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ORIGINAL ARTICLE

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Sibling risk of pervasive developmental disorder estimated by means of an epidemiologic survey in Nagoya, Japan

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Abstract Broad-spectrum autism, referred to as pervasive developmental disorder (PDD), may be associated with genetic factors. We examined 241 siblings in 269 Japanese families with affected children. The sibling incidence of PDD was 10.0% whereas the prevalence of PDD in the general population in the same geographic region was 2.1%. Both of these rates are higher than those reported previously, probably because of the expanded clinical criteria applied. The prevalence in males of the general population was 3.3% and that in females was 0.82%. The sibling incidences were 7.7 and 20.0% for families in which the probands were male and female, respectively. Because the reversed sex ratios correspond to the general rule for a multifactorial threshold model, we suggest that most PDD cases result from the cumulative effects of multiple factors (mostly genetic). The sibling incidences were 0 and 10.9% for families in which the proband had low and normal birth-weight, respectively, suggesting the risk is lower in families with low-birth-weight probands.

Keywords Autism · Pervasive developmental disorder · Sibling · Low birth-weight · Multifactorial inheritance

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Introduction

Autism is a behaviorally defined syndrome, characterized by pervasive impairment of social interaction and communication and the presence of stereotypical characteristics. Although these clinical symptoms may arise from brain dysfunction, clinical severity is modified by environmental factors. In the past decade, criteria for diagnosis of autism have been expanded, from a strict category (Kanner type) to a broad spectrum, owing to progress in neuropsychological understanding (Wing 1996). The broad spectrum of autism is defined as pervasive developmental disorder (PDD) in the DSM-IV criteria (American Psychiatric Association 1994) and the number of cases has recently increased rapidly, in line with the expanding criteria. A recent study described the prevalence in the Japanese general population to be more than 1% (Honda et al. 2005).

Previous studies of twins have suggested that autism is strongly affected by genetic factors. Ritvo et al. (1985) found that the concordance for autism by pairs was 96% in 23 monozygotic twins and 24% in 17 dizygotic twins; Steffenburg et al. (1989) reported respective values of 91 and 0%. Bailey et al. (1995) reported concordance for classical autism to be 60% in monozygotic and 0% in dizygotic twins, but for the broad spectrum disease it was 92% and 10%, respectively. These results show that autism is strongly affected by genetic factors but is also affected by the environment. Previous sibling studies have also suggested genetic effect on autism, with August et al. (1981), Baird et al. (1985), Chakrabarti et al. (2001), and Icasiano et al. (2004) reporting sibling risks of 2.8, 5.9, 3.9, and 6.3%, respectively. These frequencies are much higher than that in the general population but

much lower than that in single-gene diseases. As far as we are aware, all previous studies involving both twins and siblings were performed on Caucasian populations only. Several genome-wide investigations have proposed susceptibility loci associated with autism (PDD), but neither a single candidate gene nor an inheritance mode for autism have been determined (Shastry 2003). It has also been suggested that PDD may be caused by non-genetic factors, for example neonatal factors.

In this study we estimated the prevalence of PDD in the general population of the western region of Nagoya, Japan, and examined the overall sibling incidence and the incidence after families were classified by the sex and birth-weight of the probands. We suggest a model for the etiology of PDD based on our results.

Subjects and methods

Screening and diagnosis

This study was conducted using a regional support system for children. The western region of Nagoya is a residential area with high population density—half a million people within 97 km^2. Infants with any developmental problems are detected by a screening system which is well organized by local government. The first stage of the system is a routine health check at general health centers; the average percentage attendance in 2001–2003 was 95.3 and 86.5% for 18-month-old and 3-year-old children. Pediatricians and public health nurses examine development and all infants with developmental problems (including mild symptoms) are referred to the West District Care Center for Disabled Children (WDC center). The second stage is based on observation at kindergartens and day nurseries. Psychologists from the WDC center make regular visits and refer cases to the WDC center when necessary. Because the number of infants attending kindergartens or nurseries is 99.7% in this area, most infants with problems should be noticed. The WDC center also cooperates with general hospitals in the area. Because there are no departments of pediatric psychiatry, children are always referred to the WDC center. Medical examinations such as chromosome analyses are performed at hospitals and the results are sent to the WDC center. On initial examination at the WDC center, psychologists obtain detailed histories from parents and also conducted an intelligence quotient test (Tanaka-Binet) on all children. In addition, pediatric psychiatrists observe children's behavior carefully in a play space with the help of public health nurses. If children have developmental problems, they start educational programs (group style or individual therapy) at the center. After repeated observation both by psychologists and pediatric psychiatrists, children are finally diagnosed, at the age of four or above, using the DSM-IV (American Psychiatric Association 1994) criteria.

In this study we excluded autistic children with certain disorders (two cases with Duchenne muscular dystrophy, two with Down syndrome, one with 18p partial monosomy, and one with tuberous sclerosis).

Prevalence and siblings

In this study we first estimated the prevalence of PDD in the general population. At the center we diagnosed 281 infants who were born between 1995 and 1999 as having PDD. The number of affected children (281) was divided by the total number of age-matched children residing in the area (13,568 children, consisting of 6,949 boys and 6,619 girls). The parents were all Japanese.

For the sibling study we excluded families with siblings younger than 4 years. This resulted in a cohort of 269 families whose characteristics are listed in Table 1. The affected siblings had already been diagnosed in our regional system before this study started. To avoid

Table 1 Characteristics of the families, probands, and siblings that formed the cohort of this study

Family factors	Number of families
All families	269
Children per family	
1 child	85
2 children	136
≥3 children	41
Average	1.9
Affected children per family	
1 child	247
2 children	22
≥3 children	1
Average	1.09
Proband factors	**Number of probands**
All probands	269
Male	215
Female	54
Sex ratio	3.98
Birth weight	
≥2,500	240
< 2,500	29
Detailed clinical criteria	
Autistic	77
PDD-NOS	119
Asperger	73
Sibling factors	**Number of siblings**
All siblings excluding probands	241
Unaffected siblings	217
Male	105
Female	112
Sex ratio	0.94
Affected siblings	24
Male	13
Female	11
Sex ratio	1.18

Autistic, autistic disorder; PDD-NOS, pervasive developmental disorder not otherwise specified; Asperger, Asperger's disorder

non-detection of autistic siblings, we interviewed parents again about the behavior of their children and made further examinations at the center if they showed even minor problems. This procedure did not identify any new affected siblings. We indicate the firstborn PDD as the proband in multiple incidence families. The sibling risk (concordance rate) was determined as the number of PDD siblings divided by the total number of siblings.

Results

In the general population the prevalence of PDD was 2.1% (281/13,558), 3.3% (227/6,949) for boys and 0.82% (54/6,619) for girls. In the sibling study 23 multiple-incidence families were found as shown in Fig. 1. There were only two families (families 1 and 2) with further births after two affected children, but in family 1 the third child was also affected. Table 2 lists the incidence (concordance rate) among siblings. The incidence of PDD in all siblings was 10.0%, with values of 7.7 and 20.0% for families in which the probands were male and female, respectively. The incidences were 0 and 10.9% for families in which the probands had low and normal birth-weight, respectively.

Discussion

Pervasive developmental disorder, including classical autism, has received much attention in recent decades, especially because the criteria for clinical diagnosis of autism have been expanded from strict categorization to a broad spectrum. PDD is manifested by a difficulty in social communication, but the detailed etiology remains unclear. Although PDD (autism) seems to be strongly affected by genetic factors, several genome-wide investigations have failed to determine a single candidate gene, suggesting that several genes may be associated with this disorder.

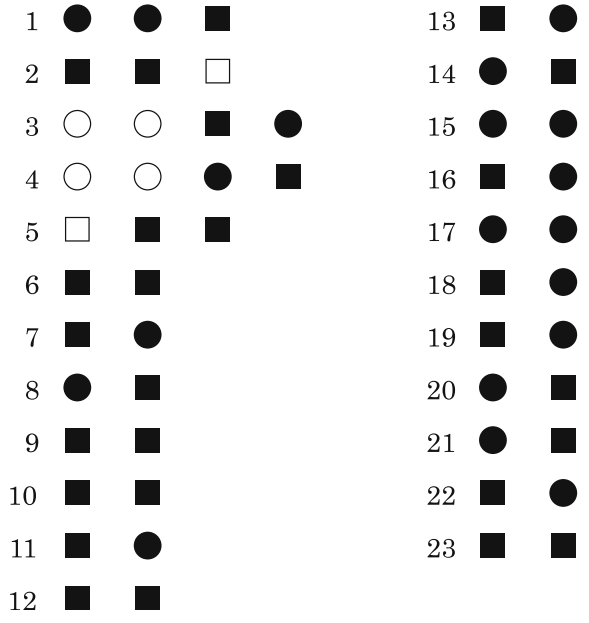

Fig. 1 Birth order of PDD probands and their siblings in 23 families with multiple affected children: *filled square*, male with PDD; *filled circle*, female with PDD; *open square*, normal male; *open circle*, normal female

In this study sibling incidence was 10.0%, in contrast with 2.1% in the general population. Both values were higher than in a previous report using DSM-III criteria (American Psychiatric Association 1980). The differences presumably reflect our application of the DSM-IV criteria. We believe our results may be used in genetic counseling for Japanese families, but further data are necessary to establish better guidelines.

The sibling incidence may also provide evidence to judge the mode of inheritance. It is unlikely that PDD has an autosomal dominant or an autosomal recessive mode of inheritance, because, theoretically, sibling incidence would then be 50 and 25%. In multifactorial inheritance, sibling incidence (Q) is estimated from the prevalence in general population (p): $Q = \sqrt{p}$ (Edwards' method; Emery 1986). Theoretical sibling incidence based on the prevalence in the population is 14.4%. Sibling incidence in our survey (10.0%) is therefore much closer to that for multifactorial inheritance mode than that for autosomal inheritance.

We examined the effect of sex on the incidence risk. The number of male probands was approximately four times that of female probands (Table 1). Sibling incidence for families with a male proband was less than half that for families with a female proband, however. The reversed sex ratios correspond to the general rule for a multifactorial threshold model (Carter 1969; Harper 2004), i.e. where there is unequal sex incidence, the risk is higher for relatives of a proband of the sex in which the condition is less common. A proband of the more rarely affected sex requires a greater genetic factor to develop the disorder. Such reversed sex ratios in autistic families were also observed by Ritvo et al. (1989). Other phenomena which corresponded to a multifactorial threshold model were also found in previous studies—a high sibling risk (35.3%) was noted in families with multiple affected children (Ritvo et al. 1989), with a wide discrepancy of risk between monozygotic and dizygotic twins (Ritvo et al. 1985; Steffenburg et al. 1989; Bailey et al. 1995).

X-linked recessive inheritance can be excluded using our data for prevalence in the general population. Because the prevalence in males was 3.3%, the expected frequency of affected females (assuming Hardy–Weinberg equilibrium) is the square of this number, 0.11%. The actual observed prevalence in females was 0.82%, however. If PDD had an X-linked dominant inheritance mode, the prevalence in females should be higher than in males. An imperfect X-linked dominant cannot, however, be excluded using the data for prevalence. It is, moreover, difficult to prove the mode of inheritance if several inheritance types are mixed or if non-genetic

Table 2 Incidence rates in siblings

Family category (Number of families)	Number of siblings and incidence rate			
	All siblings	Affected siblings	Incidence (%)	95% cl
All families [269]	241 (male 118, female123)	24 (male 13, female 11)	10.0 (male 11.0, female 8.9)	6.5–14.5 (6.0–18.1, 4.5–15.4)
Sex				
Families with male probands [219]	196	15	7.7	4.3–12.3
Families with female probands [50]	45	9	20.0	9.6–34.6
Birth-weight				
Families with NBW probands [240]	220	24	10.9	7.1–15.8
Families with LBW probands [29]	21	0	0.0	0.0

cl, confidence limits; NBW, normal birth weight; LBW, low birth weight

factors are mixed. A larger cohort is thus necessary for statistical examination and for drawing conclusions about the mode of inheritance.

Non-genetic factors have also come under consideration. A case control study showed that obstetric complications did not increase the risk of autism (Cryan et al.1996), but Indredavik et al. (2004) demonstrated that the rate of incidence with the Asperger syndrome was higher (4/56) than in controls (0/81). In this study sibling incidences were 0 and 10.9% for families in which the proband had low or normal birth-weight, respectively. Although there were few low-birth-weight siblings, this suggests the risk in families with low-birth-weight probands is lower.

Several models have been proposed for the etiology of PDD. Gillberg et al. (2000) described PDD (autism) to be a syndrome resulting from many individual diseases (factors), but this has been criticized by Jones et al. (2002), who proposed a risk factor model, supposing cumulative effects of multiple factors (mostly genes), in general agreement with a multifactorial threshold model.

Because our results for sibling incidence also provide support for such a model, we suggest that most PDD cases result from the cumulative effects of multiple factors (mostly genetic). Although there remains a possibility that one (or a few) major factor(s) could also cause PDD, this would not affect the results of our survey if the proportion were very small. Many factors, including single gene disorders and infection and neonatal factors, have been reported to be associated with PDD. For example, Jamain et al. (2003) suggested that defects in a single X-linked gene encoding neuroligin (cell-adhesion molecules at synapses) might cause autism. This needs to be taken into consideration in further investigations.

Finally we propose a model for the etiology for PDD encompassing two groups:

1 a large group in which the syndrome results from the cumulative effects of multiple factors (mostly genetic), namely a multifactorial disorder; and
2 a small group in which it results from separate individual factors.

This is in line with the classical model of Penrose (1963) who divided mental retardation into two groups:

1 a physiological group which is biased in the normal distribution for intelligence; and
2 a pathological group resulting from various kinds of neurological disease.

Further investigations of larger numbers of families, genes, and non-genetic factors are necessary for clarification.

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