The course of diagnosis in autistic patients: the delay between recognition of the first symptoms by parents and correct diagnosis

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ORIGINAL ARTICLE

Abstract

The primary aim of the research was to find the delay between the first symptoms of an autistic disorder being recognized by parents and diagnosis in our centre. A secondary objective was to evaluate the number of contacts with professionals (physicians, teachers, and speech therapists) in which parents pointed out special manifestations seen in children and, in spite of that, the children were not referred to a specialist. A retrospective study assessed 204 children (59 girls, 145 boys) in total; 126 children (39 girls, 87 boys) with childhood autism (CHA), 57 (17 girls, 40 boys) with atypical autism (AA), and 21 (3 girls, 18 boys) with Asperger's syndrome (AS). The mean age at appearance of the first signs was 29.7 months (range 0–70, median 30±17.0) in N=201, and the average age at diagnosis was 81.5 months (range 13–276, median 69.5±45.2) in N=204. The mean delay in making a diagnosis was 51.3 months (range 0–246, median 39±40.9) in N=201. The delay in diagnosis is shortest in patients with AA (a mean period of 44.4 months = 3 years and 8 months), longer in CHA patients (49.5 months = 4 years and 2 months), and longest in patients with AS (80.8 months = 6 years and 9 months). A statistically significant difference in the period to diagnosis was found between CHA and AS patients (p=0.023) and between AA and AS patients (p=0.019). The mean number of visits to physicians and other specialists before referring to a specialized centre for diagnosis in N=133 was 2.4 (range 1–5, median 2±0.9). The diagnosis of autism is made late and early educational and behavioural interventions cannot be initiated.

INTRODUCTION

The terms of autistic spectrum (continuum) and pervasive developmental disorders cover a range of severe to devastating neurobehavioral problems that were, in the past, called more simply "autism". Boys are affected more often than girls in the ratio of 2–4:l and if a mental involvement is not present as well, this ratio is even higher (Fombonne, 2005). The common features and diagnostic criteria are three basic groups of signs: deficits in the capacity for reciprocal social contacts and interactions, deficits in verbal and non-verbal communication, and limited or stereotyped interests and behaviour. It results in a disorder that penetrates all spheres (pervasive) and changes completely and deeply both cognitive behavioural phenotypes and the development of those affected (Filipek, 1999; Rapin & Tuchman, 2006).

Autism is a syndrome, not a disease. For instance, Coleman has used terminology understandable for a neurologist – symptomatic and idiopathic autism (Coleman, 2005). The research carried out in the recent two decades has shown that it is often a genetically disposed disturbance of the developing brain (Folstein *et al.* 2003; Muhle, 2004), but the etiology is multifactorial and a number of factors, e.g. serotonergic hypofunction, may also play role in the pathogenesis (Croonenberghs *et al.* 2007). Furthermore, more and more information has appeared about possible environmental factors that can share in the development of autism symptoms. For instance, the role of polyunsaturated fatty acids (Sliwinski *et al.* 2006) or the effects of mercury in maternal dental amalgam and thimerosal-containing vaccine (Mutter *et al.* 2005, Geier & Geier, 2006), the influence of cortisol related to sex or the role of androgens (Nakayama *et al.* 2007, Gier & Gier, 2006) have been discussed. However, the importance of the risks mentioned above has never been confirmed. The signs of autism gradually become clear in childhood and represent a life-long handicap for children in their integration into society and in their general social functioning. Only a small number of autistic children at least can live an independent life as adults, and enter into relationships with partners – they are exclusively those who are without associated intellect affection (Anagnostou & Schevell, 2006; Howlin *et al.* 2004).

In our opinion, children are referred late for autism diagnosis, although parents often and without result warn physicians and educational professionals "something is wrong". The reason is most likely the fact that children with autism have no obvious defect at first sight. In most autistic spectrum disorders diagnosis is feasible at the age of 36 months and in Asperger's syndrome at about 72 months (Allen, 1988; Baird *et al.* 2000; Kurita, 1985; Trillingsgaard *et al.* 2005) and early warning signals of the disorder may often be identified by the age of one year (Baghdadli *et al.* 2003; Charman, 2003; Maestro *et al.* 2005; Zwaigenbaum *et al.* 2005). The reliability of early diagnosis is high – 88% – reported by American authors who assessed it after 7 years, i.e. at the age of 9 years in children whose autistic spectrum disorder had been diagnosed at the age of 2 years (Turner *et al.* 2006). Pharmacology can influence only some accompanying manifestations of autism, e.g. aggressiveness or autoaggressiveness (Gilman & Tuchman, 1995; Ruble & Brown, 2003). However, although core symptoms of the disorder are not influenceable pharmacologically and a certain reserved approach to drug administration has been recommended by some authors (Buitelaar, 2003; Ruble & Brown, 2003) and others have suggested various therapies, for example, to decrease the level of androgens or of heavy metals (Geier & Geier 2007, Mutter *et al.* 2005, Geier & Geier 2006) and others.

Early diagnosis is very important. This is in particular an explanation and answer for parents who are puzzled, unsure and apprehensive because they can see that "something is wrong" with their child and are not able to name the condition. Moreover, according to some authors, the initiation of early educational and behavioural therapy may at least alleviate "core" symptoms of autism and, thus, improve the quality of life of a patient and his/her family (Dawson & Zanolli, 2003). Positive effects of speech therapy have been presented in the trial carried out by Turner *et al.* mentioned above. The improvement of speech was positively affected by early diagnosis, by initial cognitive and speech score at the age of 2 years and the total number of speech-therapy lessons between the 2nd and 3rd years of life (Turner *et al.* 2006). These interventions should therefore be started although some authors cast doubt on their importance (Howlin 2003; Ozonoff & Miller, 1995).

Our research was focused practically. **The primary aim** was to find the delay between the first symptoms of autism recognized by parents and diagnosis in our centre. **The secondary aim** was to evaluate the number of contacts with professionals (physicians, teachers, and speech therapists) where parents reported strange manifestations seen in their child, but where the child was not referred to a specialized centre.

MATERIALS AND METHODS

This report is a retrospective evaluation of a set of children diagnosed and followed up in our centre within 1999–2006. The set involved 204 children (59 girls, 145 boys). There were 126 subjects (39 girls, 87 boys) with childhood autism (CHA), 57 (17 girls, 40 boys) with atypical autism (AA), and 21 (3 girls, 18 boys) with Asperger's syndrome (AS). Due to the absence of the unequivocal diagnostic biological markers of a disease, the disorder diagnosis in our workplace was based on anamnesis and on clinical observations of defects in social behaviour, communication and special or stereotyped interests carried out by parents, teachers, psychologists and paediatric neurologists. The diagnostics and classification respected the WHO criteria (World Health Organization; 1992, 1993). As

a supplement, the Childhood Autism Rating Scale (CARS) was used (Schopler *et al.* 1980) and in AS the Childhood Asperger Syndrome Test (CAST) (Scott *et al.* 2002). The IQ of younger children was found by the Gessler Developmental Scale, and that of older subjects by Stanford-Binet's Intelligence Scale – the 4th edition. The average IQ of the set was 55 (range 15–104). As part of anamnesis, all the parents were asked questions about what was strange and unusual in their child compared with other children, what was conspicuous, different and incomprehensible, and what the child's age was when they noticed it. The answers were recorded in documentation and, at present, they are utilized in eliminating the symptoms of mental affection or other associated diseases. The differentiation could not be carried out in cases with deep mental retardation where the signs were described by parents as "since birth" (IQ below 20). The age at which the first symptoms of autism were recognized by parents was evaluated as parameter 1. The data could be found in N=201 (data concerning 1 girl and 3 boys were not available). Results are given in Table 1. Parameter 2 was the age at diagnosis in N=204. Results are presented in Table 2. Parameters 1 and 2 were compared, and the delay between the first signals of autism observed by parents and the disorder diagnosis was found, which was **the primary aim of the research (parameter 3)**. See Table 3.

In N=133 it was possible to find data about visits to physicians, teachers and speech therapists with complaints of peculiar and abnormal behavioural manifestations in the child up until the time those children were referred to our workplace for diagnosis, which was **the secondary aim of research**. Visits for quite different diagnoses and for other reasons, e.g. vaccination, preventive examinations and infections, were not calculated. Results are shown in Table 4.

For the abnormal distribution of values the non-parametrical Kruskal-Wallis' test was used to compare the age at first symptoms, age at diagnosis, the period between first symptoms and diagnosis as well as the number of visits of patients with different types of autism (CHA, AS and AA). When a statistically significant difference was found between sets of patients (CHA, AS, AA), multiple comparisons were then used to determine the pairs of groups (types of diagnoses) differing statistically significantly.

The non-parametrical Mann-Whitney's U test was applied to compare age at first symptoms, age at diagnosis, the period from the first signs to diagnosis and the number of visits between patients, and between girls and boys.

RESULTS

Table l summarizes the age at the first symptoms of autism reported by parents. No statistically significant differences were revealed between girls and boys (Mann-Whitney's U test: U=3672.5, N=201, p=0.204).

Evaluating the differences in the age at the first signs between patients with different diagnoses (irrespective of the patients' sex), statistically significant differences were found (Kruskal-Wallis's test: Q=47.324, N=201, p<0.001). The first symptoms appeared in patients with CHA (on average at age 23.5 months = 2 years), later in patients with AA (mean 36.7 months = 3 years and 1 month), at the latest in patients with AS (mean age 47.7 months = 4 years). The differences between all pairs of groups (diagnoses) were statistically significant (CHA vs. AA: p<0.001, CHA vs. AS: p<0.001, AA vs. AS: p=0.034).

A statistically significant difference was found between diagnoses in girls in the age of the first symptoms (Kruskal-Wallis's test: Q=13.939, N=58, p<0.001). In girls with CHA the first symptoms appeared at the mean age of 20.8 months (1 year and 9 months), while in girls with AS the first symptoms were seen later (mean age 60 months = 5 years). A statistically significant difference was revealed in the age of the first symptoms between girls with CHA and those with AA (p=0.017), and between girls with CHA and those with AS (p=0.011).

A statistically significant difference was observed in boys, similar to that in girls in the age of the first symptoms between diagnoses (Kruskal-Wallis's test: Q=32.308, N=143, p<0.001). In boys with CHA the first symptoms appeared at a mean age of 24.7 months (2 years and 1 month), while in boys with AS they appeared later (the average of 45.7 months = 3 years and 10 months). The differences in the age of the first signs between boys with CHA and AA (p=0.001) as well as between boys with CHA and AS (p<0.001) were statistically significant.

The age of autism diagnosis is summed up in Table 2.

No differences statistically significant were revealed between girls and boys in the age of diagnosis (Mann-Whitney's U test: U=3931.5, N=204, p=0.365).

The evaluation of differences in the age of establishing the diagnosis between patients with various diagnoses (irrespective of patients' sex) showed statistically significant differences between the types of autism (Kruskal-Wallis's test: Q=20.947, N=204, p<0.001). The lowest age at diagnosis was seen in patients with CHA (mean 73.9 months = 6 years and 2 months), and the highest age in patients with AS (mean 128.5 months = 10 years and 9 months). The difference at age of diagnosis between patients with CHA and those with AS (p<0.001) and between patients with AA and those with AS (p=0.005) was statistically significant.

In girls, a statistically significant difference was found between diagnoses in the age at diagnosis (Kruskall-Wallis's test: Q=6.624, N=59, p=0.037). The mean age at diagnosis was lowest in girls with CHA (72.1 months = 6 years), and highest in girls with AS (162 months = 13 years and 6 months). A statistically significant difference in the age of diagnosis was observed just between girls with CHA and those with AS (p=0.033).

In boys, a statistically significant difference between types of autism was also found in the age of diagnosis (Kruskal-Wallis's test: Q=14.221, N=145, p<0.001). The

Table 1. The age at the first symptoms of autism reported by parents in individual types of autism according to patients' sex (age in months).

Group	Typ of Autism	N	Mean	Median	Min	Max	SD
Girls	CHA	38	20.8	18	0	60	13.4
Girls	AA	17	37.6	41	3	72	20.6
Girls	AS	3	60.0	60	48	72	12.0
Boys	CHA	86	24.7	24	0	60	13.5
Boys	AA	39	36.3	36	8	72	17.2
Boys	AS	18	45.7	48	30	60	10.7
Girls + boys	CHA	124	23.5	24	0	60	13.5
Girls + boys	AA	56	36.7	36	3	72	18.1
Girls + boys	AS	21	47.7	48	30	72	11.8
Girls	CHA+AA+AS	58	27.8	24	0	72	18.9
Boys	CHA+AA+AS	143	30.5	30	0	72	16.1
Altogether	CHA+AA+AS	201	29.7	30	0	72	17.0

CHA Childhood autism; AA Atypical autism; AS Asperger´s syndrom

Table 2. The age of the diagnosis in individual types of autism according to patients' sex (age in months).

Group	Typ of Autism	N	Mean	Median	Min	Max	SD
Girls	CHA	39	72.1	57	13	172	44.1
Girls	AA	17	78.9	63	25	158	40.6
Girls	AS	3	162.0	189	107	190	47.6
Boys	CHA	87	74.7	62	13	226	41.0
Boys	AA	40	82.0	78	20	167	35.8
Boys	AS	18	122.9	112.5	57	276	58.3
Girls + boys	CHA	126	73.9	61	13	226	41.8
Girls + boys	AA	57	81.1	75	20	167	37.0
Girls + boys	AS	21	128.5	128	57	276	57.6
Girls	CHA+AA+AS	59	78.6	61	13	190	46.8
Boys	CHA+AA+AS	145	82.7	73	13	276	44.7
Altogether	CHA+AA+AS	204	81.5	69.5	13	276	45.2

CHA Childhood autism; AA Atypical autism; AS Asperger´s syndrom

mean age of diagnosis was lowest in boys with CHA (74.7 months = 6 years and 3 months), and highest in boys with AS (122.9 months = 10 years and 3 months). A statistically significant difference in age of diagnosis was revealed between boys with CHA and AS (p=0.001) and between boys with AA and AS (p=0.047).

Table 3 shows the average delay between age at first symptoms of autism and age of diagnosing the disorder. No statistically significant differences were found between girls and boys in the period from revealing the first signs to diagnosis (Mann-Whitney's U test: U=3920.5, N=201, p=0.544).

Evaluating the differences in the period from the first symptoms to the diagnosis making between patients with various types of autism (irrespective of the patient's sex), statistically significant differences were seen between types of the disease (Kruskal-Wallis's text: Q=8.166, N=201, p=0.017). The period to diagnosis is shortest in patients with AA (mean 44.4 months = 3 years and 8 months), longer in patients with CHA (49.5 months = 4 years and 2 months), and longest in patients with AS (80.8 months = 6 years and 9 months). A statistically significant difference was observed in the period to diagnosis between patients with CHA and those with AS (p=0.023), and between patients with AA and those with AS (p=0.019).

In girls, no statistically significant difference was found in the period from first symptoms to diagnosis (Kruskal-Wallis's test: Q=4.379, N=58, p=0.112). The mean period to diagnosis in girls with AS was 102 months (8 years and 6 months), in girls with AA 41.3 months (3 years and 5 months), and in girls with CHA 49.3 months (4 years and 1 month). But the differences between diagnoses were

statistically insignificant (a low number of patients with AS is manifested here).

Similarly, no statistically significant difference was seen between types of autism in boys in the period from first symptoms to diagnosis (Kruskal-Wallis's test: Q=4.557, N=143, p=0.102). The mean period to diagnosis was 77.2 months (6 years and 5 months) in boys with AS, 49.6 months (4 years and 2 months) in boys with CHA, and 45.7 months (3 years and 10 months) in boys with AA. However, the differences between diagnoses were not statistically significant.

The number of visits to physicians and other professionals before referring to a specialized workplace up to diagnosis is summed up in Table 4.

A comparison of girls and boys provided no statistically significant difference in the number of visits (Mann-Whitney's U test: U=1871, N=133, p=0.942). The mean number of visits was 2.5 in girls and 2.4 in boys.

No statistically significant difference was observed when comparing the number of visits between various types of diagnosis, irrespective of the patient's sex (Kruskal-Wallis's test: Q = 1.501, N=133, p=0.472). The mean number of visits by patients with CHA and AA was 2.5, and by patients with AS 2.2.

The number of visits to physicians and other professionals before diagnosis did not differ statistically significantly between girls with various types of diagnosis (Kruskal-Wallis's test: Q=1.411, N=41, p=0.494). On average, girls with CHA made 2.6 visits, those with AS 2.3 visits, and patients with AA 2.2 visits.

Similarly, the number of visits to physicians and other professionals before diagnosis between patients with various types of diagnosis was not statistically significant

Table 3. The average time delay between the age at the first symptoms of autism and the age of diagnosing the disorder with subject to type of autism and patients' sex (time in months).

Group	Typ of Autism	N	Mean	Median	Min	Max	SD
Girls	DA	38	49.3	38	4	166	41.7
Girls	AA	17	41.3	38	0	110	33.8
Girls	AS	3	102.0	117	47	142	49.2
Boys	DA	86	49.6	38.5	5	190	38.6
Boys	AA	39	45.7	37	5	107	30.7
Boys	AS	18	77.2	64.5	17	246	59.8
Girls + boys	DA	124	49.5	38.5	4	190	39.4
Girls + boys	AA	56	44.4	37	0	110	31.4
Girls + boys	AS	21	80.8	68	17	246	57.9
Girls	CHA+AA+AS	58	49.7	39	0	166	41.2
Boys	CHA+AA+AS	143	52.0	39	5	246	40.8
Altogether	CHA+AA+AS	201	51.3	39	0	246	40.9

CHA Childhood autism; AA Atypical autism; AS Asperger´s syndrom

Table 4. The number of visits to physicians and other professionals with subject to autism type and patients' sex.

Group	Typ of Autism	N	Mean	Median	Min	Max	SD
Girls	DA	24	2.6	2	1	5	1.1
Girls	AA	14	2.2	2	1	4	0.8
Girls	AS	3	2.3	2	2	3	0.6
Boys	DA	53	2.4	2	1	4	0.7
Boys	AA	24	2.7	2	1	5	1.0
Boys	AS	15	2.2	2	1	4	0.9
Girls + boys	DA	77	2.5	2	1	5	0.9
Girls + boys	AA	38	2.5	2	1	5	1.0
Girls + boys	AS	18	2.2	2	1	4	0.9
Girls	CHA+AA+AS	41	2.5	2	1	5	1.0
Boys	CHA+AA+AS	92	2.4	2	1	5	0.9
Altogether	CHA+AA+AS	133	2.4	2	1	5	0.9

CHA Childhood autism; AA Atypical autism; AS Asperger´s syndrom

in boys (Kruskal-Wallis's test: Q=2.537, N=92, p=0.281). Patients with AA made 2.7, those with CHA 2.4, and patients with AS 2.2 visits.

DISCUSSION

The average age on diagnosing autism was 6.8 years (81.5 months) in 204 children. In the detailed analysis, the age at diagnosing CHA was 6.2 years (73.9 months), AA 6.8 years (81.1 months), and AS 10.7 years (128.5 months). That means that in all the assessed types of autism it is higher than the generally accepted age of possible diagnosis, which is 3 years in CHA, rather higher in AA, and 6 – 8 years in AS (Attwood, 1998; Koenig *et al.* 2000; Wing, 1981; Wing, 1988; WHO, 1992).

The average delay from the first symptoms to diagnosis in N=201 was 51.3 months. Interestingly, the shortest delay was 44.4 months (3 years and 8 months) in AA, although the age at diagnosis was lowest in patients with CHA (mean 73.9 months = 6 years and 2 months). Children with autism have a significantly higher incidence of associated health problems, and they utilize health care more often than children without autism (Gurney *et al.* 2006). It is possible that so-called symptomatic autism occurs among atypical cases more often, and more conspicuous problems make the children come to professionals more frequently, which increases the probability of earlier detection of the disorder – but that is only a guess. Comparing the number of visits when parents pointed out the symptoms of autism, no statistically significant difference was observed between various subtypes of autism (Kruskal-Wallis's test: Q=1.501, N=133, p=0.472).

Our centre specializes in the problems of diagnosing autistic spectrum disorders. The reason for late diagnoses is that suspected children are referred to professionals late. This fact is also supported by the number of visits to specialists, when parents reported on the child's suspicious behaviour and this is 2.4 visits in N=133. The mean number of visits of patients with CHA and AA was 2.5, and in patients with AS 2.2. Our experience is similar to that presented by Howlin and Moor in 1997 in 1,300 families in Great Britain. The mean age at diagnosis reported by them was also 6 years, in spite of the fact that parents had had a sense that "something was wrong" since the age of 18 months and had sought medical assistance at age 2. Less than 10% of cases were diagnosed at first contact, while the other 90% at the average age of 40 months were referred to another professional, and 25% were told "not to worry, the child would grow out of it", or asked to come back in the event of persistent problems. Out of the families referred to another specialist, only 40% were diagnosed and the others were sent to 3rd and 4th professionals. Nearly 20% of families reported that they had had to exert great pressure to obtaining a diagnosis (Howlin & Moore, 1997).

CONCLUSION

Professionals who might come in contact with suspect children have insufficient information about how autism manifests itself, and therefore children are referred late for diagnosis. The awareness of paediatricians, phoniatricians, speech therapists and teachers of early symptoms of autism must be improved. There is still a persistent tendency to not take sufficiently seriously the complaints

of parents who were, in our trial, able to recognize the first suspicious signals of the disorder at a far lower age than when the diagnosis was made.

An effective pharmacological therapy for the core manifestations of autism is still missing, and early diagnosis is necessary for the application of early educational and behavioural interventions and psychological support to the family.

REFERENCES

1 Allen DA. Autistic spectrum disorders: clinical presentation in preschool children. J Child Neurol. 1988; **3**: S48.

2 Anagnostou E, Schevell M. Outcomes of children with autism In: Tuchman R, Rapin I, editors. Autism: A neurological disorder of early brain development. London: Mac Keith Press; 2006. p.308–21.

3 Attwood T. Asperger's Syndrome: A Guide for Parents and Professionals. London: Jessica Kingsley Publishers; 1998.

4 Baghdadli A, Picot MC, Pascal C, Pry R, Aussilloux C. Relationship between age of recognition of first disturbances and severity in young children with autism. Eur Child Adolesc Psychiatry. 2003 Jun; **12**(3): 122–7.

5 Baird G, Charman T, Baron–Cohen S, et al. A screening instrument for autism at 18 months of age: A 6-year follow–up study. J Am Acad Child Adolesc Psychiatry. 2000; **39**: 694–702.

6 Buitelaar JK. Why have drug treatments been so disappointing? In: Novartis Foundation. Autism: Neural basis and treatment possibilities. John Willey & Sons Ltd; 2003. p.235–49.

7 Charman T. Epidemiology and early identification of autism: research challenges and opportunities. In: Novartis Foundation. Autism: Neural basis and treatment possibilities. John Willey & Sons Ltd; 2003. p.10–25.

8 Coleman ME. The neurology of Autism. New York: Oxford University Press; 2005.

9 Croonenberghs J, Wauters A, Deboutte D, Verkerk R, Scharpe S, Maes M. Central serotonergic hypofunction in autism: results of the 5-hydroxy-tryptophan challenge test. Neuroendocrinol Lett. 2007 Aug; **28**(4): 449–55.

10 Dawson G, Zanolli K. Early intervention and brain plasticity in autism. In: Novartis Foundation. Autism: Neural basis and treatment possibilities. John Willey & Sons Ltd; 2003. p.266–88.

11 Filipek PA. Autistic spectrum disorders. In: Swaiman KF, Ashwal S. Pediatric neurology. Principles & Practice. St. Louis: Mosby Inc. 1999; 606–628.

12 Folstein SE, Dowd M, Mankoski R, Tadevosyan O. How might genetic mechanisms operate in autism? In: Novartis Foundation. Autism: Neural basis and treatment possibilities. John Willey & Sons Ltd; 2003. p.70–83.

13 Fombonne E. Epidemiologic studies of the pervasive developmental disorders. In: Volkmar FR, Paul R, Klin A, Cohen D, editors. Handbook of Autism and Pervasive Developmental Disorders. 3rd ed. New York: John Wiley; 2005. p.42–69.

14 Geier DA, Geier MR. A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. Neuroendocrinol Lett. 2006 Aug; **27**(4): 401–13.

15 Geier DA, Geier MR. A clinical trial of combined anti-androgen and anti-heavy metal therapy in autistic disorders. Neuroendocrinol Lett. 2006 Dec; **27**(6): 833–8.

16 Geier DA, Geier MR. A prospective assessment of androgen levels in patients with autistic spectrum disorders: biochemical underpinnings and suggested therapies. Neuroendocrinol Lett. 2007 Oct 8; **28**(5).

17 Gilman JT, Tuchman RF. Autism and associated behavioral disorders: pharmacotherapuutic intervention. Ann Pharmacother. 1995; **29**: 47.

18 Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism – National Survey of Children's Health. Arch Pediatr Adolesc Med. 2006 Aug; **160**(8): 825–30.

19 Howlin P. Can early interventions alter course of autism? In: Novartis Foundation. Autism: Neural basis and treatment possibilities. John Willey & Sons Ltd; 2003. p. 250–65.

20 Howlin P, Moore A. Diagnosis in autism. A survey of over 1200 patients in the UK. Autism. 1997; **1**: 135.

21 Howlin P, Goode S, Hutton J, Rutter M. Adult outcome for children with autism. J Child Psychol Psychiatry. 2004 Feb; **45**(2): 212–29.

22 Koenig K, et al. Autism and the pervasive developmental disorders. In: Zeanah CH, editor. Handbook of infant mental health. 2nd ed. New York: Guilford Press 2000; 298–310.

23 Kurita H. Infantile autism with speech loss before the age of thirty months. J Am Acad Child Psychiatry. 1985 Mar; **24**(2): 191–6.

24 Maestro S, Muratori F, Cesari A, et al. Course of autism signs in the first year of life. Psychopathology. 2005; **38**: 26–31.

25 Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004 May; **113**(5): E 472–E486.

26 Mutter J, Naumann J, Schneider R, Walach H, Haley B. Mercury and autism: accelerating evidence? Neuroendocrinol Lett. 2005 Oct; **26**(5): 439–46.

27 Nakayama Y, Takahashi T, Wakabayashi A, Oono H, Radford MH. Sex differences in the relationship between cortisol levels and the Empathy and Systemizing Quotients in humans. Neuroendocrinol Lett. 2007 Aug; **28**(4): 445–8.

28 Ozonoff S, Miller JN. Teaching theory of mind: a new approach to social skills training for individuals with autism. J Autism Dev Disord. 1995 Aug; **25**(4): 415–33.

29 Rapin I, Tuchman R. Where we are: Overview and definitions. In: Tuchman R, Rapin I, editors. Autism: A neurological disorder of early brain development. London: Mac Keith Press; 2006. p.1–18.

30 Ruble LA, Brown S. Pervasive Developmntal Disorders: Autism. In: Wolraich ML. Disorders of Development and Learning. 3rd ed. Hamilton: BC Decker Inc; 2003. p. 249–266.

31 Scott F, Baron–Cohen S, et al. The CAST (Childhood Asperger SyndromeTest). Autism. 2002; **6**(1): 9–31.

32 Schopler E, Reichler RJ, DeVellis RF, et al. Toward objective classification of childhood autism: childhood Autism rating Scale (CARS). J Autism Dev Disord. 1980; **10**: 91.

33 Sliwinski S, Croonenberghs J, Christophe A, Deboutte D, Maes M. Polyunsaturated fatty acids: do they have a role in the pathophysiology of autism? Neuroendocrinol Lett. 2006 Aug; **27**(4): 465–71.

34 Trillingsgaard A, Sorensen EU, Nemec G, Jorgensen M. What distinguish autism spectrum disorders from other developmental disorders before the age of four years? Eur Child Adolesc Psychiatry. 2005; **14**: 65–72.

35 Turner LM, Stone WL, Pozdol SL, Coonard EE. Follow–up of children with autism spectrum disorders from age 2 to age 9. Autism. 2006 May; 10(3): 243–265.

36 Wing L. Asperger's syndrome: a clinical account. Psychol Med. 1981; 11–115.

37 Wing L. The continuum of autistic disorders. In: Schiller E, Mesibov GM, editors. Diagnosis and assessment in autism. New York: Plenum Press; 1988.

38 World Health Organization. The ICD classification of mental and behavioral disorders: clinical descriptors and diagnostic guidelines. Geneva: World Health Organization; 1992, 1993.

39 Zwaigenbaum L, Bryson S, Rogers T, et al. Behavioral manifestations of autism in the first year of life. Int J Dev Neurosci. 2005 Apr–May; **23**(2–3): 143–52.