

Autistic disorders in Down syndrome: background factors and clinical correlates

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A study of a clinic-based sample of 25 individuals (12 females, 13 males; age at diagnosis 14.4 years, SD 7.4 years; age range 4 to 33 years) with Down syndrome (DS) and autism spectrum disorders, demonstrates that autism is by no means rare in DS. Results showed that there was a considerable delay in the diagnosis of autism as compared with children with autism who did not have DS. In 11 participants medical factors were identified that were likely to be of importance in contributing to the development of autism, and in four further participants there were factors of possible significance. Such factors include a history of autism or autism-related disorders in first- or second-degree relatives ($n=5$), infantile spasms ($n=5$), early hypothyroidism ($n=3$), evidence of brain injury after complicated heart surgery ($n=2$), or a combination of these factors. It is important that autism is recognised, identified, and fully assessed in individuals with DS in order for them to receive appropriate education and support.

It is widely held that most people with Down syndrome (DS) have a special talent for social interaction. This view seems to have its roots in the early description of the syndrome by Langdon Down himself in 1887 (Down 1990). The sociability in children with DS has been documented by many research groups (Carr 1994, Ruskin et al. 1994, Harris et al. 1996). Only relatively recently has this view been challenged (Gibbs and Thorpe 1983). Difficulties in social referencing (Krakow and Kopp 1983) and aberrations in mutual gaze (Sinson and Wetherick 1982) have been reported in children with DS. Studies by Wishart (1988) have shown that many children with DS seem to lack a basic motivation to go on learning new skills. There is also evidence of a significant incidence of attention deficits and conduct disorders in DS (Turk 1992, Krakow and Kopp 1983). Furthermore, there are many reports concerning an association between DS and autism (Howlin et al. 1995). It has been estimated that 5% (Ghaziuddin et al. 1992), 7% (Kent et al. 1999), or even 9% (Turk 1992) of people with DS have social interaction deficits meeting criteria for autism. In a community-based study of adolescents who had learning disability* Gillberg and coworkers (1986) found that one of 20 young people with DS had autism. In spite of this, children with DS are included in numerous studies as control participants for comparison with children with autism implying that they typically do not have autism.

It can be argued that people with DS have autism less often than other people with learning disability who do not have DS. The study by Gillberg and colleagues (1986) showed that 8% of adolescents with severe learning disability (IQ <50) met DSM-III (American Psychiatric Association 1987) criteria for infantile autism, 27% met criteria for the 'triad of social impairment' (i.e. an autism spectrum disorder) and a further 14% had severe social impairment 'only'. The corresponding figures for adolescents with mild learning disability were 4%, 6%, and 2%, respectively. In a population-based study in southern Sweden, Nordin and Gillberg (1996) found that 13.6% of children with severe learning disability had an autistic disorder and 6.8% had an autistic-like condition. The corresponding figures for mild learning disability were 5.3 and 0%, respectively. One may ask if personality characteristics in people with DS offer a partial protection against autism. If so, would it be possible to identify medical factors, known to be of aetiological importance in non-DS cases of autism, that might be responsible for, or contribute to, autism in people with DS?

The present study of a clinic-based sample of individuals with the co-occurrence of DS and autistic disorder was undertaken with a view to (1) highlighting the importance of diagnosing autism in children with DS and (2) identifying various neurobiological factors that might be of importance in the pathogenesis of autism in people with DS.

Method

PARTICIPANTS

Twenty-five individuals (12 females, 13 males) with DS and autism are reported. This group comprised all individuals with autism and DS who had been referred over a 15-year period to the child neuropsychiatric clinic at the Queen Silvia Children's Hospital, Göteborg, Sweden, for assessment

* UK usage. North American usage: mental retardation

because of marked social interaction deficits. In most cases the referral source was a paediatrician or a child psychiatrist. Participants came from different parts of Sweden although the majority lived in the Göteborg area. All participants had received a chromosomal test showing trisomy 21, including three participants with a mosaicism.

PROCEDURE

The child neuropsychiatric clinic is a national centre for assessment, treatment, and research in the field of neuropsychiatry, including autism and its spectrum disorders. Examinations of the participants in this study always included the following items: (1) detailed interview with either one or both parents and staff covering medical, developmental, psychiatric, hereditary, and psychosocial factors as well as aspects of preschool, school, or vocational adjustment; (2) behaviour questionnaires completed by parents and staff members; (3) assessment of intellectual level and cognitive profile; (4) medical and psychiatric examination; and (5) scrutiny of all relevant medical records (maternal health centre records, birth records, paediatric and general health records, and records from various specialist centres). Formal testing was performed whenever possible using the Griffiths' Mental Developmental Scales (Griffiths 1970) or the Wechsler Intelligence Scale for Children (Wechsler 1992). One or more rating scales were used, most often the Childhood Autism Rating Scale (CARS; Schopler et al. 1986), and the Autism Behavior Checklist (ABC; Krug et al. 1980). In a few children it was not possible to perform a complete psychological test and the intellectual level had to be determined on the basis of clinical evaluation. In most cases, teachers or other staff members caring for the individual were interviewed as well, and the clinical examinations were sometimes supplemented by observations, e.g. in the home or in school. Comprehensive diagnoses according to the DSM III-R (American Psychiatric Association 1987) or the DSM IV (American Psychiatric Association 1994) were made on the basis of all information obtained in connection with the various assessments. The reliability for a diagnosis of autistic disorder using this kind of diagnostic assessment is excellent and was reported to be 100% in a study performed by our group in the 1980s (Steffenburg et al. 1989).

A number of factors, known to be of possible pathogenetic importance in the development of autism, were identified by means of interview, analysis of medical records, and current medical examination. Such factors were (1) hereditary/familial factors, (2) prenatal factors, (3) perinatal factors, (4) neonatal factors, (5) congenital malformations, (6) epilepsy, (7) thyroid disorders, (8) severe infections in early childhood, (9) deficits in hearing or vision, and (10) other severe physical disorders.

Results

Age at diagnostic assessment for autism, sex, and intellectual level are shown in Table I. Intellectual level was expressed as a developmental quotient or IQ depending on the test used, or as severe learning disability (SLD, IQ <50) or mild learning disability (MLD, IQ 50 to 70) according to clinical assessment when formal testing was not possible. Number of symptom criteria met in each group of symptoms according to the DSM-III R or DSM-IV is also given in the table. In all individuals criteria for autistic disorder were met with the exception of

participant 23: one of the individuals with mosaicism who was diagnosed as having an autistic-like condition.

Among the possible pathogenetic factors, (1) through (7) are summarized in Table I and will be briefly commented on in the text. The remaining factors will be described in the text only. The clinically assigned significance of the different factors in causing autism was classified as 'not important' (-), 'possibly important' (+), or 'probably important' (++) . Missing information or data deemed to be unreliable were classified as '?'.

AGE AT DIAGNOSIS

The age at diagnosis of autism ranged between 4 and 33 years. Mean age at diagnosis was 14.4 years (SD 7.4). For comparison a recent survey of 206 consecutive patients with autism diagnosed in this department showed that the mean age at diagnosis was 6.9 years (SD 3.2; Gillberg, personal communication). According to interview data, in many cases confirmed by medical records, symptoms of autistic disorder had been present from infancy or early childhood in all participants.

HEREDITARY FACTORS

In five individuals (participants 2, 4, 5, 18, 22), there were one or more first- or second-degree relatives who had a diagnosis of autism, severe attention disorders, or learning disability. Participant 2 had a brother with severe and classical autism of unknown aetiology. Participants 4 and 5 were twin brothers, participant 4 had trisomy 21 and participant 5 had mosaicism for trisomy 21; both of them met criteria for autism. In participants 18 and 22 there were several relatives with either learning disability or with severe attention and learning problems. In eight further participants there were similar problems among relatives but to a less severe degree (four participants) or there were psychiatric disorders in the form of bipolar disorder. In participant 12 there was a history of mild autistic traits and specific reading and writing difficulties in an older brother. On chromosomal testing this boy with DS (participant 12) was found to have trisomy 21 and, in addition, a fragile site on chromosome 2. At the time of the original chromosomal analysis (repeated once) the relevance of this fragility was questioned but in the light of new knowledge further analyses are now being performed.

PRENATAL FACTORS

In seven participants there were reports of medical complications during pregnancy in the form of vaginal bleeding (participants 1, 2, 22, 23), infection (participants 4, 5), or high blood pressure (participant 7) in the mother. In 15 participants the pregnancy was described as uneventful.

PERINATAL FACTORS

In three participants (4, 6, 18), there were serious medical complications associated with parturition. Participant 4 was born 9 weeks before term and had episodes of hypoglycaemia and hypocalcaemia. Participant 6 had a moderately severe intrapartum asphyxia. In participant 18 there were signs of toxicosis in the mother and intrauterine asphyxia in the child. Less serious complications were found in two participants in which Caesarean section was performed due to breech presentation (participants 13, 15) and in three participants with preterm birth (participants 5, 11, 16).

NEONATAL FACTORS

Participant 7 had transient epileptic seizures at the age of 2 weeks in connection with a meningoencephalitis. Six more individuals (participants 3, 4, 5, 12, 18, 22) had less severe neonatal complications: surgical intervention for Hirschsprung disease (participant 3), surgery for pancreas anulare (participant 18), immature pulmonary function needing treatment with continuous positive airway pressure (participants 4, 5), prolonged need of incubator care and tube feeding due to cardiac and bowel malformations (participant 12), or prolonged monitoring of breathing (participant 22).

CONGENITAL MALFORMATIONS

Participants 3 and 12 had Hirschsprung disease necessitating surgical intervention in the newborn and early infant period, respectively. Both of them had a congenital heart anomaly as well (patent ductus arteriosus in both) for which they had surgical treatment at an age of 8 and 4 months, respectively. Following the operation there were signs of injury of the CNS in participant 3, probably due to circulatory complications during the surgical procedure. Pancreas anulare was seen in participant 18. In seven individuals there were less severe congenital cardiac anomalies with no need for surgical or other medical intervention and one further individual had hypospadias (participant 15).

EPILEPSY

Five participants (1, 3, 17, 23, 25) had experienced infantile spasms with hypsarrhythmia during infancy. Treatment with adrenocorticotrophic hormone was given in all participants. In participant 3 the spasms started following complicated cardiac surgery as described earlier. One of the individuals with mosaicism, participant 23, had experienced infantile spasms. Participant 17 still has infrequent epileptic seizures while the four remaining participants apparently are free from epileptic symptoms. Participants 18 and 19 have absence epilepsy of a complex partial type.

HYPOTHYROIDISM

Five individuals (participants 2, 6, 9, 13, 22) had hypothyroidism. In participants 2, 6, and 13 there were clear-cut diagnoses of hypothyroidism at the age of 18 months, 18 months, and 7 years, respectively. In two further individuals (participants 9, 22) hypothyroidism was diagnosed at an older age and with reasonably good evidence that the hormone deficiency had not existed for a long time. In participant 9 there were normal levels of thyroid stimulating hormone at the age of 10 years. At age 11 years a diagnosis of hypothyroidism was made. In participant 22 a diagnosis of hypothyroidism was made at age 17 years. Laboratory data of thyroid function had been normal at age 13 years. All individuals with hypothyroidism had received adequate treatment from the time of diagnosis.

Table I: Selected data from neuropsychiatric and medical assessment in a clinic-based sample of 25 individuals with Down syndrome and autistic spectrum disorders

Participant nr	Sex	Age	Heredity	Prenatal factors	Perinatal factors	Neonatal factors	Malformations	Epilepsy	Hypothyroidism	Intellectual level	Autism criteria	Probable aetiology
1	F	4	+	+	-	-	-	++	-	29 G	4, 2, 3; IV	++
2	F	5	++	+	-	-	+	-	++	50 G	4, 4, 4; III	++
3	F	7	-	?	-	+	++	++	-	SLD	4, 2, 2; III	++
4	M	7	++	+	++	+	-	-	-	30 G	4, 2, 2; IV	++
5	M	7	++	+	+	+	-	-	-	60 W	2, 4, 2; IV	+
6	M	8	+	-	++	-	+	-	++	45 G	3, 3, 3; IV	++
7	M	9	-	+	-	++	+	-	-	SLD	4, 2, 4; III	+
8	F	9	-	-	-	-	-	-	-	44 G	4, 3, 2; IV	-
9	M	11	-	-	-	-	-	-	+	30 G	4, 2, 3; IV	-
10	F	11	+	-	-	-	+	-	-	20 G	5, 3, 3; III	-
11	F	12	+	-	+	-	-	-	-	10 G	4, 2, 3; IV	+
12	M	13	+	-	-	+	++	-	-	30 G	4, 3, 4; III	++
13	F	14	+	-	+	-	+	-	++	40 G	3, 3, 2; IV	++
14	M	14	-	-	-	-	-	-	-	21 G	4, 2, 2; IV	-
15	M	14	+	-	+	-	+	-	-	55 W	3, 3, 3; IV	-
16	M	17	+	-	+	-	-	-	-	20 G	4, 3, 3; III	-
17	F	18	-	-	-	-	-	++	-	SLD	4, 3, 4; III	++
18	F	18	++	-	++	+	++	+	-	SLD	3, 3, 3; III	++
19	M	19	?	?	?	?	?	+	-	SLD	sum 10; III	-
20	M	19	-	-	-	-	+	-	?	20 G	4, 3, 4; III	-
21	M	19	?	-	-	-	+	-	-	SLD	>8; III	-
22	F	20	++	+	-	+	-	-	+	47 W	4, 3, 2; IV	+
23	F	21	-	+	-	-	-	++	?	73 W	2, 2, 3; III ^a	++
24	M	32	?	-	-	-	-	-	-	20 G	3, 3, 4; III	-
25	F	33	?	?	?	?	-	++	?	SLD	4, 1, 3; IV	++

^aCriteria for autistic-like condition only were met. Intellectual level expressed as developmental quotient (G, Griffiths' developmental scales), IQ (W, WISC), or clinical assessment without formal testing (SLD, severe learning disability, IQ <50). Autism diagnosis: number of criteria met in each group of symptoms or sum of symptom criteria according to the DSM III-R (III) or DSM IV (IV); maximum possible symptom criteria for DSMIII-R are 5, 6, and 5, and for DSM-IV are 4, 4, and 4. For explanation of +, ++, -, and ?, see Results section.

SEVERE INFECTIONS

A history of frequent infections in early childhood, not least recurrent middle-ear problems, was given in 18 participants. In one participant only there had been an infection of potentially brain damaging character. This was a meningococcal infection in the neonatal period as described above (participant 7).

VISION AND HEARING

Participants 1, 3, and 19 had severe visual impairment, while participant 18 had severe hearing impairment.

OTHER PHYSICAL DISORDERS

Juvenile chronic arthritis and a left-sided spastic hemiparesis were described in one participant each (18, 23) and coeliac disease was present in three participants (8, 11, 22).

'PROBABLE' OR 'POSSIBLE' AETIOLOGY

The comprehensive assessment disclosed one or more factors of probable importance as a cause of, or contributing to, autism in 11 participants. Hereditary factors in the form of autism in a first-degree relative were identified in three participants (2, 4, 5). In participant 2 this was combined with early hypothyroidism and in participant 4 there were severe perinatal complications as well. In participant 5 there were no medical complications and this case was classified as having a possible, rather than a probable, aetiology. Pre-, peri-, or neonatal complications, alone or in combination with each other, were not regarded as a probable cause of autism in any of the participants. The combination of perinatal complications and a history of many relatives having severe attention and learning disorders were classified as a probable explanation of the autistic syndrome in participant 18. Severe malformations were not in themselves considered a probable cause. However, in two participants the surgical correction of the heart malformation led to serious medical complications including brain damage with infantile spasms (participant 3) and prolonged need of tube feeding and a poor general physical condition (participant 12). In all five individuals who had had infantile spasms (participants 1, 3, 17, 23, 25) this was considered a probable cause of autism. With the exception of participant 3, there were no other probable factors in those who had experienced infantile spasms. Clear-cut hypothyroidism (participants 2, 6, 13) was considered a factor of probable importance. In participant 13 hypothyroidism was the only factor but in participants 2 and 6 there were other factors of possible or probable importance as well.

Factors of possible importance were identified in four individuals (participants 5, 7, 11, 22). In participants 5 and 22 there were hereditary factors and in participant 7 there were neonatal complications. In participant 11 the early psychomotor development was only slightly delayed. At a few months of age this girl experienced a period of malabsorption with failure to thrive and very poor weight gain. It was thought that she had coeliac disease or even cystic fibrosis but none of these diagnoses could be confirmed. A few months later she was in a much better physical condition and she started to gain weight in a normal way. Her psychomotor development, however, proved to be much more delayed than expected after this episode. It seems reasonable to regard this period of serious disturbance of weight gain and

emotional well-being as a factor of at least possible importance in explaining autism in this case. In 10 participants the analysis did not disclose any factors thought to be of probable or possible importance in the development of autism.

Discussion

This study refers to a clinic-based sample of children, adolescents, and young adults with Down syndrome and autism spectrum disorders. The participants had been referred for assessment because of symptoms suggestive of autism. Consequently, the series is not population based and no appropriate DS comparison group without autism was available for contrast. Conclusions have to be tempered by this knowledge and seen as suggestive rather than firm evidence. However, all assessments were performed in a multidisciplinary fashion by professionals working in a national centre with a high degree of expertise in the field. All participants met criteria for autistic disorder according to the edition of the DSM in use at the time of assessment (DSM-III or DSM-IV R) with the exception of one participant with a diagnosis of an autistic-like disorder.

In spite of several studies showing that autism is not extremely rare in DS, there is still, at least in Sweden, a widespread notion that people with DS 'do not have autism'. The participants in the present study were worked up with a view to diagnosing autism much later than are children with autism without DS. Many parents expressed disappointment, even anger, when they realised what they had missed as regards insight, education, and support of the child due to the delay in the diagnosis of autism. Many of them had felt from the beginning that their child 'was not like other children with DS'. This is very similar to the situation in the United Kingdom as described in the paper by Howlin and coworkers in 1995.

On the one hand it is important to realise that autism does exist in people with DS. On the other hand it has been argued that there is a lower prevalence of autism in individuals with DS as compared with those with a corresponding level of learning disability and without DS (Gillberg et al. 1986). Therefore, we looked for additional medical factors that might account for symptoms of autism appearing in people with DS taking into consideration what is known about the aetiology of autism in individuals without DS. We concluded from this analysis that four factors were of probable importance in explaining autism in the participants of the present study. Those factors, singly or in combination, were believed to 'explain' autism in 11 of the 25 participants. Somewhat less 'convincing' explanatory factors, i.e. factors of possible importance, were present in four further participants.

Hereditary factors of the kind often found in studies of aetiological factors in autism were present in four participants. They included autism or autism-related disorder or other severe neuropsychiatric disorders in first- or second-degree relatives. Ghaziuddin (1997) described three individuals with DS and co-occurrence of autism, all of whom had a history 'suggestive of the broader phenotype of autism' in the parents. The role of genetic factors as a major cause of autism has recently been strongly emphasized by chromosomal and genetic studies of families with more than one child with autism (e.g. Phillippe et al. 1999).

Several studies have drawn attention to a strong association between the epileptic syndrome of infantile spasms and

autism (e.g. Riikonen and Amnell 1981). A study of more than 800 children with DS (Tatsuno et al. 1984) showed that only 1.4% had active epilepsy. Among them infantile spasms appeared to be a particularly common type of epilepsy that was seen in one third of participants. By extrapolation it appears that approximately 0.5% of those with DS are affected by infantile spasms. In the present study five of 25 participants had experienced infantile spasms. In a study of 17 children with DS who developed infantile spasms, Stafstrom and Konkol (1994) concluded that the overall neurological prognosis appeared to be better than for children with infantile spasms in the general population. However, symptoms of autism were not specifically assessed in this study. In summary, it seems reasonable to regard infantile spasms as a possible aetiological factor for autism in people with DS.

It has been suggested that untreated hypothyroidism from infancy or early childhood may cause autism (Gillberg et al. 1992). It seems that the children in the present study who had an early diagnosis of hypothyroidism were given hormone treatment 'in time'. However, it has not been possible to ascertain whether or not thyroid function screening had occurred before the diagnosis was made, and we cannot exclude the possibility that low levels of thyroid hormones may have been present for a period of time before treatment started; hypothyroidism was consequently regarded as a factor of probable importance.

Severe potentially brain-damaging events in the peri- or neonatal period or postnatally may be associated with autism (Folstein and Rutter 1977). Complications causing anoxia in connection with heart surgery was suspected as a cause of autism in one participant in this study. However, the child in question also had infantile spasms. Perhaps it is a combination of factors, rather than single factors, that may be regarded as 'the cause' of autism in DS.

Conclusions

This study of a clinic-based sample suggests that: (1) autism must be considered as a possible comorbid condition in all cases of DS, (2) when present, autism is a very important 'complication', and one which parents and teachers need to be well informed about in order for the child to receive optimal interventions, (3) certain underlying pathogenetic mechanisms (genetic factors, epilepsy, hypothyroidism, and severe early brain damage), rather than DS alone, may contribute to the development of an autistic syndrome in many cases.

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