BOYS WITH ASPERGER SYNDROME GROWN UP
A LONGITUDINAL FOLLOW-UP STUDY OF 100 CASES MORE THAN 5 YEARS AFTER ORIGINAL DIAGNOSIS

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Abstract

Introduction and aims: In 1981, the diagnostic label of Asperger Syndrome (AS), was coined after the Austrian paediatrician Hans Asperger, by the English psychiatrist Lorna Wing, who reintroduced his 1944 work about "die autistischen Psychopathen im Kindesalter", so as to have a concept for relatively high functioning individuals with problems in the "autism spectrum". Little is known about the risk factors and outcome of AS and whether or not they are different from those of autism. The present study were to examine (1) a large number of background and associated factors in AS; (2) how aims of the different kinds of background factors influence IQ, neuropsychological skills, and psychomotordevelopment in males with AS; (3) the outcome of AS in males, and compare it to that of a similarlyaged group of males with autism; and (4) to what extent males with AS acknowledge problems related to their diagnosis, and agree with their parents on these matters.

Subjects and methods: Medical records of 100 clinical cases of males with AS diagnosed at least five years prior to the present study were searched for information concerning background and associated factors. Sub-grouping in accordance with operationalised "pathogenetic" factors was attempted, and the influence of subgroup on psychomotor development, IQ, and degree of autism spectrum problems was investigated. These 100 males (and their parents) were approached for inclusion in a follow-up study. Seventy-six of the families participated in this in-depth study. The individuals with AS were evaluated at neuropsychiatric examinations, neuropsychological testing, and by interview schedules and questionnaires, some of which were used with their parents as well. Those 70 males with AS whose parents/carers had been given the Diagnostic Interview for Social and Communication disorders were compared with 70 males with autism of similar age. Specific outcome criteria were used taking into consideration, employment, education/vocational training, independent living, and peer relations.

Results and Discussion: Mean age at original diagnosis was 11.3 years. In 28 cases there was a strong suspicion of autism spectrum problems in close relatives, 12 of whom had been formally diagnosed with autism or AS. Some pre- and perinatal risk factors were much more common than in the general population. No definite clue as to "pathogenesis" could be established in 13%. Intellectual ability was average, and more than half the group had a verbal over performance IQ difference of 15 points or more at original diagnosis, consistent with so called Non-Verbal Learning Disability (NVLD). However, at follow-up fewer than 20% had indications of NVLD. For the AS cases followed up diagnosis and overall IQ were stable over time. However, 12% no longer met criteria for an autism spectrum disorder. Overall outcome was good in 27% of cases, but 26% had a very restricted life, with no occupation/activity and no friends. Outcome in the autism group was significantly worse, possibly due to the much lower IQ in this group. The males with AS had a good understanding of their own problems in some areas, but disagreed with their parents regarding some core AS symptoms. In spite of the much better outcome than in the autism group, prognosis in clinical cases of AS appears to be restricted as compared with individuals at the same IQ-level in the general population. However, given the lack of a general population comparator group, no generalized conclusions can be drawn in this respect.

Keywords: Asperger Syndrome, autism, background factors, neuropsychology, medical work-up, outcome, self assessment, parent assessment.

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To Helena, Sofie and Markus

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Foreword

In the foreword to the first edition of his book “Heilpädagogik” (1952), Hans Asperger gave a description of the complexity and needs of “problematic children and adolescents”, and presented a view as to how to deal with them from different aspects in a “modern” society. Although written more than 50 years ago, these matters are as important as ever (Asperger, 1961).

“Das Buch wendet sich gleichermaßen an Ärzte wie an Lehrer, an Psychologen, an Richter wie an Sozialarbeiter, kurz an alle, welche mit problematischen Kindern und Jugendlichen zu tun haben, die an ihren Defekten oder Spannungen leiden oder mit ihrer Umwelt in Konflikt stehen. Diesem großen Kreis von Menschen will das Werk Helfer in ihrer Arbeit sein.

Eine beträchtliche Schwierigkeit liegt nun aber darin, dass die verschiedenen Gruppen von Menschen, welche mit solchen Kindern arbeiten, von ganz verschiedener Ausbildung, von anderen Erfahrungen, ja von verschiedenen Denkgrundlagen herkommen und darum nicht leicht die Sprache des anderen verstehen — also etwa der Lehrer die des Arztes —, nicht nur wegen der medizinischen Fachausdrücke, sondern mehr noch wegen der vom biologischen Denken ausgehenden Einstellung zu den Problemen. Trotzdem muss im Interesse der gemeinsamen Arbeit an den Kindern versucht werden, zu einer möglichst weitgehenden Integration der verschiedenen Wissensgebiete zu gelangen”.

List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals I-IV.

I. Cederlund, M. & Gillberg, C. (2004). One hundred males with Asperger syndrome: a clinical study of background and associated factors. *Developmental Medicine and Child Neurology, 46*, 652-660.

II. Gillberg, C. & Cederlund, M. (2005). Asperger syndrome: familial and pre- and perinatal factors. *Journal of Autism and Developmental Disorders, 35,* 159-166.

III. Cederlund, M., Hagberg, B., Billstedt, E., Gillberg, I.C. & Gillberg, C. (2007). Asperger syndrome and autism – a comparative longitudinal follow-up study more than 5 years after original diagnosis. *Journal of Autism and Developmental Disorders* (accepted for publication).

IV. Cederlund, M., Hagberg, B. & Gillberg, C. Asperger syndrome in young adult males. Interview, self and parent assessment of social, emotional and cognitive problems (submitted).

Abbreviations

A	Average intelligence (IQ 85-114)
ABC	Autism Behaviour Checklist
AD	Autistic Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADHD	Attention Deficit Hyperactivity Disorder
ADOS	Autism Diagnostic Observation Schedule
ANCOVA	Analysis of Covariance
APA	American Psychiatric Association
AS	Asperger Syndrome
ASD	Autism Spectrum Disorder
ASDI	Asperger Syndrome Diagnostic Interview
ASSQ	Asperger Syndrome/Autism Spectrum Screening Questionnaire
BADS	Behavioural Assessment of the Dysexecutive Syndrome
BMI	Body Mass Index
DAMP	Deficits in Attention, Motor control and Perception
DEX	Dysexecutive Questionnaire
DISCO	Diagnostic Interview for Social and COmmunication disorders
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders - Third Edition - Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
DQ	Developmental Quotient
FSIQ	Full Scale IQ
GAF	Global Assessment of Functioning
HBS	Handicaps, Behaviours, and Skills
ICD-10	International Classification of Diseases - Tenth Edition
IQ	Intelligence Quotient
MMR	Mild Mental Retardation (IQ 50-69)
NA	Near Average intelligence (IQ 70-84)
PDD	Pervasive Developmental Disorder
PIQ	Performance IQ
SMR	Severe Mental Retardation (IQ <50)
SQ	Social Quotient
VABS	Vineland Adaptive Behavior Scales
VIQ	Verbal IQ
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WAIS-III	Wechsler Adult Intelligence Scale-Third Edition
WHO	World Health Organisation
WISC-R	Wechsler Intelligence Scale for Children-Revised
WISC-III	Wechsler Intelligence Scale for Children-Third Edition

Introduction

Asperger Syndrome (AS) was first described in 1944 by the Austrian paediatrician Hans Asperger, who named the condition "autistic psychopathy" (Asperger, 1944). He later argued that the children he saw had a disturbance that was in a separate category from that of children with classic autism, as described by Leo Kanner in 1943 (Kanner, 1943). The Dutch physician Art van Krevelen presented Asperger´s work to English readers in 1971 (van Krevelen, 1971), but it was not until 1981, when the English psychiatrist Lorna Wing reintroduced Asperger´s work and named the condition after him, originally so as to draw attention to the group of relatively able people with autism, that AS became known to researchers (Wing, 1981). Diagnostic criteria for research were not published until 1989 (Gillberg & Gillberg, 1989). Interestingly, many years later the Scottish psychiatrist Sula Wolff reintroduced a paper from 1926, by the Russian neurology assistant Ewa Ssucharewa, in which 6 boys with virtually identical characteristics to those later outlined by Asperger were presented (Wolff, 1996). However, her work had been known to, and commented on by Kanner already in 1971, but he never mentioned Asperger´s work in any of his papers.

Lorna Wing did not make a categorical separation between autism and AS, she merely presented AS as a term for "higher-level autism" (Wing, 1981). However, this was the start of an ongoing debate about whether or not individuals with AS could be separated from individuals with autism (or "atypical autism") in the high functioning range (e.g. Gillberg, 1998; Mesibov, Kunce & Schopler, 1998; Wing & Potter, 2002). Even if some evidence about differences between the two groups has been presented (e.g. that individuals with AS have higher IQ, especially higher verbal IQ, and often have language onset before the age of 3), no clear-cut differences have been documented that could be used with reliability in clinical diagnostic work (e.g. Eisenmajer, et al., 1998; Gilchrist, et al., 2001; Howlin, 2003).

The first set of diagnostic criteria for research and clinical work was formulated by Gillberg and Gillberg (1988/1989) and elaborated in Gillberg (1991). The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and the ICD-10 classification of Mental and Behavioural Disorders, did not publish diagnostic criteria for AS until well into the 1990s (APA, 1994; WHO, 1993). These criteria have been widely criticized (e.g. Miller & Ozonoff, 1997; Leekam, Libby, Wing, Gould & Gillberg, 2000), and there is still no consensus as to how AS should best be delineated.

Table 1 outlines the major sets of diagnostic criteria for Asperger syndrome (and for a newly suggested set of operationalised criteria proposed by Gillberg for atypical autism) that are currently available. The main difference between the criteria by Gillberg and those of the DSM-IV is that the Gillberg´s six criteria for making the diagnosis of AS are based on Hans Asperger´s original publication. They require major problems with social interaction, narrow interests, repetitive routines, speech and language peculiarities, non-verbal communication problems, and motor clumsiness. At least 9 symptoms are required for a diagnosis of AS according to Gillberg.

The DSM-IV criteria for AS specify impairments in social interaction (defined as for autism), restricted, repetitive, stereotyped behaviour (defined as for autism), and absence of clinically significant delay in language or cognitive development, including self-help skills, adaptive behaviour and curiosity about the environment, in the first 3 years of life. Only 3 symptoms are required for a diagnosis of AS.

Table 1. Diagnostic criteria for Asperger syndrome (and proposed criteria for atypical autism according to DSM-IV/Gillberg)

Gillberg & Gillberg 1989/1991 Asperger Syndrome

1. **Social impairment (extreme egocentricity)** (at least two of the following)
   a) inability to interact with peers
   b) lack of desire to interact with peers
   c) lack of appreciation of social cues
   d) socially and emotionally inappropriate behaviour

2. **Narrow interest** (at least one of the following)
   a) exclusion of other activities
   b) repetitive adherence
   c) more rote than meaning

3. **Repetitive routines** (at least one of the following)
   a) on self, in aspects of daily life
   b) on others

4. **Speech and language peculiarities** (at least three of the following)
   a) delayed development
   b) superficially perfect expressive language
   c) formal pedantic language
   d) odd prosody, peculiar voice characteristics
   e) impairment of comprehension, including misinterpretations of literal/implied meanings

5. **Non-verbal communication problems** (at least one of the following)
   a) limited use of gestures
   b) clumsy/gauche body language
   c) limited facial expression
   d) inappropriate expression
   e) peculiar, stiff gaze

6. **Motor clumsiness**
   a) poor performance on neuro-developmental examination

DSM-IV APA 1994 Asperger's disorder

Qualitative impairment in social interaction, as manifested by at least two of the following:

1. marked impairment in the use of multiple non-verbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gesture to regulate social interaction
2. failure to develop peer relationships appropriate for developmental level
3. lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (by lack of showing, bringing, or pointing out objects of interests to other people)
4. lack of social or emotional reciprocity

Restricted repetitive and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following:

1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2. apparently inflexible adherence to specific, non-functional routines or rituals
3. stereotyped and repetitive motor-mannerisms (hand- or finger-flapping or twisting or complex whole-body movements)
4. persistent preoccupation with parts of objects

The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning

There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years)

There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behaviour (other than in social interaction), and curiosity about the environment in childhood

Criteria are not met for another Pervasive Development Disorder or Schizophrenia

DSM-IV APA 1994 Autistic Disorder

Qualitative impairment in social interaction, as manifested by at least two of the following:

1. marked impairment in the use of multiple non-verbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gesture to regulate social interaction
2. failure to develop peer relationships appropriate for developmental level
3. lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (by lack of showing, bringing, or pointing out objects of interests to other people)
4. lack of social or emotional reciprocity

Qualitative impairments in communication, as manifested by at least two of the following:

1. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
2. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
3. stereotyped and repetitive use of language or idiosyncratic language
4. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

Restricted repetitive and stereotyped pattern of behaviours, interests, and activities, as manifested by at least one of the following:

1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2. apparently inflexible adherence to specific, non-functional routines or rituals
3. stereotyped and repetitive motor-mannerisms (hand- or finger-flapping or twisting or complex whole-body movements)
4. persistent preoccupation with parts of objects

Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play

The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

DSM-IV criteria for Atypical Autism modified by Gillberg 2006

Autistic/Asperger´s disorder criteria for qualitative impairment in social interaction

At least 4 autistic disorder symptoms

Not full criteria for autistic disorder or Gillberg´s AS

Hans Asperger believed “autistic psychopathy” to be caused by genetic factors or brain damage (Asperger, 1944). Systematic empirical data on the etiology and pathogenesis of AS are very limited. However, recently, a Finnish group reported on a genome-wide-scan for genetic susceptibility loci identifying at least two loci (on chromosomes 1 and 3) that had previously been identified as susceptibility loci for autistic disorder (Ylisaukko-Oja, et al., 2004; Rehnström, et al., 2006).

The present study was launched trying to fill in some gaps in our knowledge of the background and associated factors in AS, as well as of the “natural” outcome for AS (in males) on a long term basis. To the best of my knowledge it is the first study ever to present a really long-term perspective (into adulthood) on the natural outcome of a reasonably large group of males with AS. Given that AS is regarded by many as a disorder within the autism spectrum (and, hence, in many respects similar to autism), we also wanted to compare the outcome of the AS group to a group of individuals with autism/atypical autism followed up - with the same instruments - separately at our clinic (Billstedt, Gillberg & Gillberg, 2005).

Earlier reports on the outcome of AS, have either referred to small, or highly selected, clinical case samples without comparison groups, and have reported low levels of employment and social functioning (Wing, 1981; Tantam, 1991; Green, Gilchrist, Burton & Cox, 2000; Tsatsanis, 2003). Some degree of intellectual decline over time, as measured by the Wechsler scales, was reported in one study of the intermediate term outcome of AS (Nydén, Billstedt, Hjelmqvist, Gillberg & 2001), but has not been observed in later studies. Recent studies of the short-term outcome of AS have suggested a substantially better outcome than in autism, which may have been due to earlier and more effective interventions, intrinsically better outcome in AS than in autism, or other factors (Starr, Szatmari, Bryson & Zweigenbaum, 2003; Szatmari, Bryson, Boyle, Streiner & Duku, 2003; Tsatsanis, 2003).

Outcome in classic cases of autism has been investigated in number of studies in the past. The rate of poor or very poor psychosocial outcome (isolated life with high degree of dependency on others) has been around 70-90% (e.g. Gillberg & Steffenburg, 1987; Howlin, Mawhood & Rutter, 2000; Howlin, Goode, Hutton & Rutter, 2004), and IQ has been reported to decrease over time (Billstedt, et al., 2005).

Aims of the present thesis

The aims of this thesis were to:

- examine a large number of background and associated factors in AS;

- investigate how different kinds of background factors, such as hereditary and pre-, peri-, and neonatal factors, influence IQ, neuropsychological skills, and psychomotor development in males with AS;

- assess the outcome of individuals with AS in late adolescence/young adult life, and compare it to that of a similarly aged group of males with autism; and

- analyse to what extent males with AS acknowledge problems related to their diagnosis, and whether or not they agree with their parents on these matters.

Methods

Subjects

Overview of cases included in the studies

One hundred males were included in the study of background and associated factors.

These 100 males were also all targeted for inclusion in the follow-up study (see below), but a proportion refused or were not available for study for other reasons, meaning that 76 males participated in the outcome study. Of these, 70 had had the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing, Leekam, Libby, Gould & Larcombe, 2002) completed. They were contrasted with 70 males with autism who had had the DISCO completed when they were in roughly the same age range.

Original diagnostic assessments

All individuals included in the study had been assessed at least five years prior to the follow-up study by experts in the field of autism/AS, working at the CNC, with "autism spectrum instruments" that were state-of-the-art at the time of the diagnostic evaluations. These included in-depth clinical interview in all cases, plus two or more of the following: the Handicaps, Behaviours, and Skills Schedule (Wing, 1980), the Childhood Autism Rating Scale (Schopler, Reichler, DeVellis & Daly, 1980), the Autism Behaviour Checklist (Krug, Arick & Almond, 1980) and the Asperger Syndrome Diagnostic Interview (ASDI) (Gillberg, Gillberg, Rastam & Wentz, 2001). Many had had parent and/or teacher Asperger Syndrome/Autism Spectrum Screening Questionnaires (ASSQs) completed for them. The Autism Diagnostic Interview (ADI) (Le Couteur, et al., 1989), and the DISCO were used in the assessment at original diagnosis only in a small number of cases, because they were not available in Swedish at the time when the oldest individuals in the study originally came for diagnostic assessment.

Procedure when locating cases for the present study

The following procedure was followed in the recruitment of cases for the background and follow-up studies. Our original goal was to include at least 100 males and a sample of at least 30 females with the diagnosis. However, using our inclusion criteria, we could only locate 7 females, and, so, because of the very small number, decided that we would not include them in the present report.

The register of the Child Neuropsychiatric Clinic (CNC) in Göteborg was searched with a view to locating 100 males with AS. The CNC is a state-wide, regional, and local centre for autism spectrum disorder diagnosis and early intervention implementation that has been in operation since 1985. AS has been systematically diagnosed in the clinic (on the basis of criteria that were later published by Gillberg & Gillberg 1989) from 1986. Consecutive cases of males diagnosed with AS at 5.5 – 24.5 years of age (Gillberg & Gillberg criteria) during the years 1985 to 1999, were recruited if they met the following inclusion criteria: a) $\geq$ 16 years of age; b) diagnosed with AS $\geq$ 5 years ago; and c) having a Full Scale IQ (FSIQ) $\geq$ 70. Psychiatric records were reviewed for confirmation of the clinical diagnosis of AS and checking that the relevant diagnostic criteria were met. The final sample included a small group of males originally recruited during the course of a population survey of AS performed in Göteborg (Ehlers & Gillberg, 1993). All these later became clinical patients at the clinic.

Included in the sample were also those five cases (all of whom were patients at the CNC), who had previously participated in a PET-scan study published by the Göteborg group (Happé, et al., 1996). Several individuals had also taken part in the Gillberg (1989) controlled study of Asperger syndrome and autism. However, no data relating to outcome has ever been published on any of the individuals included in the present sample.

The final group of 100 individuals (including the group of 76 participating in the outcome study) are considered representative of clinical cases of AS as they presented (and were diagnosed) during the years 1985-1999. The majority of all cases had been diagnosed with AS in the early 1990s.

Attrition
There was no attrition in the group of 100 males in the study of background factors and sub-grouping for "pathogenetic"/risk factors.

Twenty-four individuals of these originally targeted group of 100 failed to participate in the follow-up study for the following reasons: parent refused participation because his/her son was unaware of the diagnosis (5); mother refused participation in the study because her son did not have the diagnosis anymore (2); did not want to participate in the study (14); failed to attend two appointments (1); did not respond to telephone calls or letters (2).

The study of background and associated factors (I)

The medical records of the 100 males with AS were systematically reviewed for information. The following information was distracted: (1) age at diagnosis; (2) social demographic factors; (3) familial/hereditary factors (as reported for "close relatives" = first- and second-degree relatives); (4) maternal age at birth of child; (5) pregnancy complications; (6) gestational duration; (7) perinatal and neonatal events; (8) weight, length, and head circumference at birth; (9) early development; (10) presence of macrocephalus at diagnosis; (11) body mass index (BMI) at diagnosis; (12) co-existing psychiatric diagnoses and problems; (13) physical findings and medical disorder/laboratory findings at the time of original diagnosis; (14) ASSQ scores; (15) neuropsychological test results including Full Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ); and (16) education.

The study of pathogenetic/risk factor subgroups (II)

This sub-study was conducted for the purpose of investigating whether or not "pathogenetic subgroups" defined according to strict criteria, could be identified within the broad group lumped under the strictly behaviourally defined group of AS. The aim was also to investigate whether these pathogenetic subgroups – if identifiable - could be differentiated from each other on a number of different, independent items: (1) age at diagnosis; (2) age at unassisted walking; (3) late speech onset; (4) mean FSIQ; (5) non-verbal learning disability, percentage of individuals with a difference of ≥15% between VIQ and PIQ, and (6) ASSQ score.

The outcome study (III)

This comparative sub-study of outcome included two groups of males, one originally diagnosed with AS (AS group), and one originally diagnosed with Autism or Atypical Autism (Autism group) (both groups diagnosed more than 5 years ago. In the AS group – recruited from the group of 100 individuals included in sub-studies I and II - the follow-up period was 5-19 years (mean 9.8 years). The individuals in the Autism group were followed up for a similar, but, statistically, slightly longer period of time (13-22 years). The autism cases were recruited from a group of originally 84 males (3 of whom had died, and 4 of whom refused

follow-up) with autistic disorder/atypical autism followed up with a partly identical protocol to that used in the follow-up of the males with AS (Billstedt, et al., 2005). Of the 76 individuals, in the AS group, who participated in the follow-up study, 70 had had a DISCO-interview (see below), and they were selected for comparison, with those 70 males from the Autism group, closest in age to the AS group, who also had had a DISCO-interview performed. Outcome was analysed and compared on the basis of results obtained at these DISCO-interviews.

The interview and questionnaire study (IV)

The final sub-study was based on interview, and questionnaires administered to all those of the 100 males with AS and their parent(s), who agreed to participate in the follow-up study. Results from (1) seven items of the ASDI, i.e. those that are common to the teenage/adult and parent interview versions (items 1, 2, 3, 4, 5, 8, and 9) (Gillberg, et al., 2001); (2) the Leiter-R, self- and parent assessment questionnaires (Roid & Miller, 1997); (3) the Beck´s Depression Inventory (BDI) (Beck & Steer, 1996), and (4) the Dysexecutive Syndrome Questionnaire (DEX; from the Behavioural Assessment of the Dysexecutive Syndrome (BADS)) (Wilson, Alderman, Burgess, Emslie & Edwards, 1999) were analysed. In this sub-study 64 males with AS and their parent(s) were included in the ASDI part, 63 in the Leiter-R part, and 71 males (no parents) were included in the BDI and the DEX parts of the sub-study.

Diagnostic criteria used

For the diagnosis of Asperger Syndrome, in all the studies, the criteria for AS, developed by Gillberg & Gillberg (1989/1991), were used, both to confirm that a diagnosis of AS was present at original diagnosis and at follow-up. The DSM criteria for autism were also used in substudies III and IV (DSM-III (APA, 1980); DSM-III-R (APA, 1987); DSM-IV (APA, 1994)) (See Introduction, and below). For non-autism psychiatric diagnoses, the criteria of the DSM-IV were used.

Instruments used

Proforma for reviewing *medical records (I, II)*

A proforma was developed for reviewing the medical-psychiatric records as regards the 16 factors referred to above (page 18). ”Close relatives” was defined as first- or second-degree relatives.

Proforma for pathogenetic/risk factor sub-grouping (II)

Subgroups were defined before data analysis according to the following criteria:

(1) Medical syndromes/chromosomal abnormalities: cases with a known medical syndrome, a combination of stigmata suggesting a syndrome, or a chromosomal abnormality visible at karyotyping;
(2) Definitely familial/genetic: cases with at least one first- or second-degree relative who had been formally clinically diagnosed with autistic disorder or AS;
(3) Probably familial/genetic: cases with at least one first- or second-degree relative who had not been formally clinically diagnosed, but for whom sufficient information (full symptom description) was available in the medical records to strongly suggest a diagnosis of autistic disorder or AS;
(4) Possibly familial/genetic: cases with at least one first- or second-degree relative who had not been formally clinically diagnosed, but for whom some information (several symptoms but not full criteria) was available in the medical records to suggest a diagnosis of autistic disorder or AS;

(5) Pre-/perinatal combined with familial/genetic: cases with documented asphyxia (Apgar scores under 10 for more than 10 minutes, and at least one score of 6 or under at 1, 5, or 10 minutes), severe prematurity (32 weeks gestation or under), birth weight under 1500g, severe maternal alcoholism and newborn signs of fetal alcohol syndrome (FAS) or fetal alcohol effects (FAE), congenital hypopituitarism or hypothyroidism not treated from first month of life, ablatio placentae or threatening ablatio with bleedings throughout pregnancy, ecclampsia and pre-ecclampsia with raised blood pressure, proteinuria, and generalised oedema, neonatal septicaemia, cerebral haemorrhage or neonatal seizures *in combination with* (2), (3) or (4) above;
(6) Pre-/perinatal only: cases with any of the pre-/perinatal conditions listed under (5), *but not combined with* (2), (3) or (4) above;
(7) No clear clue: cases not falling into any of the above groups.

The Diagnostic Interview for Social and Communicative Disorders (DISCO-10) (III)
The DISCO is a 2-4 hour investigator-based interview, developed by Lorna Wing, Judith Gould, and colleagues, intended for use with a person (often a parent), who knew the individual with a suspected autism spectrum disorder from early childhood. The DISCO-10 has excellent inter-rater and test-retest reliability, and is highly valid for assigning diagnoses in the autism spectrum (Wing, Leekam, Libby, Gould & Larcombe, 2002). It also includes sections on common co-existing problems in autism. The DISCO was chosen in favour of the Autism Diagnostic Interview (ADI) (Le Couteur, et al., 1989) because the latter was designed for use in the diagnosis of classic autism, whereas the DISCO includes a range of items intended to detect milder forms of autism spectrum disorders. In addition, the DISCO has a developmental perspective and is designed for use from early childhood into adult life (Wing, et al., 2002).

The Wechsler scales (I, II, III, IV)
The Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974), the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) (Wechsler, 1992), the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1999), were used in this study. The Wechsler scales are the most widely used psychometric instruments. The scales provide measures of global intelligence (FSIQ), and in addition both verbal (VIQ), and performance (PIQ) sub-scores. The WISC-R, WISC-III, and the WAIS-R comprise the following subtests in the verbal part: Information (IN), Similarities (SM), Arithmetic (AR), Vocabulary (VO), Comprehension (CM), and Digit Span (DS). In the performance part the following subtests are included: Picture Completion (PC), Picture Arrangement (PA), Block Design (BD), Object Assembly (OA), and Coding (CD). In the WAIS-III the subtest Matrix Reasoning (MR), has been added to the former performance tests, and Letter-Number Sequencing (LS) to the verbal tests. The WISC-R, WISC-III and WAIS-R were used for 40, 52, and 8 individuals respectively in the original AS assessments. At follow-up all the 71 tested individuals had the WAIS-III administered. In the Autism study group only a minority could be tested on the Wechsler scales (WAIS-R or WISC-III) at follow-up, and the majority were categorised in terms of IQ/DQ/SQ-band using the Vineland Adaptive Behaviour Scales (see below).

Kaufman factors (I)
In the retrospective study, in which information was collected from the medical records, exploration of the WISC-R, WISC-III, and the WAIS-R results from the testing at original diagnosis relative to Kaufman's factor analytic concept of Verbal Comprehension (IN, CM, SM and VO), Perceptual Organisation (PC, PA, OA and BD), and Freedom from Distractibility (CD, AR and DS) (Kaufman, 1990; Lincoln, Allen & Kilman, 1995) factors, was performed.

The Asperger Syndrome/Autism Spectrum Screening Questionnaire (ASSQ) (I, II)
This questionnaire was developed by Ehlers and Gillberg (Ehlers & Gillberg, 1993), and further tested by Ehlers, Gillberg & Wing (Ehlers, Gillberg & Wing, 1999), and Posserud, Lundervold & Gillberg, 2006), in collaboration with special teachers in Göteborg, and teachers in Bergen, respectively. It contains 27 items rated on a 3-point scale (0, 1, 2; where 0 indicates normality, 1 some abnormality, and 2 definite abnormality). The range of possible scores is 0-54. The items included are those considered to best reflect impairments in social interaction, communication, behaviour, and circumscribed interests in children 7-16 years of age. In addition, some items reflecting frequently associated features (including motor and vocal tics) were included. This questionnaire was designed for completion by lay informants, and needs no training before completion. Cut-off scores for this questionnaire was established (Ehlers, et al., 1999) to be 19 points for parent scoring and 22 points for teacher scoring in school children 7-16 years of age. However, the results from the recent study from Bergen, Norway, on a very large population of children, indicates that a cut-off level of about 15 points might be the most useful level for identifying possible ASD cases, at least in children of young school-age (Posserud, et al., 2006).

The Global Assessment of Functioning (GAF) scale (III, IV)
The DSM-IV Global Assessment of Functioning scale (GAF) (APA 1994) was used conjointly by the first and second author in all cases in the AS group and conjointly by the third and fourth author in all cases in the Autism study group. This measure yields scores from 0-100, where a score of 70 and above, indicates good functioning or only mildly abnormal psychosocial situation. In this study the GAF scale was used separately from other diagnostic instruments, so as to determine if GAF-scoring would differ in groups of individuals with ASD and non-ASD. Most GAF-studies have found it to be a reliable and useful instrument in measuring a person´s psychosocial functioning, requiring only minor pre-scoring information (e.g. Hilsenroth, Ackerman, Blagys, Baumann, Baity, Smith, et al., 2000; Startup, Jackson & Bendix, 2002; Billstedt, et al., 2005).

Vineland Adaptive Behavior Scales (VABS) (III)
The VABS (Sparrow, Balla & Cicchetti, 1984) is a semi-structured interview with a parent/caregiver of an individual that offers a comprehensive assessment of adaptive behaviour and systematic basis for preparing individual habilitation or treatment programs. For those individuals in the Autism group included in this thesis who could not be tested on the Wechsler scales intellectual ability was assessed using the VABS, and cases were categorised in DQ/SQ bands (Developmental Quotient/Social Quotient) on the basis of the results on the VABS.

The VABS has been reported to be a valid instrument in establishing the cognitive level for an individual functioning at an IQ-level below 70-75 (APA, 1994; Luckasson, et al., 1992). The VABS has also been widely used to map the overall functioning of an individual in socialization, communication, and daily living skills, regardless of IQ in order to be used as a

prognostic and intervention tool for habilitation (Rhea, et al., 2004; Balboni, Pedrabissi, Molteni & Villa, 2001; Gilotti, Kenworthy, Sirian, Black & Wagner, 2002).

Outcome criteria (III)
The criteria used for the classification of outcomes, were similar to those employed in an earlier study of autism in our centre (Gillberg & Steffenburg, 1987), which was based on the outcome criteria published by Lotter (Lotter, 1978). Reliability studies – to our knowledge – have not been performed on the use of these criteria. The classifications were based on all available information (including the DISCO) at the time of examination.

The outcome criteria were:
(a) being employed or in "higher" (age and IQ-appropriate ("normal")) education or vocational training, and
(b) if 23 years of age or older, living independently, or if 22 years or younger, having two or more friends/a steady relationship.
Good outcome: both (a) and (b);
Fair outcome: either (a) or (b), but not both, under good outcome;
Restricted outcome: neither (a) nor (b) under good outcome, and not meeting criteria for a major psychiatric disorder other than autistic disorder or another autism spectrum disorder (ASD). This category refers to a group of people with the characteristics of poor outcome, but who have been accepted by a group of peers or personnel to such an extent that their handicaps are not so readily obvious;
Poor outcome: Obvious severe handicap, with either of, no independent social progress or presence of a major psychiatric disorder, but with some clear verbal or non-verbal communicative skills;
Very poor outcome: Obvious very severe handicap, unable to lead any kind of independent existence, no clear verbal or non-verbal communication.

Asperger Syndrome Diagnostic Interview (ASDI) (IV)
The ASDI (Gillberg, et al., 2001) is a diagnostic interview containing 20 items based on the Gillberg & Gillberg criteria for AS, subdivided into six areas covering problems with social interaction, narrow interests, imposing of routines/rituals, speech and language peculiarities, non-verbal communication problems, and motor problems. Each item is scored 1, 2 or 3. A score of 1 represents "does not apply", 2 "applies sometimes or somewhat", and 3 "definitely applies. In this thesis, a small sub-study comparing the teenage/adult version and the parent version of the ASDI only presents data from about one third of the items included at the follow-up. Seven of the 20 ASDI items (items 1, 2, 3, 4, 5, 8 and 9) were selected, because they are comparable across the teenage/adult and parent versions (in the teenage/adult version the interviewer scores all remaining items based on the clinical impression of the teenager/adult). The selected items cover problems with social interaction (item 1-4), narrow interests (5), and imposition of routines/rituals (8-9). Items were presented, on separate occasions, in a similar fashion, and by the same interviewer (first author), to both the male with AS and the parent(s). The interviewer did not interfere in the scoring process, except to make clarifications about the questions, whenever needed. Total ASDI scores for the 7 item-scale were calculated (7-21). All (but two) of the cases (n=66) for whom there were interview data and questionnaires both from the individual with AS and his parent(s) were selected for comparison. One man was excluded, because it was obvious, during the ASDI-interview, that he did not possess sufficient intellectual ability to understand and interpret the questions in a proper way (he had MMR). Another case was excluded because the parent ASDI had not been

completed. Thus, altogether 64 individuals with AS and their parent(s) were left for comparison.

Leiter-R self- and parent-assessment questionnaires (IV)
The Leiter-R self- and parent questionnaires (Roid & Miller, 1997), contain 35 and 51 items respectively. Each item is scored 1, 2 or 3, low scores indicating more "abnormality". For both questionnaires raw scores were collapsed into two groups covering "cognitive/social skills" and "emotional/adaptive skills". Raw scores were transformed into standard scores, making comparison of types of skills across results from both self- and parent questionnaires feasible. I distributed the self- assessment questionnaires to the males with AS, and the psychologist gave the parent assessment questionnaires to the parents. All Leiter-R questionnaires (n=66) for which both the male with AS and his parent(s) had responded were selected for comparison. In 2 cases the male with AS had failed to answer all questions on the backside of the questionnaire, and in one case a mother did not receive it. These three cases were excluded from the comparison, leaving 63 for analyses.

Beck Depression Inventory (BDI) (IV)
This revised version of the original BDI (Beck & Steer, 1996) is an instrument that contains 21 items, which are scored 0-3 (range of scores 0-63), and has been constructed so as to measure the degree of depression in adolescents, and adults. It has become one of the most widely used instruments in clinical psychology and psychiatry. It has been used to investigate the prevalence of depression in various population studies. The BDI was given to all males with AS, who participated in the study. Questions were scored according to recommendations in the BDI manual, (if more than one number was ticked, the highest number was chosen). Total scores were allocated to "depression severity groups" based on earlier studies (Olsson & von Knorring, 1997; Gorenstein, Andrade, Zanolo & Artes, 2005): "*no depression*" ≤15 p, *"dysphoria"* 16-20 p, *"depression"* 21- 29 p, and *"severe depression"* ≥30. All participants scoring ≥16 p on the BDI, and/or were clinically judged to have depressive feelings were referred for further psychiatric assessment at the CNC, where a clinical diagnosis of depression was made according to the DSM-IV in cases meeting diagnostic criteria for that disorder. All participating males with AS (n=71) were included in this part of the study.

Dysexecutive Syndrome Self Assessment Questionnaire (DEX) (IV)
The DEX *(Wilson, et al., 1999)* is a 20-item self-assessment questionnaire (possible scores 0-80) "constructed to sample the range of problems commonly associated with the dysexecutive syndrome", especially aspects of executive dysfunctions as they present in daily life (Wilson, Evans, Emslie, Alderman & Burgess, 1998). Items are scored 0-4 on a Likert scale ("never" (0), "occasionally" (1), "sometimes" (2), "fairly often" (3), and "very often" (4)), where a higher score indicates more daily life problems. Scores were collapsed to provide a "total score", and sub-scores for four areas ("*Behaviour*" (item 2,7,9,12,13,15,16,20), "*Cognition*" (3,6,14,18,19), "*Emotion*" (5,8,11) and "*Motivation*" (1, 4, 10, 17)). In addition, a five factor subdivision system was used (Burgess, Alderman, Evans, Emslie & Wilson, 1998): Factor 1 (*Inhibition*: item 1, 2, 9, 13, 15, 16, 20), Factor 2 (*Intentionality*: item 4, 7, 17, 18, 19), Factor 3 (*Executive Memory*: item 3, 6, 14), Factor 4 (*Positive Affect*: item 5, 10, 12), Factor 5 (*Negative Affect*: item 8, 11). The DEX was distributed to all participating males with AS (n=71) by the first author.

Ethics

All of the studies from which the information of this thesis was taken were approved by the Medical Ethics Committee of Gothenburg University.

Statistical Analyses

$p<.05$ were used as minimum significance level in all the sub-studies. Chi-square tests (with Yates's correction whenever appropriate) were employed in the comparison of group frequencies. Multiple comparisons in study I and II were re-evaluated using the Bonferroni or the Tukey-Kramer test to adjust for false positive significances. Wilcoxon's rank sum test was used for comparing mean age, and of outcome, of AS and autism groups at follow-up in study III. Analysis of covariance was used to adjust for age when comparing outcome in study III. Fisher's exact tests were used when comparing means in study IV. Correlation coefficients were calculated in some cases in study IV.

Results

The study of background and associated factors (I)

(1) Age at original diagnosis

Mean age at original diagnosis was 11.3 years (SD 3.8 years, range 5.5 y – 24.5 y). Eighty-nine percent of the individuals were younger than 15 years at original diagnosis.

(2) Social demographic factors

Parent occupation was registered in 84 cases concerning the fathers and in 98 cases concerning the mothers. Fifteen of the fathers (18%) were "engineers". Altogether, "engineer" was the most common parent profession (17 children had a father or a mother who was an "engineer"), followed by "nurse" (n=11) and "teacher" (n=10).

Two of the boys were in foster-homes, both because of alcohol abuse in the mothers. None of the boys in the study was adopted. Two had been born in another country (Chile and Great Britain). In 17 cases one or both parents had been born outside Sweden (11 mothers and 11 fathers). A total of 8 individuals had mothers/fathers who came from Finland, 3 from Poland, 2 each from France, Great Britain and Chile, and, finally, one each from the Czech Republic, Yugoslavia, Hungary, USA and India. None of the mothers had migrated to Sweden during the pregnancy.

(3) Familial/hereditary factors

(i) Autism spectrum problems

The study group included two pairs of brothers with AS. In 70 cases there was at least one relative (parent, sibling, grandparent, cousin, grandparent's sibling or their children), who had (had had) documented major problems in the field either of (one, two or three) of (autistic-like) social interaction, reciprocal communication and/or behaviour/interest patterns (the broader autism phenotype) (LeCouteur, et al., 1996). Four of these 70 families contained at least one individual (1 brother, 2 sisters, and 1 sibling of a grandparent), who had been diagnosed as suffering from childhood autism. Another 8 families included at least one individual formally diagnosed with Asperger syndrome or atypical autism. In 28 families there was at least one relative with full symptom description consistent with a diagnosis of AS, according to the examining doctor and based on the criteria by Gillberg & Gillberg (1989/1991), (5 brothers, 1 sister, 15 fathers, 1 paternal uncle, 3 maternal grandfathers, 1 maternal grandmother, 1 maternal aunt and 1 maternal cousin). The remainder (n=38) had at least one relative with one to five (usually two to four) symptoms of autism as listed in the DSM-IV.

(ii) Learning problems

Reports of learning problems in close relatives were frequent: reading/writing disorders and/or dyscalculia (32 cases), learning disability (12, 3 of whom had Down syndrome), and late development of language (11).

(iii) Psychiatric problems

Psychiatric problems – diagnosed by psychiatrists according to report by parent (usually the mother) - were quite common among close relatives: depression requiring medication (15

cases), schizophrenia (2), hypomania (3), mania (1), severe alcoholism (13), and drug addiction (3). Other psychiatric disorders (16, panic attacks, paranoia, psychosis, and unspecified psychiatric problems). Many of these individuals had been hospitalised and were highly suspicious to have had a severe psychiatric illness, but descriptions in the medical records were too limited to arrive at a more specific diagnosis. In 5 cases a relative had committed suicide. Other co-existing disorders were: anorexia nervosa (2), ADHD (1), "hyperactivity" (9), tics (4), and OCD (1).

(iv) Epilepsy
Seven boys with AS had a close relative with epilepsy documented in the medical records.

(4) Maternal age at birth of child
Mean maternal age at time of birth of the index child was 28.5 years (SD 4.2) (n=93) range 18.5-41.5 years, compared to 27.6 years (SD 0.8) in the general population during this period (Swedish Medical Birth Registry 2004; Statistics Sweden 2004).

(5) Pregnancy complications
Major infections (10 cases, e.g. suspected mumps, suspected HSV II infection, influenzae A infection, streptococcal tonsillitis, pyelonephritis). Second and third trimester bleedings (10), and preeclampsia (10), occurred at approximately double the rate seen normal pregnancies (Berglund & Lindmark, 2000). Other complications during pregnancy: nephrolithiasis (3), sciatic pain (2), diabetes mellitus (1), Crohn's disease (1, the mother of two boys with AS), alcoholism (2). One mother fainted twice during the sixteenth week of pregnancy. There was one twin pregnancy. Alfa-fetoprotein was elevated in one mother, who suffered bleedings in the first and second trimester and trauma against the abdomen in the 6th month of pregnancy. This child was later found to have ataxic diplegia**.** Infertility problems were reported in a small group (4).

(6) Duration of pregnancy
Nineteen per cent had been born either prematurely (≤ 36 weeks) or postmaturely (≥ 42 weeks), compared to approximately 11% of children in the general population in the years studied (Swedish Medical Birth Registry, 2001).

(7) Perinatal and neonatal events
(i) Parturition data
"Normal delivery" (without induction) occurred in 63%, compared to 80% in the general population. Caesarean section had been performed in 17% of the cases, compared to 10.4% of deliveries in the general population over the period studied (Swedish Medical Birth Registry, 2001). The vast majority of the boys in our study were born at a University clinic, where Caesarean section occur more often (15%). Of the caesarean sections 7 were emergencies (ablatio placentae (2), threatening asphyxia (4) and suspected maternal HSV II infection (1)), and 10 were performed electively. Instrumental delivery (vacuum extraction (10); forceps delivery (1)). In the general population approximately 6% had an instrumental delivery (Swedish Medical Birth Registry, 2001). Breech presentation (5), which was double the incidence compared to the normal population (Berglund & Lindmark, 2000).

(ii) Apgar scores
The frequency of postnatal asphyxia at one minute was about twice that seen in the general population, and the frequency of individuals scoring ≤ 7 Apgar points at 1 and 5 minutes,

respectively, was also higher than within the normal population (Berglund & Lindmark, 2000; Swedish Medical Birth Registry, 2001).

(iii) Neonatal events

Twenty-four of the newborns had been admitted to a paediatric ward because of various problems (treatment of hyperbilirubinemia uncounted), but only 11 of these (including 7 with premature birth) had been treated for more than 3 days. Respiratory problems (9) was the most common cause of admission to paediatric care, followed by suspected infection (3), postnatal asphyxia (2), and seizures (2). Twenty-two had hyperbilirubinemia (plasma bilirubin > 200 μmol/l), but only 10 had a medical record of having been treated with phototherapy. Hyperbilirubinemia occurs in about 10% of neonates in the general population (Clarkson, Cowan & Herbison, 1984).

(8) Birth-weight, length, and head circumference

The mean weight, length, and head circumference at birth was approximately the same as for the general population of boys born during the relevant period (Swedish Medical Birth Registry, 2001). Three boys had a head circumference above the 97.5th percentile (Knudtzon, Waaler, Skjaerven, Solberg & Steen, 1988).

(9) Early development.

Mean age at walking unsupported was 13.8 (SD 3.2) months (n=85), which is later than in the general population, where the mean age for independent ambulation is around 12 months of age (Stanitski, Nietert, Stanitski, Nadjarian & Barfield, 2000; Carruth & Skinner, 2002).

Forty-five children out of 92 (49%) for whom fairly detailed data about early language development was available clearly did not have normal language development at 2 years of age.

(10) Presence of macrocephalus at diagnosis

Twelve of 78 boys (15%) who had had their head circumference recorded at the time of diagnosis of AS had a head size corresponding to the 97.5th percentile or higher (Knudtzon, et al., 1988). Mean head circumference for the study group was 55.1cm (SD 2.4) (which at 11.3 years is slightly above the 60th percentile compared to Scandinavian growth charts (Knudtzon, et al., 1988)).

(11) Body Mass Index (BMI) at diagnosis

For 94 boys, height and weight were registered at the time of diagnosis. Twenty-three boys (24%) had a Body Mass Index (BMI) for age above the 90th percentile, 18 of whom had a BMI above the 97th percentile. Three were below the 10th percentile, and one additional was below the 3rd percentile. This was in contrast to earlier reports (Bolte, Ozkara & Poustka, 2002; Hebebrand, et al., 1997; Sobanski, Marcus, Henninghausen, Hebebrand & Schmidt, 1999).

(12) Co-existing diagnoses and problems at original assessment

Thirty-three cases had a registered additional diagnosis (six of these had more than one additional diagnosis). At the time of the original diagnosis of AS at the CNC, co-existing diagnoses were registered in cases where it was felt that an additional diagnosis contributed equally to the impairment of the child as did the condition of AS per se. This means that the

result represents a very conservative estimate of co-existing disorders in AS. Tic disorders were the most commonly registered additional diagnoses (Tourette syndrome in 10 and simple tics in 6 cases). Only 4 cases of ADHD were recorded. However, the Wechsler profiles showed poor results on the Distractibility factor in a majority of all cases, *suggesting* a strong link between AS and ADHD symptoms.

(13) Physical findings and medical disorder/laboratory findings at the time of diagnosis

(i) Neuroimaging

SPECT had been performed in 16 cases, 15 of whom showed "abnormal" results (without there being any indication of abnormality on MRI (n=1) or CT (n=6) in those 7 who were exposed to these more "neuroanatomical" investigations). The most common SPECT-finding was pronounced hypoperfusion in the temporal region (n=14), with left-sided predominance in 9 cases and right-sided predominance in 5 cases. There was additional hypoperfusion in the frontal lobe (6 cases), parietal lobe (4), and the occipital lobe (7), with an even distribution of the observed hypoperfusion except for the occipital lobe where there was a right-sided predominance in a majority of the cases. MRI was pathological in 2 out of 9 cases (one individual had a widened perivascular spatium close to the temporal horns bilaterally, and in the putamen/globus pallidus; and one had a malformation of the cerebellum). CT was considered “non-pathological” in all 30 cases performed.

(ii) Neurophysiology

EEG:s was pathological in 36% of examined cases, and in 13% of those examined clear epileptogenic discharges were seen. Auditory Brainstem Responses (ABR) was pathological in 18% compared to approximately 2 % of the general population of children (Rosenhall, Nordin, Brantberg & Gillberg, 2003).

(iii) Chromosomal examinations

Chromosomal analysis for Fragile X had been performed in 52 patients and all had been found to be negative. There was no clinical suspicion of this syndrome in the remaining 48 cases. Karyotyping had been pathological in 5 out of 53 examined cases. Three of these 5 were translocations - one with (1;15)(p32.1;q24.1) (mother had same abnormality and recognized that she had some similarities with her son, but so did the father and he had no chromosomal abnormality), one with (13;17)(q1;p1) (de novo) (this boy had a sister with autism, a mother with anorexia and an aunt (mother´s father´s half-sister) with learning disability, and one boy with (5;11)(q13;q13.3) (father with AS symptoms had similar (5;11)(q14;q14.4). One boy had fragile Y (father had the same, but there was no report of AS-problems in the father in the medical records), and one had 21p+ (with the extra chromosomal material originating from chromosome 15), and was described as “a copy of his father”, but the father had no chromosomal abnormality.

(14) ASSQ results at diagnosis

Parents had completed the ASSQ for 79 of their sons at the time of the original diagnosis. The range of scores in this group was 5-43, and the mean 23.3 (SD 8.7). Sixty-six per cent had a score of 19 or above (which has been shown to be strongly associated with a diagnosis of AS or another autism spectrum disorder). A full 82% had scores of 15 or above. In the general population, ASSQ scores are very much lower (Ehlers and Gillberg, 1993). The highest scores were found in the 10-15 year old group 23.9 (SD 9.2) (n=39). The scores were lower in the 5-9 year-old group 20.2 (SD 10.2) (n=31) and in the 16 years-and-above age group 20.5 (SD 9.1) (n=9). In twenty-seven cases, the ASSQ had been completed both by a parent, and a

teacher. In these cases the parents scores mean result was 21.5 (SD 9.5) and the teacher scores mean was 27.0 (SD 9.6).

(15) Neuropsychological test results at diagnosis
FSIQ-scores did not differ significantly across the three different Wechsler scales used (Table 2). There were significant VIQ over PIQ differences on all three scales ($p<.001$ for the child scales, $p<.05$ for the adult scale). Fifty of the 98 boys (51%) had a VIQ>PIQ discrepancy of 15 points or more; in 30 of these the difference was of 20 points or more. Six individuals had a PIQ>VIQ difference of 15 points or more, and five of these had a difference of 20 points or more. The VIQ>PIQ versus PIQ>VIQ difference was highly significant ($p<.001$). There were also significant differences across the 3 Kaufman factors Verbal Comprehension (11.6, SD 3.2), Perceptual Organisation (9.6, SD 2.7), and Distractibility (8.5, SD 2.9) ($p<.01$).

Table 2. Results on the Wechsler scales in 98 cases of AS at original diagnosis

Test used	*N*	*Mean FSIQ (SD)*	*Mean VIQ (SD)*	*Mean PIQ (SD)*	*Sign.diff. VIQ>PIQ*
WISC-R	38	105 (19.2)	110 (19.3)	98 (20.4)	p<.001
WISC-III	52	98 (17.5)	104 (18.5)	91 (16.7)	p<.001
WAIS-R	8	106 (18.3)	110 (15.9)	99 (19.7)	p<.05
All	98	101 (18.4)	107 (18.7)	95 (18.7)	p<.001

Given the mean IQ of 101 in the AS group, we considered all subscale scaled scores (range 1-19, mean 10) of 7 or under as being indicative of an unexpectedly poor performance. Coding (Digit symbol) was the subtest that most consistently (54% of all cases) showed a trough (Table 3). We tested all subscale scores against all other subscale score, and found 40 significant differences ($p<.05$; the Tukey-Kramer test was used to adjust for the effect of multiple comparisons).

Table 3. Wechsler scales subtests at original diagnosis

Subtest	*Mean result*	*N (%) with scaled score ≤ 7*	*p<.05*	*p<.01*	*p<.001*
Verbal subtests					
IN (Information)	12.3	12/85 (14%)	AR, PA	DS, OA	CD
VO (Vocabulary)	12.2	9/84 (11%)		AR, PA	DS, OA, CD
AR (Arithmetics)	9.4	29/84 (35%)	IN, SM, CD	VO	
CM (Comprehension)	10.5	18/85 (21%)			CD
SM (Similarities)	11.2	12/85 (14%)	AR, PA	DS, OA	CD
DS (Digit Span)	8.9	32/80 (40%)		IN, SM	VO
Performance subtests					
PA (Picture Arrangement)	9.5	31/92 (34%)	IN, SM, CD	VO	
PC (Picture Completion)	9.7	18/91 (20%)			CD
OA (Object Assembly)	8.6	35/92 (38%)		IN, SM	VO
BD (Block Design)	10.5	21/92 (23%)			CD
CD (Coding)	7.3	49/90 (54%)	AR, PA		IN, VO, CM, SM, PC, BD

The proportion with a low result on each subtest was tested individually against the whole proportion with a low result on each of the other subtests (p values refer to these X2 tests comparing proportions). The Tukey-Kramer test was used to adjust for the effect of multiple comparisons

(16) Education/special education

The vast majority of cases were of compulsory/comprehensive school age at the time of first diagnosis (n=82). Since all the schoolboys were of normal or near normal IQ they would have been expected to attend mainstream classrooms without special education support. However, this applied in only 42 of the 82 individuals. The others had (or had had), an assistant in the class-room (half- or full-time) (13), special education provided by a special education teacher in the mainstream classroom (9), special needs classrooms or schools (9), classrooms for individuals with autism spectrum disorders (3), schools for children with learning disability (3), individual education with the help of an assistant (1), special education or service provision specifically because of their social and communication problems (2).

The study of pathogenetic/risk factor subgroups (II)

Pathogenetic subgroups

The attempt to subgroup cases into seven different “pathogenetic”/risk factor subgroups is shown in Table 4.

Table 4. Pathogenetic/risk factor subgroups

Subgroup	n	accumulated %
(1) Medical syndrome/chromosomal	8	8
(2) Definitely genetic/familial	12	20
(3) Probably genetic/familial	19	39
(4) Possibly genetic/familial	24	63
(5) Probably/possibly genetic/familial + pre- perinatal risk	11	74
(6) Pre- perinatal risk only	13	87
(7) No clear clue	13	100

(1) Medical syndromes/chromosomal abnormalities
The eight individuals in this subgroup included three with obvious syndromes and the five with chromosomal abnormalities (presented above under study I). One patient, had Rubinstein-Taybi syndrome; one had hypospadia, ptosis and coloboma of the left eye, and had been extremely floppy at birth; and one had a suspected Greig syndrome (born at 33 weeks gestation, macrocephalus, operated craniomeningocele, polydactylia, slight hypertelorism, and epilepsy) (Debeer, et al., 2003). Three patients in this group (the Rubinstein-Taybi syndrome, suspected Greig syndrome, and Fragile Y cases) had no index of familial autism spectrum disorder.

(2) Definitely familial/genetic
All 12 individuals in this subgroup had a close relative with diagnosed autistic disorder or AS. Nine of these had a first-degree relative, and 3 had first-cousins. In seven of those with diagnosed first-degree relatives there was at least one further first-degree relative with a strong suspicion of (undiagnosed) autistic disorder or AS.

(3) Probably familial/genetic
The 19 cases in this subgroup included 12 with one or more first-degree relatives raising strong suspicion of meeting full criteria for autistic disorder or AS. The vast majority of these (n=12) were the fathers of the patients, who had usually been seen by the experienced clinician diagnosing the index case at the time of the original diagnosis).

(4) Possibly familial/genetic
The 24 patients in this subgroup had one or more first- and/or second-degree relative raising some suspicion of suffering from autistic disorder or AS. These were equally distributed across the paternal and maternal lines of the families.

(5) Pre-/perinatal combined with familial/genetic
This group of 11 patients comprised only those individuals with severe pre- and/or perinatal problems and a family history suggestive or strongly suspect of autistic disorder or AS. Except for one case where the mother probably had AS, the family history was always paternal, and involved the father having probable or possible AS in 8 cases.

(6) Pre-/perinatal only
The 13 males in this group all had severe indices of pre- and/or perinatal risks but no family history suggestive of autism spectrum disorder.

(7) No clear clue

There were 13 individuals in the group with no clear clue as to pathogenetic risk factors (as defined in the present context). However, one of these was born after 34 weeks gestation, developed hyperbilirubinemia and received phototherapy. His mother had been treated for infertility for 7 years and had had spontaneous abortions both before and after the pregnancy resulting in the boy with AS. Another boy in this group had a mother with mild signs of preecclampsia, one further boy had indirect signs of prenatal asphyxia (meconium-stained amniotic fluid), and one had a mother who ran a high temperature prompting artificial induction of parturition.

Validating subgroups against certain external clinical indices and neuropsychological tests

There were few associations of "pathogenetic" subgroup with particular clinical findings or neuropsychological tests that were independent of the subgroup definitions (Table 5). We looked at age at diagnosis, age at walking unsupported, record notes of not talking in sentences at 2 years, full-scale IQ (FSIQ), verbal over performance IQ discrepancy of 15% or more (as an index of possible non-verbal learning disability/NVLD), and ASSQ scores.

Table 5. Pathogenetic/risk factor subgroups against external validating criteria

Subgroup and n	*Diagnosis age years (SD)*	*Walking age months (SD)*	*Late talking (after 24 months) %*	*FSIQ (SD)*	*NVLD %*	*ASSQ score (SD)*
(1) 8	11.4 (2.9)	17.3* (3.9)	50	96.4 (20.1)	50	27.6 (5.6)
(2) 12	10.5 (3.8)	13.5 (4.2)	42	100.5 (17.9)	42	23.4 (10.4)
(3) 19	11.0 (2.8)	13.5 (2.9)	41	105.2 (18.8)	63	26.8 (9.4)
(4) 24	11.5 (4.7)	12.2 (1.5)	42	106.3 (20.0)	54	22.1 (8.0)
(5) 11	11.1 (3.1)	13.6 (2.4)	60	92.2 (6.9)	27	23.6 (9.3)
(6) 13	12.3 (2.9)	15.3 (3.7)	54	102.6 (17.5)	69	21.4 (6.5)
(7) 13	11.5 (5.5)	13.6 (2.3)	64	96.6 (20.1)	38	18.7 (8.5)

Diagnosis (n.s.); Walking (*p< .01 (1) vs (4)); Talking (n.s.); FSIQ (n.s); NVLD (n.s.); ASSQ (n.s.)

There was only one significant difference across these groups on the independent items assessed. The *possibly familial/genetic group* walked significantly earlier than the *medical syndromes/chromosomal group*. However, the males in the *definitely familial/genetic group*, were diagnosed somewhat earlier, than the males in the other groups, probably because the definitive clinical ASD diagnosis of a relative had brought the attention to the child´s (similar) problems earlier.

The *pre-/perinatal combined with familial/genetic factor group* had a lower FSIQ, and the percentage of individuals with clear NVLD was lower in this group. In addition the percentage of late talkers was higher in this group. The *pre- and/or perinatal factors only group* resembled the "familial only" groups both as regards mean FSIQ, and high rates of possible NVLD. The high rate of *late walkers* in this group is mainly due to the prematurity subgroup included in this group, and age at walking was not adjusted for prematurity in this study.

The outcome study (III)

Mean age

Mean age in the AS study group at follow-up was significantly lower than in the Autism study group (Table 6).

Table 6. Age in AS and Autism study groups at follow-up

Age distribution in study groups	*AS*	*Autism*
Mean age (SD), range years	21.5 (4.4), 16.0-33.9	24.5 (5.4), 16.1-36.1
16-19	32	12
20-24	24	33
25-29	10	13
>30	4	12

p<.001 for mean age difference between AS and Autism study groups (Rank sum test for age)

Diagnosis at follow-up and diagnostic stability over time

Fifty-nine individuals in the AS study group (84%) still met clinical (Gillberg, 1991) diagnostic criteria for AS, three (4%) met criteria for atypical autism, and 8 (12%) no longer met criteria for a clinical diagnosis in the autism spectrum, at follow-up. In the autism study group 81% of those originally diagnosed with AD still had a diagnosis of AD at follow-up. Nine had a clinical diagnosis of atypical autism, but only one man did not have a clinical autism spectrum diagnosis at follow-up. Fifteen of the 17 individuals with atypical autism at original diagnosis had a diagnosis of AD at follow-up, and only 2 still had a diagnosis of atypical autism at follow-up.

The DISCO-classification (Gillberg, DISCO-algorithm criteria) concurred with that of the clinical assessment in the vast majority of cases, in both the AS and the Autism groups at follow-up (Table 7).

Table 7. Clinical and DISCO-10 autism spectrum diagnoses at follow-up

Clinical/DISCO diagnosis	*AS (n=70)*	*Autism (n=70)*
Clinical diagnosis of AS	52	0**
Clinical diagnosis of autistic disorder	7*	58
Clinical diagnosis of atypical autism	3	11
No clinical diagnosis of autism spectrum disorder	8	1
DISCO algorithm diagnosis of AS	59	11
DISCO algorithm diagnosis of autistic disorder	55	56
DISCO algorithm diagnosis of atypical autism	10	14
No DISCO algorithm autism spectrum disorder diagnosis	1	0

*7 cases meeting both Gillberg and Gillberg criteria for AS and DSM-IV criteria for autistic disorder, but clinically better fitting autistic disorder
** 5 cases meeting Gillberg & Gillberg criteria for AS, but clinically better fitting autistic disorder
In the DISCO part of this table more than one diagnosis is possible, since for AS the Gillberg & Gillberg DISCO algorithm criteria were used and for Autistic Disorder and Atypical autism the DSM-IV/ICD-10 DISCO algorithm criteria were used

Intellectual functioning at follow-up

All individuals in the AS study group seen face-to-face at follow-up (n=66) were able to take a complete WAIS-III test. Average FSIQ was 103.0 (SD 14.8, range 66-143). Two individuals scored above IQ 130, and one below IQ 70. Mean VIQ was 104.0 (SD 15.7) and PIQ 101.3 (SD 15.7). Compared to at original diagnosis the FSIQ was stable for the AS group, although there were significant differences in FSIQ on an individual basis between evaluation at original diagnosis and at follow-up (Table 8). Among those who were tested on both occasions, there was a significant VIQ>PIQ difference (≥ 15 points) in 13 (19%) at follow-up, compared to 31 (45%) at original diagnosis ($p<.01$). The gap between VIQ and PIQ for the group had decreased from 11 IQ-points at original diagnosis to less than 3 IQ-points at follow-up. The subtests included in PIQ at original diagnosis were not all identical to those used at follow-up. Matrix reasoning (MR) was included in this score at follow-up instead of Object Assembly (OA). The males scored much better on MR at follow-up than at OA at original diagnosis. However, the result on OA at follow-up was also better than OA at original diagnosis, and the results on OA and MR at follow-up were similar. The individuals who no longer had a diagnosis in the autism spectrum did not differ in intellectual capacity from the group who did (FSIQ 101.9 (SD 12.3) compared to 103.1 (SD 15.2)).

In the Autism study group, Wechsler scale testing (WAIS-R or WISC-III) was only possible in 16 individuals. The mean FSIQ in this small tested group was 59.6 (SD 17.9, n=16), VIQ 63.2 (SD 19.8, n=15) and PIQ 58.9 (SD 12.3, n=15). Those individuals who could not be tested on the Wechsler scales were categorized for level of functioning according to results on the VABS. The results in the Autism study group were significantly lower than at original evaluation, and contrasted to those of the AS group, in which mean FSIQ had not changed over time (Table 8).

Table 8. IQ/DQ/SQ distribution in AS and Autism study groups

IQ/DQ/SQ-band	*AS original diagnosis (n=70) (%)*	*AS follow-up (n=66) (%)*	*Autism original diagnosis (n=70) (%)*	*Autism follow-up (n=70) (%)*
≤ 49	0 (0%)	0 (0%)	33 (47%)	50 (72%)
50-69	0 (0%)	1 (2%)	24 (35%)	15 (21%)
70-84	15 (21%)	4 (6%)	10 (14%)	2 (3%)
85-114	41 (59%)	45 (68%)	3 (4%)	3 (4%)
115-129	10 (14%)	14 (21%)	0 (0%)	0 (0%)
≥130	4 (6%)	2 (3%)	0 (0%)	0 (0%)

p<.001 for IQ-level comparing AS group at original diagnosis (and at follow-up) vs autism group at original diagnosis and at follow-up. The change in the AS group is without trend. In the autism group there is a downward shift in intellectual capacity (p<.001)

Overall outcome

Of the 70 males in the AS study group, 19 (27%) had good outcome. Seven of these 19 no longer met clinical criteria for AS diagnosis (Table 9). Outcome in the autism group was significantly worse (Table 9). Lower intellectual ability contributed to poorer outcomes in both groups (Table 10a and 10b).

Table 9. Overall outcome categories in AS and Autism study groups

Outcome categories/Independent living (n=70)	*AS*	*Autism*
Good outcome	19 (27%)	0 (0%)
Fair outcome	33 (47%)	5 (7%)
Restricted outcome	16 (23%)	12 (17%)
Poor outcome	2 (3%)	14 (20%)
Very poor outcome	0 (0%)	39 (56%)
Independent living (23 years of age or older)	14/22 (64%)	3/40 (8%)

p<.001 for outcome AS group vs Autism group (Wilcoxon rank sum)
p<.001 for independence AS group vs Autism group

Table 10a. Outcome related to WAIS-III FSIQ, VIQ, and age in AS study group

Outcome AS (n=70)		*FSIQ (n=66) (SD)*	*VIQ (n=66) (SD)*	*Age at follow-up years (n=70) (SD)*
Good	19	107.8	109.3	21.5
Fair	33	105.0 *	104.3 *	20.7
Restricted	16	97.4	98.6	23.5
Poor	2	82.0	92.0	18.5
Very poor	0			

*n=29 (four males in this subgroup did not participate in the follow-up)
Analysis of covariance found age-difference to be non-significant when overall outcome was related both to FSIQ and VIQ. However, there was a significant difference between Good and Poor outcome (FSIQ & VIQ) ($p<.05$), and between Good-Fair and Restricted-Poor outcome (FSIQ & VIQ) ($p<.05$)

Table 10b. Outcome related to intelligence level and age in Autism study group

Outcome Autism (n=70)		*Intellectual level (n=70)*				*Age at follow-up (SD) years*
		A	*NA*	*MMR*	*SMR*	
Good	0					
Fair	5	1	2	2	0	26.1 (5.9)
Restricted	12	2	0	7	3	25.9 (7.1)
Poor	14	0	0	5	9	25.5 (5.1)
Very poor	39	0	0	1	38*	23.5 (4.9)

* $p<.001$, intellectual level vs outcome (Chi square)

When participants in the AS study group were divided into groups according to age at original diagnosis, good outcome was seen in 9/26 (35%) of the youngest group (5.5 to 9.5 years at diagnosis), in 9/35 (26%) of the "in-between-group" (10.0-15.5 years at diagnosis), and in 2/9 (22%) of the oldest group (16.0- 24.5 years at diagnosis) (n.s.).

Education
Eight of the AS males did university studies, and a further two had a university degree (computer science, civil engineering). Two AS males were studying at a Folk High School. Twenty-one of the 33 (64%) males, who were still in (or had currently finished) high school, were or had been, following ordinary study programs. Eight males with AS were (or had been) in a school for adolescents with mild learning disabilities, albeit all but one of these males had an intellectual ability within the normal distribution. Two males had finished school after nine years of compulsory school.

In the Autism study group the vast majority were or had been in schools for adolescents with mild learning disabilities or in special training schools. Only six males in this group were in, or had currently finished, high school (4 of whom had IQ >70), one males was studying at a Folk High School, but no individual in the Autism study group did or had done, university studies.

Occupation
Seven men in the AS group held ordinary jobs, and a further six individuals had "daily occupational activities" in a group centre. In the Autism study group one man held an ordinary job, and four individuals had "daily occupational activities" in a group centre. Less than 30% of those in the AS group, who had finished school held an ordinary job, and fewer than (an additional) 25% had "daily occupational activities" in a group centre.

More than 40% of the males at or above 23 years of age in the AS group had no organised daily activity at all and were dependent on social services and/or the Swedish insurance system for their welfare. In the Autism study group one man held an ordinary job, and 8% of the individuals had "daily occupational activities" in a group centre. Sixty-five percent in the Autism study group had regular individually tailored daily activities, but 16% of the males at or above 23 years of age had no organised activity at all.

Independent living
In the AS study group 14/22 (64%), and in the Autism group 3/40 males (8%), of those who were ≥23 years, were living independently. Although living away from their parents, they were all dependent upon them for support. Three males in the AS group, and one man in the Autism group were living in a long-term relationship, and a further 10 males in the AS group and one man in the Autism group had had relationships for varying periods of time in the past.

GAF-scores
The mean GAF-score for the AS study group was 58.9 (SD 9.4 range 35-82). Twelve males (17%) in the AS group, had a GAF score of 70 or above, indicating normal or near normal functioning (Table 9). However, six of these 12 men no longer met criteria for an autism spectrum diagnosis. Of the males, who were still regarded clinically to have sufficient impairment from their symptoms to warrant a clinical diagnosis of AS, five had a GAF-score of 70, and one had a GAF-score of 72. All these individuals fulfilled diagnostic criteria, and had an overall clinical impairment (including problems in daily life according to the VABS) sufficient for a diagnosis of AS, despite of having GAF-scores in the "normal functioning" area. The GAF scores in the Autism group were much lower (Table 11).

Table 11. GAF-scores in relation to intellectual ability

GAF-scores	*AS*	*AS FSIQ (SD)*	*Autism*	*Autism Intellectual ability*
Mean GAF-score (SD)	58.9 (9.4)	103.0 (14.8)	22.2 (16.5)	
GAF-score 70-	12	109.7 (15.2)	0	-
GAF-score 50-69	51	102.7 (14.2)*	8	A (3) NA(2) MMR (3)
GAF-score 31-49	7	91.9 (13.7)	13	MMR (5) SMR (8)
GAF-score -30	0	-	49	MMR (4) SMR (45)

*n= 47
p<.001 for mean GAF-scores AS vs Autism group
p<.001 for intellectual ability related to GAF score

Involvement with the police and the law
The vast majority in the AS study group were considered very law–abiding. However, according to parent report, seven males (10%) with AS, had been involved with the police and the law for different reasons. There was no report by informants in the Autism group of involvement with police or the law.

Psychotic disorder
Three individuals in the AS study group and four individuals in the Autism study group had been diagnosed as suffering from "psychosis" by independent psychiatrists. One of the males in the AS group had received a diagnosis of bipolar disorder, and there was suspicion of such disorder in at least one further case. In none of the cases in the Autism group had a diagnosis of bipolar disorder been made. No individual had been diagnosed with schizophrenia in either group. In terms of intellectual ability two of the three AS males with psychosis (the third one had not been assessed) had had a significant drop (≥ 20 IQ-points) in their FSIQ as measured on the WAIS-III. In the Autism group, two of the four males had dropped in intellectual capacity, and the other two were in the SMR category to begin with, and had stayed in the same category after intellectual assessment at follow-up.

The interview and questionnaire study (IV)

ASDI
When the scores of the whole participating group of males with AS, who completed the ASDI, were compared with corresponding parent scores there were significant differences between scores on 3 of the selected 7 items, viz. item 1 (social ability), item 3 (social cues) and item 5 (narrow interest). On all of these items parents scored significantly higher than the male with AS. For the remaining four items there was no significant difference (Table 12a). At follow up seven individuals did no longer fulfil criteria for an ASD. If those individuals were excluded, an additional item showed significant difference between the individuals with an ASD at follow-up, and their parents. (Table12b). The group of seven non-ASD males

scored somewhat higher, however non-significant, scores on some items than what their parents did (Table 12c). When the non-ASD group was compared to the group who still had an ASD diagnosis at follow-up (ASD group), the non-ASD group scored significantly lower in three items (peer interaction, making friends, and understanding social cues) than the males in the ASD-group did (Table 12d). The mean "total" ASDI 7-item score was also calculated and is presented below, arranged for the different groups as mentioned above (Table 12a-12d).

Table 12a. ASDI mean (SD) scores: young adults vs parents all participants (n=64)

Item	*Teenager/adult*	*Parents*	*p-value*
ASDI Total score (SD)	12.8 (3.4)	14.1 (4.1)	p<.001
1. Peer interaction	1.9 (0.7)	2.2 (0.9)	p<.01
2. Problems making friends	2.0 (0.8)	1.9 (0.8)	n.s
3. Understanding social cues	1.8 (0.8)	2.3 (0.8)	p<.001
4. Social/emotionally inappropriate behaviour	1.6 (0.7)	1.6 (0.8)	n.s
5. Narrow interest	2.0 (0.9)	2.3 (0.9)	p<.05
8. Imposition of routines/rituals on self	1.9 (0.9)	2.1 (0.9)	n.s
9. Imposition of routines/rituals on others	1.4 (0.7)	1.6 (0.9)	n.s

Table 12b. ASDI mean (SD) scores: young adults with ASD vs parents (n=57)

Item	*Teenager/adult*	*Parents*	*p-value*
ASDI Total score (SD)	13.3 (3.3)	14.9 (3.6)	p<.001
1. Peer interaction	2.0 (0.7)	2.4 (0.8)	p<.01
2. Problems making friends	2.0 (0.8)	2.0 (0.8)	n.s
3. Understanding social cues	1.9 (0.7)	2.5 (0.7)	p<.001
4. Social/emotionally inappropriate behaviour	1.6 (0.8)	1.7 (0.8)	n.s
5. Narrow interest	2.1 (0.9)	2.4 (0.8)	p<.05
8. Imposing routines/rituals on self	2.0 (0.9)	2.3 (0.8)	p<.05
9. Imposing routines/rituals on others	1.5 (0.7)	1.7 (0.9)	n.s

Table 12c. ASDI mean (SD) scores: young adults without ASD vs parents (n=7)

Item	*Teenager/adult*	*Parents*	*p-value*
ASDI Total score (SD)	7.9 (1.5)	8.6 (1.1)	n.s
1. Peer interaction	1.1 (0.4)	1.1 (0.4)	n.s
2. Problems making friends	1.3 (0.5)	1.0 (0.0)	n.s.
3. Understanding social cues	1.0 (0.0)	1.0 (0.0)	n.s
4. Social/emotionally inappropriate behaviour	1.1 (0.4)	1.1 (0.4)	n.s
5. Narrow interest	1.6 (0.5)	1.4 (0.8)	n.s
8. Imposing routines/rituals on self	1.4 (0.8)	1.1 (0.4)	n.s.
9. Imposing routines/rituals on others	1.1 (0.4)	1.0 (0.0)	n.s

Table 12d. ASDI, FSIQ, and GAF mean (SD) scores: young adults with/without ASD

Item	*Teenager/adult ASD*	*Teenager/adult non-ASD*	*p-value*
Age	21.6 (4.6)	22.4 (3.8)	n.s.
FSIQ	103.9 (14.6)	101.9 (12.3)	n.s.
GAF	57.4 (8.0)	74.4 (6.6)	p<.001
ASDI Total score	13.3 (3.3)	8.6 (1.1)	p<.001
1. Peer interaction	2.0 (0.7)	1.1 (0.4)	p<.01
2. Problems making friends	2.0 (0.8)	1.3 (0.5)	p<.05
3. Understanding social cues	1.9 (0.7)	1.0 (0.0)	p<.01
4. Social/emotionally inappropriate behaviour	1.6 (0.8)	1.1 (0.4)	n.s.
5. Narrow interest	2.1 (0.9)	1.6 (0.5)	n.s.
8. Imposing routines/rituals on self	2.0 (0.9)	1.4 (0.8)	n.s.
9. Imposing routines/rituals on others	1.5 (0.7)	1.1 (0.4)	n.s.

When self- and parent- agreement on the different items were compared “imposition of routines on others” had the highest agreement score with 66% agreement across self- and parent assessment. “No interest in seeking friends” was the item with the lowest agreement (39%) (Table 13).

Table 13. Young adult vs parent agreement in percentage on ASDI (n=64)

Item	*-2*	*-1*	*0*	*1*	*2*
1. Peer interaction	8	31	47	12	2
2. Making friends	2	29	39	19	11
3. Understanding social cues	12	38	41	6	3
4. Social/emotional inappropriate behaviour	8	17	53	17	5
5. Special interest	14	22	48	11	5
8. Imposing routines/rituals on self	14	20	47	13	6
9. Imposing routines/rituals on others	9	12	66	11	2

A score of zero (0) means agreement between parent and teenager/adult score (i.e. both scored the same value, regardless of value). Negative numbers means that the parent scored a higher score than the son and vice versa

Leiter-R

The mean scaled scores of the whole participating group of males with AS on the Leiter-R self- and parent assessment questionnaires were quite similar (Table 14a). When those individuals, who did not have an ASD diagnosis at follow-up, were excluded the mean scaled scored results dropped with approximately 2 p overall (Table 14b). The non-ASD males and their parents scored similar scores on both skills (Table 14c). The non-ASD group had a significantly better score on both the cognitive/social part and the emotional/adaptive part than the ASD group (Table 14d). All the mean scores presented were within the normal range (standard score 86-114).

Table 14a. Leiter-R self/parent assessments: young adults vs parents (n=63)

Self assessment scale	*Teenager/adults*	*Parents*	*p-value*
Leiter-R Cognitive/social skills	98.0 (13.5)	94.4 (15.0)	n.s.
Leiter-R Emotional/adaptive skills	90.6 (13.0)	86.0 (12.1)	n.s.

Table 14b. Leiter-R self/parent assessments: ASD young adults vs parents (n=56)

Self assessment scale	*Teenager/adults*	*Parents*	*p-value*
Leiter-R Cognitive/social skills	96.2 (12.1)	92.3 (14.1)	n.s.
Leiter-R Emotional/adaptive skills	88.3 (12.4)	83.8 (11.5)	n.s.

Table 14c. Leiter-R self/parent assessments: non-ASD young adults vs parents (n=7)

Self assessment scale	*Teenager/adults*	*Parents*	*p-value*
Leiter-R Cognitive/social skills	112.6 (12.3)	111.6 (20.9)	n.s.
Leiter-R Emotional/adaptive skills	109.1 (7.0)	103.0 (12.4)	n.s.

Table 14d. Leiter-R self-assessment ASD young adults vs non-ASD young adults

Item	*ASD*	*Non-ASD*	*p-value*
Age	21.6 (4.6)	22.4 (3.8)	n.s.
FSIQ	103.9 (14.6)	101.9 (12.3)	n.s.
GAF	57.4 (8.0)	74.4 (6.6)	p<.001
Leiter-R Cognitive/social skills	96.2 (12.1)	112.6 (10.3)	p<.01
Leiter-R Emotional/adaptive skills	88.3 (12.4)	109.1 (7.0)	p<.01

BDI

The mean BDI (n=71) score was 7.2 (SD 7.0, range 0-31) (Table 15). This was higher as compared to epidemiological studies performed in Sweden in adolescent boys (Olsson & von Knorring 1997; Larsson & Melin, 1990). Twelve individuals (17%) scored zero points. Altogether 62 individuals (88%) scored within the range of "no depression" (0-15 p), 6 (8%) had "dysphoria", 2 (3%) had "depression", and 1 (1%) had "severe depression". This was in line with findings reported earlier (Moo-Estrella, Pérez-Benítez, Solís-Rodríguez & Arankowsky-Sandoval, 2005). One of the males in the depression group (who scored 29 p on the BDI) had committed a serious suicide attempt in the recent past. All seven males, who did not fulfil an ASD diagnosis at follow-up scored in the "no depression" group. All individuals scoring ≥16 p, were found to have clinical depression or depressive feelings. Two of those males were already on anti-depressants. One of the individuals scoring below 16 was clinically judged to have a depression, and was given anti-depressant medication. Eleven of the individuals scoring ≤ 15 p on the BDI were already on medication with anti-depressants when participating in this study.

DEX

The mean result on the DEX was 26.8 (SD 12.9). The items with the most "abnormal" mean scores were, "apathy and lack of drive" (1.9), "abstract thinking problems" (1.8), "poor decision making ability" (1.8), and those with the lowest mean scores were "confabulation" (0.6), "variable motivation" (0.9), and "aggression" (0.9). Results from the DEX subdivision groups/factors are shown in table 15. The correlation between the three highest ranking DEX-items and the total BDI score was 0.31, 0.44, and 0.39 respectively.

The results from this study indicated more problems in the AS group concerning "dysexecutive functioning" than in "normal" individuals (Evans, Chua, McKenna & Wilson,

1997; Hart, Whyte, Junghorn & Vaccaro, 2005), and as many or more problems than in individuals with traumatic brain injury (TBI) (Hart, et al., 2005; Bogod, Mateer & McDonald, 2003; Bennett, Ong & Ponsford, 2005). Studies of individuals with schizophrenia have shown diverging results with mean scores both above and below the results of our current group (Krabbendam, de Vugt, Derix & Jolles, 1999; Evans et al., 1997). The non-ASD group had a mean result similar to that of normal groups presented in the studies mentioned above.

Table 15. BDI, DEX, FSIQ and GAF mean (SD) scores in ASD and non-ASD groups

Item	*ASD (n=64)*	*Non-ASD (n=7)*	*p-value*
Age	22.0 (4.8)	22.4 (3.8)	n.s
FSIQ	104.0 (15.6)	101.9 (12.3)	n.s
GAF	57.1 (7.9)	74.4 (6.6)	p<.001
BDI Total score	7.7 (7.2)	2.9 (4.0)	n.s
BDI ≥16 (%)	9/64 (14%)	0/7 (0%)	n.s
DEX Total score	28.2 (12.8)	14.1 (4.4)	p<.01
DEX Cognition	1.3 (0.7)	0.6 (0.2)	p<.001
DEX Emotion	1.4 (0.7)	0.8 (0.4)	p<.01
DEX Motivation	1.7 (0.8)	1.0 (0.3)	p<.001
DEX Behaviour	1.4 (0.8)	0.6 (0.3)	p<.001
DEX Inhibition	1.4 (0.7)	0.7 (0.4)	p<.01
DEX Intentionality	1.5 (0.8)	0.7 (0.2)	p<.001
DEX Executive Memory	1.2 (0.8)	0.7 (0.5)	p<.05
DEX Positive Affect	1.3 (0.9)	0.7 (0.5)	p<.05
DEX Negative Affect	1.8 (0.9)	1.1 (0.2)	p<.001

p-value refers to difference between ASD and non-ASD, equal variances not assumed

Discussion

This study has shown that the background factors and outcomes in AS in males are variable, and that there does not appear to be a firm basis for predicting outcome on the basis of what is known about the background in each individual case. Familial/hereditary factors (autistic features, autism or AS in close relatives) appear to be important AS "risks" in many cases, but the influence of pre-, and perinatal factors cannot be disregarded. The majority of the individuals in the present study had been subjected to special educational measures during the school years, and it seems that the Swedish school system is not well equipped to "harbour" these youngsters (with average or above average intellectual functioning) within the existing mainstream framework. Psychosocial outcome in late adolescence and young adult age varies from excellent to poor, and even though higher IQ and early diagnosis *might* be important in predicting better outcome, the trends noted in these respects were not statistically significant, meaning that conclusions cannot be drawn at this stage.

The conclusions that can be drawn are contingent upon the size and representativeness of the sample. The outcome study is the largest that has ever been performed in AS. However, it did not include females with the condition, meaning that any conclusions are restricted to males. The sample was not population-based (even though a small number of cases from a general population study of AS was included), and most cases were diagnosed at a time when AS was not well known in the medical community, meaning that it is difficult to determine how representative the cases included are of AS as diagnosed in clinics today. Nevertheless, the males included in the study were consecutive male AS cases seen in a clinic with expertise in autism syndromes (including AS) and other neuropsychiatric disorders with childhood onset, which argues in favour of the sample being representative of moderately to severely affected males with clinically impairing AS in the general population. It needs to be stressed that the criteria used for diagnosing AS were *not* those of the ICD-10 or the DSM-IV, which have been shown to be unrealistic in clinical practice, and which do not accord with the clinical descriptions published by Hans Asperger (e.g. Miller & Ozonoff 1997, Leekam et al., 2000). Instead the Gillberg criteria were used, given that these are in widespread use internationally and are based on Asperger´s own case reports.

A comparison group of males with autism was used in the outcome study. For obvious reasons, given that AS is considered to be one of the conditions in the so called autism spectrum, autism was selected as the most reasonable comparator. The failure to include a normal comparison group, or another, non-autism psychiatric comparison group might be seen as a weakness, but economic and clinical realities prevented us from including large groups of individuals with no suspicion of autistic symptomatology in time-consuming interviews (such as the DISCO) that focus very strongly only on autism and related features. In the study of background factors we used data from the general population for contrast without specific statistical testing. It seemed more appropriate than matching a relatively much smaller group in a case-control design. However, the reported prevalence rates of background factors in the general population are for boys and girls pooled, which somewhat limits the strength of any conclusions drawn as regards our AS group of males.

In the following, I shall first discuss the findings of each sub-study before concluding with a brief summary discussion of the whole study.

The study of background and associated factors (I)

The age at diagnosis (11.3 years), was in line with previous findings from the UK (Howlin & Ashgarian, 1999). This is much later than the common diagnostic age for children with autistic disorder, which, in most cases, is well before the age of 6 years. The diagnostic age for AS in my study group is also at the uppermost end of the "core" AS years, i.e. the period when AS symptoms are often said to be the most typical (age 7-12 years). In many cases parents had not experienced major problems with their child (even though they might have reflected that their child was "unusual" much earlier) until the start of preparatory school or primary school, which in Sweden occurs at 6 and 7 years of age, respectively. However, those parents, who did worry, were often either disbelieved, or "reassured" that the children would "grow out of their problems". The main problem, for the boys with AS in pre- and primary school period, was usually their lack of interest and/or ability to interact with other children, and the refusal or failure to do what was expected of them at school. Oftentimes, before the child actually got a diagnosis of AS, the mothers and fathers were blamed for the behaviour of their child, and "accused" of being bad parents (this was evidenced not only by parental report, but by scrutiny of the child´s records).

In 28 cases, there was at least one other (extended) family member (most often the father) who had a diagnosis of AS or autism, or presence of many symptoms consistent with such a diagnosis. Even if this cannot be taken as evidence of a strong genetic/familial propensity for AS, it is a remarkably high rate of familial problems, which would tend to support the idea that AS is often familial/genetic (Gillberg, Gillberg & Steffenburg, 1992; Szatmari, Boyler & Offord, 1993).

A large proportion of the parents, especially the fathers, were engineers (17%), which is in line with what has been reported earlier (Baron-Cohen, et al., 2001), and is significantly higher than the percentage of engineers within the normal Swedish population. Historically, many successful engineers, mathematicians and scientists have been proposed to have AS (clinical or sub-clinical). Scientists might benefit from single-mindedness and persistence, which are two of the key features of AS, when doing something that interests them, and it is possible that such qualities, if nurtured, may turn out in a positive way. However, the experience from my investigation was sometimes very depressing; we met many individuals with AS, who had average or above average intellectual ability, who had had problems achieving grades in all subjects at school, and a few individuals had even been following programs for children with learning disabilities.

Reading and writing disorders and dyscalculia were common among relatives, and family problems of this type were present in almost 1/3 of the cases. Interestingly, few of the males themselves appeared to be affected by these types of problems. However, no formal study was performed in this respect, meaning that conclusions in this respect cannot be drawn. Psychiatric disorders, depressive disorders in particular, were also common in the extended family. The relationship between affective disorders and AS is unclear, but there is some evidence, that familial clustering of the two conditions may be considerably more common than expected by chance (deLong, 1994).

At least one of the young men in the study had made a serious suicide attempt, but he did not belong to any of the extended families in which other members had committed suicide. Wing (1981) remarked on the relatively high rate of suicide attempts in her series of 34 individuals with AS, but that observation was not borne out by the results of the present study.

The rate of pre-, peri-, and postnatal complications, was much higher than in the general population. However, we could not control for gender effects, and, so, conclusions can only be tentative. Further studies are needed to assess whether or not our findings are representative of males with AS in a broader context.

Age at walking unsupported, was relatively late, and the ability to speak in sentences at age 2 years was acquired in only about half the group. Given that the findings relate to a group of children in which intellectual ability was in the average or above average level in the vast majority of cases, these findings are probably important. Taking the difficulties in acquiring speech into account, the suggestion that AS should be discriminated from "high-functioning autism" on the basis of language onset, seems somewhat artificial.

We found large head circumference ($\geq 97.5^{th}$ percentile) to be present in a rate that was about six times that of the general population. These results provide further support for previously published data (Gillberg & de Souza, 2002; Deutsch & Joseph, 2003; Woodhouse et al., 1996), reporting high rates of macrocephalus in AS. However, they also show that the great majority of all males with AS *do not* have large head size. BMI was also found to be $\geq 97.5^{th}$ percentile in quite a number of individuals (18%), which was in contrast to earlier findings (e.g. Bolte, et al., 2002). It is possible that at least some of the high prevalence of macrocephalus could be accounted for by generally large body size. However in our AS group only 50% of the individuals with macrocephalus had BMI ≥ 24, and 25% had a BDI < 19.

In 14 of the 16 cases in which SPECT had been performed, there was pronounced hypoperfusion in the temporal region, with *left-sided* predominance in 9 cases and *right-sided* predominance in 5 cases. Thus, there was no SPECT-indication of a distinct right-sided hemisphere dysfunction to support the "NVLD-theory" that VIQ>>PIQ (found in this study) is generally associated with right hemisphere dysfunction (Klin, Volkmar, Sparrow & Cichetti, 1995; Rourke, 1988). Of the nine individuals, who had a left-sided predominance, four had a VIQ>>PIQ discrepancy supportive of the NVLD-theory, and two had an opposite, i.e. PIQ >> VIQ discrepancy. In addition, of the five individuals with a right-sided temporal hypoperfusion, two had a VIQ >> PIQ discrepancy, and one had an opposite discrepancy. Seven of the originally 50 individuals with a VIQ >> PIQ discrepancy were investigated with SPECT, and of these 4 had a left-sided hypoperfusion, and two had a right-sided hypoperfusion. One individual had a temporal hypoperfusion without definite differences between the left and the right side. For fifteen of the individuals, where SPECT had been performed, handedness was known, and all but two of those individuals were right-handed. One was left-handed, and one was ambidexter, but with a right-sided predominance.

The high rate of pathological EEGs, including EEGs with epileptogenic activity, is in line with several studies of EEG findings (e.g. Tuchman & Rapin, 1997; Chez, Chang, Krasne, Coughlan, Kominsky & Schwartz, 2006) in autism spectrum disorders. These pathological EEGs, which are present in many individuals with AS *without* epilepsy, could indicate an underlying ongoing "pathological brain process" that might influence social, communicative and motor development (Binnie & Marston, 1992; Deonna, 1993; Oberman, Hubbard, McCleery, Altschuler, Ramachandran & Pineda, 2005).

The pathology rate reported for ABR findings in the AS group, compared to a much lower rate in the general population (Rosenhall, et al., 2003), also indicates that auditive and/or brainstem dysfunction might play a role in the difficulties experienced. A Positron Emission

Tomography activation study (using auditory Theory of mind tasks) showed reduced activation in the occipitotemporal area and increased activation in the cerebellum in a group of individuals with AS (Nieminen-von Wendt, et al., 2003), suggesting that several areas of the central nervous system are involved in the pathophysiology.

Fragile X analysis was negative in all investigated cases, but karyotyping had a pathology rate of almost 10% in individuals investigated. Although the same or similar chromosomal changes were found in relatives in two of the five individuals, the importance of these findings remains unclear.

Regarding all of the above (SPECT, EEG, ABR, Fragile X analysis and karyotyping) it is important to remember that only a minority (up to half) of all individuals with AS in the study were subjected to each of these examinations. It is impossible to determine whether those examined constituted atypical subgroups of the whole sample, and, so, generalized conclusions cannot be drawn.

The results on the ASSQ indicate that it is a relevant tool for use in the process of diagnosing ASD. Two thirds of the AS males in our group had a score at diagnosis which was above the cut-off level for probable ASD. New data suggests that a lower score than that originally suggested by Ehlers et al (1999) may be relevant as an ASD cut off level on this questionnaire (Posserud, et al., 2006); more than 80% in my sample scored above that "new" cut-off level.

At original diagnosis, there were significant VIQ over PIQ differences on all the Wechsler scales used, and 50% of the individuals had a VIQ over PIQ discrepancy of 15 points or more, providing support for a significant VIQ over PIQ discrepancy (or NVLD) at that age. The results of the 3 Kaufman factors Verbal Comprehension (11.6), Perceptual Organisation (9.6), and Distractibility (8.5), further supported the theory of better verbal than performance "intelligence". Taken together, all the findings supported the theory of similarities between AS and NVLD (Klin, et al., 1995; Rourke, 1988).

The study of pathogenetic/risk factor subgroups (II)

The pathogenetic subgroups *definitely familial/genetic, probably familial/genetic, and possibly familial/genetic groups,* were separated only on the basis of the level of support for documentation of a diagnosis within the autism spectrum among the close relatives of the male with AS included in this study. Different clinicians had taken the family history, albeit in a similar way, meaning that the subdivision of the pathogenetic groups used in this study might be confounded, and, hence, might be considered "artificial". This is supported by the fact that there was only one significant difference across these groups on the independent items assessed. The *possibly familial/genetic group* walked significantly earlier than the *medical syndromes/chromosomal group*. However, the males in the *definitely familial/genetic group*, were diagnosed somewhat earlier, than the males in the other groups, probably because the definitive clinical ASD diagnosis of a relative had brought the attention to the child´s (similar) problems earlier. The *possibly familial/genetic group* on the other hand walked at a normal age in contrast to the other groups, and had the highest mean FSIQ. This might reflect the fact that in this group more *talented* relatives, with eccentricities and/or a very small circle of friends (possibly "caused" by a very limited range of possibilities finding peers with a similar level of intellectual superiority) may have been "misinterpreted" as having ASD.

The *pre-/perinatal combined with familial/genetic factor group* had a lower FSIQ, and the percentage of individuals with clear NVLD was lower in this group. In addition the

percentage of late talkers was higher in this group. These findings beg the question of whether or not these individuals would have been more like the individuals in the collapsed group with "only" familial/genetic risk factors, had they not been negatively affected by adverse pre- and/or perinatal events. This seems to be a reasonable hypothesis, but it is interesting to note in this context that the *pre- and/or perinatal factors only group* resembled the "familial only" groups both as regards mean FSIQ, and high rates of possible NVLD.

The outcome study (III)

The vast majority of the individuals with AS examined in late adolescence-early adult life, still had a clinical diagnosis of AS at follow-up. However, generally speaking, there was improvement of difficulties related to AS in a majority, and eight of the males who had been diagnosed with AS more than five years prior to follow-up no longer met full criteria for this diagnosis at the later age. On the other hand, some individuals had more severe symptoms at follow-up, than at original diagnosis, and were now considered "autistic", or had other severe psychiatric problems, which had strongly affected their intellectual and functional capacity, and had contributed to a negative course in their lives. In the Autism study group, the vast majority of those originally diagnosed with autism, had the same diagnosis at follow-up. However, in this group, unlike in the AS group, there had been a downward shift in intellectual ability, and more than 90% of all in the group had persistent social impairment and abnormal reactions to sensory stimuli. Informants reported that a decrease in intellectual functioning, became visible when the individuals had finished school, and was not "intellectually stimulated" in a more formalised way anymore. By, and large, this group was much more severely handicapped than the AS group, even though there was one individual who no longer met criteria for an ASD at follow-up.

Intellectual functioning did not change on the group level in the AS group. However, one man scored below FSIQ 70 at follow-up, and 2 males, both with psychotic episodes had a drop of 20 FSIQ points between original diagnosis and follow-up. At the individual level there were also some IQ-changes with some AS males scoring significantly higher and others scoring lower compared to at original diagnosis. The difference between VIQ and PIQ, that was present on all the Wechsler scales used at original diagnosis had disappeared in many cases at follow-up. The percentage of individuals scoring >15 points on VIQ than on PIQ had dropped from 45% to 19% in the individuals followed up and hence clear support for presence of the NVLD theory was no longer as obvious in adult age. The subtests used for the calculation of PIQ had changed, but this probably could not explain all of the discrepancy between the early and later tests, since subtests used earlier also showed higher scores at follow-up. Nevertheless, it is conceivable that the WAIS in itself might be less sensitive than the child versions of the Wechsler scales to picking up NVLD. Some support for this was found in that even at the time of original diagnosis, WAIS-scores tended to be higher than WISC scores.

Overall outcome was good in about one quarter of the males in the original AS group, and these included 7 of the 8 males, who no longer had a diagnosis of AS at follow-up. Two AS individuals, because of a history of psychosis, had *poor outcome.* Altogether, the outcome result was much worse than expected taken the intellectual ability of the group and the very stringent criteria for poor outcome used into account. However, it was much better than in the intellectually much lower functioning group of males in the Autism group in which more than three quarters of the group had poor, or very poor, outcome. Lower intellectual ability contributed to poorer outcome in both groups. It is possible that lower IQ is at least as important a predictor of poorer outcome as the "autism" itself (be it the "autism" of "Autism" or the "autism" of "AS").

There was a non-significant trend towards a relationship between early diagnosis and good outcome. Given that children being diagnosed at a very early age would be more likely to have more severe problems, we would suggest that even this non-significant trend might be a hopeful marker for early diagnosis being important in promoting better outcome in AS. However, it is clear that no definite conclusions in this regard can be drawn on the basis of the results from the present study.

Almost 30% of the males with AS who had left school had an ordinary job. In the Autism study group only one man (2% of the corresponding Autism study group) had an ordinary job. On the other hand, 16 % in the Autism study, and more than 40% in the AS study group, at or above 23 years of age had no organised activity at all. This might well reflect the way society interacts with people with AS and autism. Many individuals with AS are considered "too able" to have the right to basic services, such as a daily activity. On the other hand, males with AS really usually *are* too able for the services provided, and unfortunately too impaired, by their social- and communication problems to manage an ordinary job.

The term independent living, as used in the present context is, in fact, a modification of *real* independent living, since very few of the individuals we met during the follow-up were independent and completely self-supporting. Those few who were really independent and self-supporting no longer met full clinical diagnostic criteria for AS. All the other individuals, who were living "independently", were still, in many ways, dependent on their parents or other relatives for support.

The mean GAF-score for the AS study group was within the moderate symptoms score area. I would like to argue that, on the basis of the findings from this study of young males with AS, the GAF scale appears be a good-enough measure of psychosocial functioning, since only six individuals still meeting criteria for an AS diagnosis, scored ≥ 70 (with a maximum score of 72). It may well be used in the process of deciding whether or not an individual who fulfils symptom criteria for an ASD should also in fact have the diagnosis (based on clinical impairment).

The vast majority of the AS study group were considered very law–abiding. However, according to parent report, 10% of the males were described to have been involved with the police and the law for various acts of crime. In this age group in Sweden, a rate of 10% criminality is not surprisingly high (National Council for Crime Prevention, Sweden, 2005). Nevertheless, the nature of the acts of crime performed by the young men with AS clearly high-lighted the typical AS difficulties with perspective-taking, and difficulties in appreciating the consequences of one´s own actions, which have been reported in a previously published study (Murphy, 2003).

A small, but not insignificant**,** group of individuals in both the AS and Autism study groups had been diagnosed by independent psychiatrists as having "psychosis". "Schizophrenia" had not been diagnosed in a single individual, and even though cases of this condition might well appear with time, it seems clear that neither AS, nor autism is associated with a much increased risk for schizophrenia in early adult life. At least two of the three males in the AS group, who had been diagnosed with psychosis had had severe decline in intellectual functioning between original diagnosis and follow-up (the third of these men was not tested at follow-up).

The interview and questionnaire study (IV)

We found that, to quite a large extent, males with AS recognise the consequences of the problems inherent in a diagnosis of AS. However, at the ASDI-interview, four out of seven items showed a significant difference between the self- and parent assessment (parents reporting more problems), viz. those relating to "peer interaction", "social cues", "narrow interest", and "imposition of rituals and routines on self". These items might be the ones that are the most difficult to view objectively "from the inside". Interestingly, the non-ASD group scored higher (=more problems), albeit non-significantly so, for "making friends" and "imposition of routines on self" than did their parents.

There was no significant difference in the scores on the Leiter-R between the males with AS, and their parents. However, the results indicated that problems involving emotional/adaptive issues were felt to be more severe than cognitive/social problems in early adult life. Those no longer meeting criteria for ASD scored significantly "less abnormal" than those who still did, both according to parents and the men themselves. These findings could be taken to indicate that self- and parent assessment questionnaires might prove useful in the diagnostic processing, and that they could be used together with the GAF to decide whether an individual has enough difficulties in daily life to be given a diagnosis of AS or not.

The mean BDI score in this group was higher, than what had been reported from epidemiological studies made earlier on teenagers in Sweden (Olsson & von Knorring, 1997; Larsson & Melin, 1990). All but one of the individuals, who were clinically judged to have depressive feelings or a depression, was identified by the BDI (i.e. a score ≥ 16). In addition, eleven males were on current anti-depressive treatment when participating in this study, which must be considered to have influenced the results. Many of these were not clinically depressed at the time of assessment, but would have been, had the study taken place at the time just before they were started on such medication.

The results on the DEX indicate that young adult individuals with AS experience many problems in daily life related to executive functioning. The mean score for this group was as high (or higher) than those presented in earlier studies of traumatic brain injury, and in most studies of schizophrenia, indicating that problems in daily life constitute a major problem in AS.

Limitations

Of the 100 males approached for inclusion in this study, 24 did not participate. Considering that the follow-up period was often more than 10 years, that cases were recruited from clinic registers, and that none of the clinical follow-up investigators knew these individuals from before, this recruitment rate must be considered acceptable. According to the data available to us in the medical psychiatric records from the time of original diagnosis, the non-participants did not differ in any major way from those who participated.

The autism contrast group may not be regarded as ideal because of its much lower IQ. Nevertheless, it would be unrealistic (and, clinically, probably impossible) to recruit an autism study group matched for IQ, particularly given speculation that the main difference across cases clinically diagnosed as AS and autism is the much higher IQ in the former group, and that there are no clinically diagnosed cases of autism who have IQ in the superior range. We believe that, as regards the social deficits, the two groups were roughly comparable in

childhood and/or adolescence, and that they therefore constituted reasonable contrast groups for the purpose of follow-up of psychosocial adjustment and general outcome in adult life.

There is always a risk that individuals with problems try to portray themselves as more "normal" by scoring as low as possible on various assessment forms and questionnaires. Nevertheless, in most areas covered, this did not appear to be a major bias in the present study given the relatively high level of endorsed "deviance" (from the "norm"). Some of the males with AS had difficulties understanding parts of the questionnaires administered. Comments from the males about the exact meaning of the words were quite common, as were questions related to details about the questionnaires, irrelevant to the questions as such. It is unclear to what extent findings may have been influenced by this aspect of concrete thinking on the part of the participants.

Concluding remarks

Overall outcome was good in fewer than 20% of the males, who still met clinical criteria for an ASD diagnosis at follow-up. Lower intellectual level contributed to poorer outcome in both the AS and the autism groups, and it might be possible that lower IQ is at least as important a predictor of poorer outcome as the "autism" itself (be it the "autism" of "Autism" or the "autism" of "AS").

The diagnosis of AS proved to have overall stability in the vast majority of cases. However, there were also individuals, who no longer met criteria for a clinical diagnosis of AS at follow-up. There were also individuals, who, if anything, were more severely disabled at follow-up, than at original diagnosis, and in some cases a diagnosis of autism would have been more "adequate" to describe their current status. Co-existing psychiatric disorder was a very negative prognostic factor in AS, just as it was in the autism group.

Age at diagnosis (11.3 years), was in line with previously reported findings in AS, but much later than the common diagnostic age for children with autism. Given that symptoms of AS are usually present long before five years of age, that impairment from the condition often surfaces early on, and that parents often worry about their child´s development already in infancy or the toddler period, this age for diagnosis appears to be much too late in the majority of cases. Although no definite factors speaking in favour of an earlier diagnosis could be documented, there were indirect indications in this study that early problem recognition might be important for better outcome.

In the Autism study group, but not in the AS study group, there had been a significant drop in intellectual ability over the years. Informants reported that decrease in intellectual functioning, often became visible when the individuals had finished school, and was no longer "intellectually stimulated" in a more formalised way.

The reduction over time in the rate of individuals with AS showing a significant VIQ>PIQ difference, when assessed on the Wechsler scales, at original diagnosis and at follow-up, was surprising. Does the discrepancy disappear with development, or are other factors (such as the WAIS "overestimating" PIQ relative to the child versions of the test) responsible for these changes? Intellectual functioning did not change at the group level in the AS group. However, at the individual level there were those who had significant changes of FSIQ from original diagnosis through follow-up. The VIQ>PIQ discrepancy as evidence of the NVLD theory, proposed earlier, was no longer as striking at follow-up. It could be that this discrepancy is

more pronounced within the "core" AS years (7-12 years of age), and that it "disappears" with time, or that it may be due to other factors, currently poorly understood.

The very high rate of individuals in our AS study group not having had completely normal language development in spite of normal intelligence does not support the theory of language development as a reliable distinguisher between AS and so called high-functioning autism.

Further investigation of "pathogenetic subgroups" is needed to establish vulnerability factors that could influence normal development. My findings provided strong support for Hans Asperger´s original notion that familial or perinatal factors (or both combined) are at the root of "autistic psychopathy".

I believe that the use of formalised interviews and questionnaires are relevant tools, in the diagnostic process, but it must be emphasized that interviews and questionnaires cannot be used as the sole instruments for diagnosis in this field.

I found it to be of particular interest that many males with AS do recognise the full consequences of the problems inherent in a diagnosis of AS, and the impact they have on their daily-life functioning. However, parents often acknowledge more severe problems, more consistent with clinician´s judgment, in many cases.

The number of males in both the AS, and autism groups having an ordinary, or a sheltered job was quite low, reflecting the difficulties in finding suitable activities for males with ASD. However, the majority of the males in our groups seemed quite happy with their current situation, and did not ask for anything else. Nevertheless, only a few males were really independent, and almost all of those no longer met clinical diagnostic criteria for an ASD.

This was not a study of the effects of schooling and school attitudes to children with AS. Nonetheless, I believe that the fact that the vast majority of all males in this study had needed special education help (in one way or another), speaks to the role of the school system not "tolerating" this group of unusual children within its mainstream framework, being important. In view of the many successful scientists purported to have suffered from AS (clinical or sub-clinical), and the relatively poor academic and psychosocial outcome of the (normally intelligent) individuals with AS in this study, one cannot but wonder whether the present day Swedish school system could do better than they appear to be doing with this group. Social and communicative skills are fast becoming more important in the school (and life) of today. Given that these are not the strongest sides of children with AS, I believe that, unless schools can accommodate these children with a more understanding approach, their academic and psychosocial outcomes will continue to be poor for a long time to come.

Clinical implications

AS is a clinical diagnosis with considerable diagnostic stability over time. Nevertheless 16% of the males with AS in this study no longer qualified for a clinical AS diagnosis at follow-up, which supports the importance of clinical re-evaluations, as time goes by. Even though no definite conclusions can be drawn from this study regarding the positive effects of an early diagnosis in relation to the long-term outcome in AS, it is my belief that an early diagnosis is of importance for providing children with AS with instruments for overcoming/adapting to their difficulties. I also believe that the results from the follow-up speaks in favour of tailored *individual* support programs at school in order to create a satisfactory educational environment for these often talented, but *special* children, with special needs.

Males with AS were not generally unaware of their problems, and this fact ought to be taken more seriously, both in the original diagnostic process, and in the tailoring of educational programs. I believe that if individuals with AS become more "engaged" in their own problems at a younger age, it is more likely that they will be better able to deal with them.

Future research

This thesis presents data from a long-term follow-up of males clinically diagnosed with AS. From the present follow-up study additional neuropsychological data is available, which will be analysed in the near future. It is envisaged that the present study will be used as the basis for additional follow-up studies within the next decade. Girls were not included in this study. Given that many girls are now diagnosed at the CNC, long-term follow-up studies of females with AS should be embarked upon without delay.

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