Twins with KBG Syndrome and Autism

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In 1975, Herrmann et al. first described KBG syndrome. The letters “KBG” were derived from the surnames of three unrelated families from which seven patients with the syndrome were identified. In the original report KBG was assumed to be an autosomal dominant condition characterized by short stature, skeletal abnormalities, mental retardation, dental abnormalities and distinct craniofacial anomalies. Since then an additional 51 patients have been reported. Monozygotic twins diagnosed with KBG syndrome were described as having autistic features in a recent article (Skjei et al. 2007). Here we report additional findings on the same twins. Through appropriate diagnostic testing, it was established that they did meet criteria for autism. We also reviewed the literature of previously published cases of KBG for reports of autism symptoms.

Each boy was assessed at home at 12 years, 7 months of age by two separate assessors in order to eliminate bias. The assessments were videotaped and a child psychologist recoded the tests using the videotapes. In addition a thorough history was obtained by a child and adolescent psychiatrist.

The following assessments were completed: Autism Diagnostic Interview-Revised (ADI-R) (Le Couteur et al. 1989; Rutter et al. 2003), Autism Diagnostic Observation Schedule- Generic (ADOS-G) (DiLavore et al. 1995) and the Stanford-Binet Intelligence Scales, Fifth Edition (SB5) (Roid 2003).

Medical history of the twins: The twins were the 7th pregnancy for the mother. They have five older siblings and one younger sibling. Their mother had one early miscarriage at her 5th pregnancy at 6 weeks gestation when she was ill with the varicella virus. The twins’ gestation was complicated by preterm labor treated with bed rest, morphine and terbutaline. At 34 weeks the twins were delivered via C-section due to transverse presentation of twin 2. At birth they had multiple problems including an inguinal hernia, jaundice and nursing difficulty. By 4 months of age, they were noticeably different, showing no interest in other people and not making eye contact while nursing. Physically they were weaker and had poor muscle tone and poor balance. Motor developmental milestones were delayed, sitting at 11–12 months¹ old, walking at 15–16 months old, and running at 2½ years old. Toilet training was achieved at 5–6 years old. Language development was delayed. First words, “cup” and “that”, were spoken at 4–5 years of age. First phrases, “go home” and a few echolalic responses to a movie were displayed at 7–8 years of age. Both developed partial complex and absence seizure disorder at 8–9 years old. Concomitantly, parents noticed a loss of

language and motor skills, especially balance and fine motor skills involving the hands, which lasted about 3 months. At 5 years of age they were diagnosed with mental retardation (MR), at 6 years with autism and ADHD (at an academic center via a videoconference with a psychiatrist) and at 11 they were diagnosed with KBG syndrome.

Both twins received speech and occupational therapy at age five. Medications were started at age 7 years. The twins had been on seven different medications to treat ADHD symptoms. Current medications targeting their psychiatric symptoms are amphetamine/dextroamphetamine, clonidine and melatonin. The twins started divalproex sodium for their seizure disorder at 8 years of age and are currently taking levetiracetam and oxcarbazepine.

Family History revealed neurological and psychiatric disorders including migraines, ADHD, substance abuse, dyslexia and schizophrenia in first degree relatives. ADHD, schizophrenia and alcohol/substance abuse diagnoses were found in second degree relatives. There was no family history of autism or KBG.

Assessments: On the ADI-R both twins clearly met criteria for a diagnosis of autism for all three domains. On the ADOS, both were found to be in the autism spectrum range. On clinical exam by the child psychiatrist, the twins also met criteria for autistic disorder through DSM-IV TR criteria.

On IQ testing, both twins scored as moderately delayed in most domains on the SB5. Twin 1's full scale IQ (FSIQ) was 45, his verbal IQ (VIQ) was 47 and his nonverbal IQ (NVIQ) was 48. Twin 2's FSIQ was 45, VIQ was 49 and NVIQ was 46. Both twins were moderately delayed in fluid reasoning, quantitative reasoning and working memory. Twin 1 tested as moderately delayed in knowledge and mildly delayed in visual-spatial processing while twin 2 tested as mildly delayed in knowledge and visual-spatial processing.

Based on the assessment, both twins fulfill the criteria for autism on the ADI-R and DSM-IV TR and score within the autistic spectrum range on the ADOS. The ADOS has been shown to be better at discriminating between autistic and non autistic disorders than differentiating between autism and PDD NOS (Lord et al. 2000). At a minimum we can conclude that both twins fulfill criteria for an autistic spectrum disorder, and that the clinical history and assessment support the autism diagnosis of the ADI.

To our knowledge these twins are the first to have a formal comorbid diagnosis of autism or autism spectrum disorder with KBG. We performed a literature review in PubMed in English using the search term "KBG" to examine whether there were any autistic features described in previous cases. Forty-six case reports were identified from 13 papers including the twins in this manuscript.

Out of the 46 cases reviewed, 32 were male and 14 were female. None of these KBG cases were evaluated for autism using a structured validated instrument, such as the ADI-R or ADOS, nor did any receive a diagnosis of autism or an autism spectrum disorder. However, KBG and autism share a surprising number of features: developmental delay, especially in the area of language, limited verbal expression, poor social skills, and male preponderance. Both KBG and autism are familial and believed to be genetic (Brancati et al. 2004; Devriendt et al. 1998; Fryns and Haspeslagh 1984; Herrmann et al. 1975). Both have features of ADHD with a hyperkinetic state and poor concentration (Brancati et al. 2004; Devriendt et al. 1998; Herrmann et al. 1975; Mathieu et al. 2000; Soekarman et al. 1994; Tekin et al. 2004). The majority of cases of KBG displayed some type of atypical behavior (Brancati et al. 2004; Devriendt et al. 1998; Herrmann et al. 1975; Maegawa et al. 2004; Mathieu et al. 2000; Soekarman et al. 1994; Tekin et al. 2004). In addition some cases demonstrated problems with compulsive activity as well as mood problems, irritability,

aggressiveness, and compulsive behavior (Devriendt et al. 1998; Maegawa et al. 2004; Mathieu et al. 2000), commonly found in autism spectrum disorders (Matson and Nebel-Schwalm 2007; McClintock et al. 2003).

Children with autism or KBG have many co-morbid medical problems. The most common medical problem found in KBG children is seizure disorder, which is also found in approximately 15–35% of children with autism (Tuchman et al. 1991). Children with autism have a high prevalence of motor impairments (Ming et al. 2007). Hypotonia was the most common finding in autistic children and gross motor delay was found in 9% of autistic children. Interestingly, both hypotonia and gross motor delay are also found frequently in children with KBG syndrome.

It has been estimated that 11–37% of cases with autism are organic in origin (Gillberg and Coleman 1996). Many genetic syndromes have been associated with autism, including: fragile X syndrome, tuberous sclerosis, Angel-man syndrome, duplication of 15q11–q13, Down syndrome, San Filippo syndrome, Rett syndrome, phenylketonuria, Smith Magenis syndrome, 22q13 deletion, adenylosuccinate lyase deficiency, Cohen syndrome, and Smith-Lemli-Opitz syndrome (Cohen et al. 2005). Syndromic autism is often associated with lower mean IQ (Ritvo et al. 1990). The twins described here also scored in the low IQ range. This fits with the concept that children with autism and low IQ are an etiologically more heterogeneous group and more likely to be syndromic than those with autism that score average to above average on IQ tests (Lotspeich et al. 2004; Rutter et al. 1994).

Being a twin has been reported to be risk factor for developing autism. Comparing the rate of autism in twin births compared to rate of autism in total births, epidemiologic samples have reported the increase in risk to be in the range of 1.3–1.7 (Hallmayer et al. 2002; Croen et al. 2002). In addition, several non-twin cases with KBG in the literature had autistic features which would suggest that the twinning process itself was not the cause of being associated with autism as much as having KBG syndrome.

The results of this case study in addition to the existing literature on KBG suggest that comorbid autism spectrum disorders may be common in KBG syndrome. It is important to note that this is only one confirmed twin pair with KBG and autism. However, the overlap in symptoms between autism and KBG suggests that children diagnosed with KBG should be more thoroughly examined for symptoms of autism. The use of a structured, validated instrument such as the ADI or ADOS may help to rule out the diagnosis of autism or another pervasive developmental disorder. The importance of early treatment intervention in pervasive developmental disorders such as autism is essential, so that the children have the advantage of appropriate treatments during the earliest years of development (Kasari et al. 2006).

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