in risk of hip fractures in both children and also adults with ASD of both male and females, and a higher risk of forearm and spine fractures in adult women with ASD compared to controls without ASD. These data are consistent with our previous report of low BMD measures, particularly at the hip, in peripubertal boys with ASD (Neumeyer et al. 2013). The increased risk of fractures is likely consequent to incident low BMD, as well as reduced bone accrual leading to reductions in peak bone mass, which would contribute to low BMD and increased fracture risk in adults with ASD. These novel and critical data indicate that it is of great importance to systematically examine children and adults with ASD for factors that contribute to low BMD, and thereby to develop the appropriate management strategies to optimize bone accrual during childhood and adolescence, and BMD in adults with ASD. Furthermore, data are needed to determine bone accrual rates in children with ASD before and during puberty.

The risk for hip fractures was higher in both children and adults with ASD, and may relate to lower impact loading on bone from reduced physical activity. Weight bearing and impact loading are critical for optimizing bone accrual at weight bearing sites (such as the hip and spine) (Behringer et al. 2014; Meyer et al. 2013; Scerpella et al. 2011), and in our previous study, physical activity was significantly lower in peripubertal children with ASD than in

typically developing controls (Neumeyer et al. 2013). Commensurate with this, bone density measures in these children were most affected at the total hip and femoral neck, and spine BMD was also reduced (Neumeyer et al. 2013). Other factors that may contribute include reduced dietary vitamin D intake (Neumeyer et al. 2013) and use of specific medications such as antipsychotics (Roke et al. 2012).

Hip and spine fractures are considered osteoporotic fractures (rather than resulting from violent trauma) and are very uncommon in typically developing children (Hedstrom et al. 2010; Lyons et al. 1999) and healthy young adults (Court-Brown and Caesar 2006). Thus, the higher risk of hip fractures in children and adults with ASD than in those without ASD, and the higher risk of spine fractures in adult women with ASD is of concern. Hip fractures often require surgical intervention for optimal outcome (Bali et al. 2011), and are associated with significant morbidity including avascular necrosis, coxavara (hip angle deformity), malunion, non-union and leg length discrepancy, all of which can cause lifelong disability (Azouz et al. 1993). In children with ASD, complications of surgery for hip fractures are particularly problematic because these children have difficulties expressing pain, sitting still and cooperating with the intense rehabilitative therapies after surgery. Furthermore, these fractures are associated with significant health care costs (Riggs and Melton 1995; Kanis et al. 2001; Johnell et al. 2005; Melton et al. 2003), and it is important to systematically examine factors that contribute to the increased risk of such fractures in ASD and thereby implement appropriate preventive strategies. Although not assessed in this study, the risk for hip fracture may be even higher in postmenopausal women and in older men above 50 years old.

Interestingly, the lower risk of forearm fractures in boys with ASD may also relate to reduced physical activity in this group compared with those without ASD. Distal forearm fractures are the most common fractures in growing children, and are related to physical activity levels and the increased risk of falls and trauma during sports and play (rather than low bone density) (Hedstrom et al. 2010; Lyons et al. 1999; Wren et al. 2012), both of which are limited in children with ASD. One study reported that the majority of long bone diaphyseal fractures in growing children were from activities associated with significant trauma such as soccer, snowboarding, downhill skiing, skateboarding and equestrian activities (Hedstrom et al. 2010), all of which are less common activities in individuals with ASD. Normally developing boys are known to have a higher risk of upper extremity fractures than normally developing girls (Lyons et al. 1999; Wren et al. 2012), likely related to the nature of sports activities favored by boys versus girls leading to a greater predisposition for traumatic falls in boys (Hedstrom et al. 2010). Therefore, lower physical activity and reduced participation in such sports in boys with ASD would protect them against a higher risk of upper extremity fractures, while this may not be evident in girls with ASD. Similarly, adult men with ASD have a lower risk of upper extremity fracture than controls, possibly because of lower levels of intense physical activity. In contrast, although there was no difference in girls with ASD versus those without ASD for risk of upper extremity fractures, adult women with ASD did have a higher risk of such fractures than those without ASD.

There are a number of comorbid diseases associated with ASD which could predispose to fracture risk. These include attention deficit disorder (ADHD) (Chou et al. 2014) and seizure disorder (Prasad et al. 2014), and the contribution of these comorbid diseases to fracture risk in ASD needs to be determined. Poor awareness of risky behavior, developmental disabilities (Glick et al. 2005) and delayed reaction responses could further contribute to the increased risk for fracture in children with ASD, and may impact certain sites more than others.

There are a number of limitations to this study that should be considered. Only patients who were sent to the ED for fractures are considered in this study and some patients might have had fractures evaluated outside the ED such as at a physician's office. However, we would expect an even distribution across the study groups (those with ASD vs. those without ASD) for visits outside the ED for evaluation of fractures. We acknowledge that the diagnosis of ASD for ED codes is not "research reliable" and that the diagnosis is based on parent report, ED clinician education, or review of electronic medical records. However, even in regional specialized autism centers the diagnosis of ASD is not always consistent (Lord et al. 2012). Furthermore, the Diagnostic and Statistical Manual 5 (DSM5) was published after the period of data collection (2011), hence DSM5 criteria were not used in this data set. Using the NEDS database, we were not able to assess nutritional status, calcium and vitamin D intake, specific diets, exercise activity and concurrent diseases or medications that might impact bone development and fracture risk in children and adults with ASD. This will be important to evaluate in a future systematic study. Finally, we were unable to reliably assess differences in fracture risk in prepubertal versus pubertal children with ASD because of the limited number of children with ASD in the NEDS database. This will be important to assess in future larger studies. In addition, given that puberty is characterized by marked increases in bone accrual in typically developing children, it will be important to determine whether bone accrual rates differ in prepubertal versus pubertal children with ASD compared with a control population.

We report for the first time a higher risk of hip fracture in children and adults with ASD than in those without ASD, and a higher risk for forearm and spine fracture in women with ASD. With the increasing prevalence of ASD (to above 1 % of the population), we will need to address this increase in fracture rate. Particularly, the morbidity of hip fractures is significant, especially in the ASD population given the reduced communication skills of such individuals. The childhood years will be specifically important to target, as bone accrual during the childhood years is a critical determinant of future bone health. Future directions include examination of nutritional, behavioral and metabolic concerns that would put an individual with ASD at risk for fractures.

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Table 1

Association between ASD diagnosis and the frequency of hip and upper limbs fractures in patients 3–22 years old

	ED visits for patients with ASD diagnosis Weighted n (% or SE of mean)	ED visits for patients without ASD diagnosis Weighted n (% or SE of mean)	Weighted X^2 or t test	Weighted OR (95 % CI)	p value	Weighted and age adjusted OR (95 % CI)	p value
ED visits	82,615 (0.29 %)	28,379,587 (99.71 %)					
Males	66,628 (80.6 %)	13,132,986 (46.3 %)					
Females	15,987 (19.4 %)	15,246,601 (53.7 %)	7,636.8	0.21 (0.20–0.22)	<0.0001	0.23 (0.22–0.24)	<0.0001
Age (years)	11.29 (0.13)	13.90 (0.09)	162.8		<0.0001		
Hip fractures	43 (0.052 %)	4,466 (0.016 %)	15.8	3.33 (1.77–6.28)	<0.0001	3.46 (1.84–6.52)	0.0001
Males[a]	33 (0.050 %)	3,238 (0.025 %)	3.5	2.00 (0.95–4.20)	0.0605	2.22 (1.06–4.64)	0.0352
Females[b]	10 (0.063 %)	1,228 (0.008 %)	12.0	8.08 (1.96–33.33)	0.0005	7.23 (1.76–29.77)	0.0061
Upper limb fractures	1,455 (1.76 %)	818,437 (2.88 %)	62.5	0.60 (0.54–0.68)	0.0001	0.54 (0.48–0.61)	<0.0001
Males[a]	1,211 (1.82 %)	557,876 (4.25 %)	173.3	0.42 (0.37–0.47)	<0.0001	0.41 (0.37–0.47)	<0.0001
Females[b]	244 (1.53 %)	260,561 (1.71 %)	0.6	0.89 (0.67–1.19)	0.4302	0.69 (0.52–0.91)	0.0090

Total unweighted ED visits for patients with ASD diagnosis was 18,152. Total unweighted ED visits for patients without ASD diagnosis was 6,311,505

[a] Percent of the ED visits due to fractures in males

[b] Percent of the ED visits due to fractures in females

Table 2

Association between ASD diagnosis and the frequency of hip and upper limbs fractures in patients 23–50 years old

	ED visits for patients with ASD diagnosis Weighted n (% or SE of mean)	ED visits for patients without ASD diagnosis Weighted n (% or SE of mean)	Weighted X^2 or t test	Weighted OR (95 % CI)	p value	Weighted and age adjusted OR (95 % CI)	p value
ED visits	19,520 (0.04 %)	51,575,556 (99.96 %)					
Males	14,436 (74.0 %)	21,917,952 (42.5 %)					
Females	5,084 (26.0 %)	29,657,604 (57.5 %)	660.5	0.26 (0.23–0.29)	<0.0001	0.25 (0.22–0.28)	<0.0001
Age (years)	32.45 (0.21)	35.77 (0.03)	1,190.2		<0.0001		
Hip fractures	65 (0.333 %)	14,722 (0.029 %)	82.8	11.68 (5.95–22.96)	<0.0001	14.42 (7.30–28.46)	<0.0001
Males[a]	45 (0.312 %)	10,111 (0.046 %)	39.8	6.83 (3.41–13.68)	<0.0001	8.07 (4.02–16.21)	<0.0001
Females[b]	20 (0.393 %)	4,611 (0.016 %)	37.6	24.81 (5.36–114.81)	<0.0001	32.89 (7.14–151.63)	<0.0001
Upper limb fractures	200 (1.02 %)	588,658 (1.14 %)	0.4	0.90 (0.65–1.24)	0.5072	0.91 (0.66–1.25)	0.5531
Males[a]	124 (0.86 %)	392,256 (1.79 %)	15.7	0.48 (0.33–0.69)	<0.0001	0.45 (0.31–0.66)	<0.0001
Females[b]	76 (1.49 %)	196,402 (0.66 %)	8.4	2.27 (1.28–4.03)	0.0038	2.47 (1.40–4.38)	0.0019
Spine fractures	17 (0.09 %)	28,399 (0.06 %)	0.5	1.60 (0.40–6.45)	0.5014	1.77 (0.44–7.11)	0.4226
Males[a]	6 (0.04 %)	22,153 (0.10 %)	1.8	0.40 (0.10–1.59)	0.1794	0.44 (0.11–1.72)	0.2370
Females[b]	11 (0.22 %)	6,246 (0.02 %)	8.6	10.61 (1.47–76.52)	0.0034	11.84 (1.65–85.03)	0.0140

Total unweighted ED visits for patients with ASD diagnosis was 4,215. Total unweighted ED visits for patients without ASD diagnosis was 11,438,194

[a]Percent of the ED visits due to fractures in males

[b]Percent of the ED visits due to fractures in females