A QUANTITATIVE CONTROLLED MRI STUDY OF THE BRAIN IN 28 PERSONS WITH ASPERGER SYNDROME

Niemin-von Wendt T1 MD
Salonen O2 MD, PhD
Vanhala R1 MD, PhD
Kulomäki T1 MD,
von Wendt L1 MD, Prof
Autti T2 MD, PhD

ABSTRACT

Background: As structural brain abnormalities have been reported in infantile autism, the aim of this study was to determine whether such findings also exist in Asperger Syndrome (AS).

Methods: The diagnosis of Asperger Syndrome was based on the criteria in ICD-10 and DSM-IV. Brain magnetic resonance imaging (MRI) was performed with a 1.5 T imager. T2-weighted axial and coronal slices and T1-weighted three dimensional sagittal slices were obtained and visual and quantitative analysis were performed.

Subjects: There were 28 Asperger individuals, 17 children and adolescents (age 6-19 years, mean 12.4 years), 11 adults (age 20-60 years, mean 37.9 years) and 28 healthy age and gender matched controls.

Results: Mild inconsistent alterations were detected in 13/28 of the individuals with Asperger Syndrome compared to 6/23 in the comparable controls. There were no differences between the right and left hemispheres, nor was there any abnormality in terms of myelination or migration. The anterior-posterior diameters of the mesencephalon were statistically significantly shorter in the Asperger syndrome individuals than in the controls.

Conclusions: No consistent focal brain abnormalities for Asperger Syndrome were detected. The reduced diameters of the mesencephalon in the Asperger group support the hypothesis that the mesencephalon may be involved in the pathogenesis of Asperger Syndrome.

Keywords: Asperger Syndrome, MRI, mesencephalon, reduced diameter
Impairment in social interaction, dependence on routines and rituals, formal and pedantic speech and interests in unusual and odd hobbies characterise Asperger Syndrome (AS) (1-4). At present, the diagnosis of Asperger Syndrome is based on sets of criteria incorporated in DSM-IV (American Association of Psychiatry) (1) and ICD-10 (WHO) (4) classification. The ICD-10 inclusion criteria are qualitative abnormalities in reciprocal social interactions and restricted repetitive and stereotyped patterns of behaviour, interests and activities. The exclusion criteria are a clinically significant general delay in speech or in other cognitive development (4). The DSM-IV has the same criteria but also postulates that the syndrome causes significant disturbances in social and occupational areas of functioning. It also requires the exclusion of childhood-onset schizophrenia (1).

Asperger Syndrome is one of the autism spectrum of disorders. The prevalence has been reported to be 4-7/1,000 in the 7-16 year age group in Sweden (5), whereas data on the prevalence in other populations and age groups is scanty. The aetiology of the syndrome is unknown, but there is evidence that genetic factors play a role. An autosomal dominant mode of inheritance has been suggested (3). A number of chromosomal regions have been linked to autism and AS, but so far no specific genes have been found (6-9).

Until now, neuroimaging techniques have rarely been applied to individuals with AS. However, positron emission tomography (PET) has revealed abnormalities of brain metabolism, suggesting an abnormal activation of the left medial prefrontal cortex while performing ‘theory of mind’ tasks (10). In infantile autism and particularly in high-functioning autism, several structural brain abnormalities have been reported. Hashimoto et al. (11) reported a reduction of the size of midbrain and pons in children with autism. The same authors also reported the areas of the midbrain and medulla oblongata to be significantly smaller in high-functioning autistic children than in controls (12). On the other hand, also an increased brain volume, particularly in the parietal, temporal and occipital lobes, has been reported (13). The weight of the brain in patients with infantile autism (21 patients) was normal in the majority of the patients in the study by Courchesne and coworkers (14). Fombonne et al found macrocephaly in 16.7% of their series and microcephaly in 15.1%, supporting the theories of an increased rate of macrocephaly in autism (15). The volume of the hippocampus has been reported to be
normal (16), whereas abnormalities in the corpus callosum have been detected in some individuals with infantile autism (13).

The literature does not contain any controlled series of brain magnetic resonance imaging (MRI) consisting exclusively of individuals with AS. The functional characteristics of AS have been thought to reflect a right hemisphere dysfunction (17,18). Many of the clinical features characteristic for infantile autism are to a less severe degree present also in AS (3). The aim of the present study was therefore to determine whether any of the neuroimaging features reported in autism or high-functioning autism could also be demonstrated in AS and whether there were any neuroimaging signs of a right hemispheric dysfunction.

METHODS
Subjects
The Department of Child Neurology of the Helsinki University Central Hospital is the tertiary referral unit for paediatric neurology in the southern part of Finland (pop. 1.4 million) and hosts the only unit specialised on autism spectrum disorders in this area. The children and adolescents (three girls and 14 boys, age 6-19 years, mean 12.4 years) with Asperger syndrome were after informed consent recruited among those referred to the unit for diagnosis and rehabilitation between December 1998 and May 1999. During the same time period, 11 adults (four women and seven men, age 20-60 years, mean 37.9 years) were recruited for this study among those who visited the Helsinki Asperger Center for diagnosis. The entire series thus consisted of 28 individuals fulfilling the diagnostic criteria for Asperger syndrome. In the entire series, there were two father and son combinations, where the first one was an adult/child combination and the other was an adult/adult combination. In the group of children and adolescents group, there was one sister/brother combination.

All the individuals included in the series underwent the same diagnostic procedure, including an Asperger Syndrome Screening Questionnaire (ASSQ) (19,20) if they were children or adolescents and an Asperger Syndrome Diagnostic Interview (ASDI) if they were adults. An experienced neuropsychologist performed the neuropsychological test battery (WISC, WAIS) or other standardised intelligence tests. All included individuals except for three children, had an IQ of more than 80, the children were attending ordinary schools and all the ado-
adolescents and adults had finished their education or were university students. In the diagnostic procedure, individuals with medical conditions such as fragile-X syndrome, chromosomal aberrations, epilepsy, cerebral palsy, schizophrenia or neurocutaneous syndromes were excluded. All the included individuals fulfilled the diagnostic criteria for Asperger Syndrome according to DSM-IV and ICD-10 (1,4).

Controls
The controls were healthy volunteers and they matched the Asperger individuals with respect to age and sex.

MRI procedures
All individuals with AS underwent a 1.5T brain MRI. Fast spin-echo T2-weighted axial and coronal slices (TR/TE=3000/85, 14), axial fluid attenuated inversion recovery (FLAIR) sequence (TR/TE 9999/105) and a three dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE, TR/TE=9.7/4.0) were obtained. T1-weighted sagittal slices (slice thickness 1 mm) covered the entire brain. The same imaging protocol was used in all but five of the controls. One child was imaged for other purposes and only T1-weighted (MPRAGE, slice thickness 1 mm) sagittal images were therefore available. T2-weighted images (with various parameters) were missing in four adult control individuals.

As the spectrum of MRI findings in infantile autism and high-functioning autism is wide, two radiologists (T.A, O.S) made a joint evaluation of the images for:
1. Cerebral cortical abnormalities
2. Cerebral white matter alterations (foci < 2 mm were excluded)
3. Enlargement of cerebral CSF spaces
4. Enlargement of cerebellar fissures and atrophy of vermis
5. Enlargement in the size of CSF spaces within the posterior fossa

In addition to visual analysis a total of 11 measurements were obtained:
1. The midsagittal diameters of the genu (diameter 1)(Fig. 1), body (diameter 2)( Fig. 1) and splenium (diameter 3)(Fig. 1) and the surface area of the corpus callosum were measured from T1-weighted sagittal images (Fig. 3) (21).
2. The anterioposterior diameters of the brainstem were measured from midsagittal T1-weighted images at the mesencephalon (diameter 4) (Fig. 1), pons (diameter 5) (Fig. 1), and medulla oblongata (diameter 6) (Fig. 1) (22).

3. The anterioposterior diameter (diameter 1) was also measured from an axial image of the mesencephalon reconstructed from T1-weighted sagittal three-weighted images (Fig 2A-C).

4. The horizontal diameter (diameter 2) was measured from an axial image of the mesencephalon (Fig. 2A-C). The surface area was measured from an axial image of the mesencephalon (Fig. 2D).

5. The area of the cerebrum was measured from a midsagittal images (Fig. 3).

The study was approved by the ethics’ committee of the Helsinki University Central Hospital.

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Fig. 1. A T1-weighted (3D MPRAGE) midsagittal image demonstrating the measured diameters of the corpus callosum (genu; diameter 1, body; diameter 2, splenium; diameter 3) and the brainstem (mesencephalon; diameter 4, pons; diameter 5, medulla oblongata; diameter 6).

Fig. 2. A-D T1-weighted (3D MPRAGE) midsagittal slice (Fig. 2A). The horizontal line has been drawn through the lowest point of the frontal lobe and through the mesencephalon-pontine angle. The vertical line (Fig. 2A) is perpendicular to the horizontal line and crosses the mesencephalon-pontine angle (Fig. 2A). With these hallmarks, we get a coronal slice (Fig. 2B) in which a horizontal line has been determined by the upper poles of the hippocampi. Thereby an axial slice (Fig. 2C-D) was obtained showing the...
RESULTS

Visual analysis

In subjects up to the age of 19 years (n=17) MRI did not reveal any specific abnormalities of the brain. There were no differences between the right and left hemispheres, nor was there any abnormality in terms of myelination or migration.

In six children or adolescents there were mild structural alterations (Table 1).

Two children (Nr 9 and 11) had slightly enlarged lateral ventricles and a large cisterna magna (Fig 4A-4B). The same nine-year-old boy (Nr 9) had also a thin corpus callosum, diffusely increased signal intensity in the periventricular white matter on T2-weighted images. One additional child (Nr 14) had a large cisterna magna. The corpus callosum was thin in one child (Nr 13) who also had a slightly atrophic mamillary bodies and tractus opticus. On this slice (Fig 2C) the anterioposterior diameter has been marked as diameter 1 and the widest horizontal diameter of the mesencephalon has been marked as diameter 2 (Fig 2C). The measured area of the mesencephalon is shown in Fig. 2D.

Fig. 3. A T1 weighted (3DMPRAGE) midsagittal image showing the measured areas of the cerebrum (1) and the corpus callosum (2).
vermis. The superior cerebellar cistern was enlarged in one child (Nr 5). In the 11- years old boy (Nr 9) with a large cisterna magna, the grey/white matter differentiation was slightly lowered in the anterior temporal lobes. One patient (Nr 12) had a small pineal cyst.

Fig. 4. Two T2-weighted axial images (TR= 3000ms, TE= 85 ms) of a nine-year-old boy with Asperger Syndrome show a wide cisterna magna (Fig. 4A) and a slightly enlarged lateral ventricles (Fig. 4B).
When small high-signal foci (under 2 mm in diameter) were excluded, only two of 16 control children had any minimal brain alterations. One eight-year-old boy had a small venous anomaly and one 15-year-old boy had slightly enlarged cerebral ventricles and sulci.

There were some alterations on brain MRI in seven out of eleven adults in Asperger individuals (aged 19 and over) (Table 2).

| Nr of patient | Age (y) | Gender | IQ | No MRI alterations | Supratentorial regions with enlarged sulci | Infratentorial findings |
|---------------|--------|--------|----|--------------------|----------------------------------------|------------------------|
| 1             | 21     | M      | 117|x       | x                           | x                      |
| 2             | 60     | M      | 126|x       | x                           | x                      |
| 3             | 20     | F      | 128|x       | x                           |                         |
| 4             | 36     | M      | 121|x       | x                           |                         |
| 5             | 23     | M      | 125|x       | x                           |                         |
| 6             | 47     | M      | 112|x       | x                           |                         |
| 7             | 40     | F      | 117|x       | x                           |                         |
| 8             | 40     | M      | 140|x       | x                           |                         |
| 9             | 37     | M      | 137|x       | x                           | x                      |
| 10            | 53     | F      | 120|x       | x                           | x                      |
| 11            | 39     | F      | 110|x       | x                           |                         |

Five individuals (Nr 4, 8, 9, 10, 11) had slightly enlarged cerebral fissures; in two individuals (Nr 4 and 10) the alterations were present in the frontal and parietal lobes, in other two individuals (Nr 8 and 11) there were alterations only in the frontal lobes and in the fifth individual (Nr 9) in the parietal and occipital lobes. One male (Nr 5) had a cavum septi pellucidae vergae. Two individuals (Nr 5 and 10) displayed wide superior cerebellar cistern, one of them as the one having enlarged sulci in frontoparietal region (Nr 10). One female had a slightly atrophic vermis (Nr 7) (Fig. 5). Non-specific, small, high-signal foci were detected in five adults in the white matter in the watershed areas on T2-weighted images.
Of the comparable seven controls, four out of ten subjects had some minor brain alterations. Three of them had slightly enlarged cerebral sulci. One 50-year-old male had an enlarged cisterna magna and many high-signal foci larger than 3 mm in diameter in the cerebral white matter (vascular degeneration).

**Measurements**

The mean anterior-posterior diameter measured from an axial plane image of the mesencephalon was significantly smaller in the entire group of Asperger individuals \( (p<0.05, \text{Mann-Whitney U}) \) as compared to the controls (Table 3). In the group of children this same diameter \( (p<0.05, \text{Mann-Whitney U}) \) and also the anterioposterior diameter measured from an midsagittal image \( (p<0.05, \text{Mann-Whitney U}) \) of the mesencephalon were significantly smaller than in the age-matched controls (Table 3). All the other measurements did not differ between Asperger subjects and controls.

**DISCUSSION**

This study was the first controlled brain MRI study of Asperger Syndrome. The subjects were recruited from units operating within a geographically defined area and the examined individuals can therefore be expected to be representative of the Asperger group. The method used for the measurements has been shown to be highly reliable, as the inter-rater reliability has been as high as 0.91 (22).

Neither the visual analysis nor the measurements yielded any support for the concept of AS as being a right hemisphere disorder. The visual analysis revealed minor alterations to be more common in AS.
individuals than in controls, but the findings did not show any pattern suggesting any relationship with the functional characteristics. In MRI studies of the brain in individuals with infantile autism, one the most common findings has been an increase in brain volume (13-15,23). Although we did not perform volumetric measurements, the surface areas of various brain structures did not differ from our healthy controls. We therefore conclude that an increased brain volume is not a feature of AS.

The cerebellar vermis has been found to be significantly smaller in autistic children (24). In the present study, we detected a slightly reduced vermis in two patients. It has been shown that the posterior region of the corpus callosum in infantile autism was smaller than in controls (13), but only two of the individuals in our series had this feature. In a case-control study, Hashimoto et al. (12) found that the mesencephalon and medulla oblongata areas were significantly

Table III. Main diameters in mm showing mean (sd) and areas in cm² of the brain structures in children and adolescents (n=17) (≤ 19 years) and adults (n=11) with Asberger syndrome as compared to the healthy controls (in brackets).

| TABLE III | MAIN DIAMETERS OF THE BRAIN STRUCTURES | CHILDREN ADOLESCENTS | ADULTS | ALL | REFERENCE DATA |
|-----------|--------------------------------------|----------------------|--------|-----|----------------|
| CNS | BRAINSTEM | Anteroposterior diameter measured from a midsagittal image of | | | |
- the mesencephalon | 16.5 (0.3) [17.4] | 16.4 (1.3) [16.4] | 16.4 (0.9) [17.4] | 13 |
- the pons | 21.1 (1.4) [21.4] | 22.4 (1.7) [22.5] | 21.6 (1.6) [21.8] | 16-25 |
- the medulla oblongata | 11.9 (0.9) [11.9] | 12.5 (2.0) [12.2] | 12.1 (1.5) [12.4] | 8-14 |
| | Anteroposterior diameter measured from an axial image of the mesencephalon | 18.2 (1.9) [19.6] | 18.6 (2.0) [19.6] | 18.4 (1.9) [19.6] | |
| | Horizontal diameter measured from an axial image of the mesencephalon | 36.7 (2.4) [36.4] | 38.3 (3.6) [38.4] | 37.3 (2.7) [37.3] | |
| | Surface area measured from axial image of the mesencephalon | 7.83 (0.6) [7.26] | 7.50 (0.7) [7.66] | 7.20 (0.7) [7.40] | |
| CORPUS CALLOSUM | Mid sagittal diameters of | | | | |
- the genu | 16.4 (2.3) [16.6] | 16.4 (1.4) [16.8] | 10.9 (1.6) [10.8] | |
- the rostrum | 5.40 (0.9) [5.50] | 6.70 (1.0) [6.10] | 6.07 (1.1) [5.70] | |
- the splenium | 7.70 (1.1) [8.00] | 10.3 (1.8) [9.50] | 9.30 (1.6) [9.20] | |
| | Surface area | 6.30 (0.8) [6.20] | 7.10 (1.1) [6.90] | 6.60 (1.3) [6.50] | |
| CEREBRUM | Mid sagittal surface area | 157 (11.8) [164] | 161 (5.40) [161] | 159 (10) [163] | |
smaller in high-functioning autistic children than in controls, but
the groups did not differ significantly from one another in terms of
the entire brainstem area (12).

The visual analysis of the present study did not reveal any struc-
tural changes specific for AS, but there were still various more fre-
quent, non-specific small alterations than in controls. There were no
migration abnormalities, reference to metabolic or progressing dis-
eases or anomalies of the centre line. This may be an indicator of
some abnormality in the development or maturation of the brain,
although the pattern does not provide any basis for functional inter-
pretations.

On a general level the visual analysis findings of the present study
appear to be as little conclusive as the corresponding ones in infant-
tile autism. The conclusion is that there is no evident indication for
routine MRI examination in AS individuals.

The measurements suggest that there may be some slight struc-
tural abnormality in the mesencephalon of Asperger individuals. The
findings was most evident in the group of children, which may re-
fect the fact that variation due to external factors over time obscure
the difference in adults. Nevertheless it is evident that the magnitude
of the observed abnormality is relatively subtle. The statistically sig-
nificant differences represented the magnitude of 1.0 mm whereas
the resolution (slice gap) was 1.0 mm. Therefore it is not quite clear
whether this smaller diameter of mesencephalon in the Asperger
group (at group level) really reflects a clinically significant change,
although all the other measurements were highly identical with mini-
mal variation throughout the groups.

Despite the fact that our study is not directly comparable with
respect to the measurements, the results of the study by Hashimoto
and coworkers parallel those of our ones in terms of the mesen-
cephalon. The technical difference between these two studies; the MRI
sections used by Hashimoto and co-workers were 5 mm thick (12),
as compared to 1.0 mm in our study, probably does not play any
major role. In the same way, it is not probable that a minor difference
in the choice of controls would interfere. In our study, the controls
were age- and gender-matched healthy individuals, while in
Hashimoto’s study the controls were examined because of headaches
or mild head trauma (12).

The most interesting question is whether the possible alterations
in the mesencephalon could be related to the behavioural or neuro-
physiological characteristics of AS. Unfortunately, the technique used in this study did not allow us to measure different structures (tectum, tegmentum and basis peduncle) separately and, as a result, the specific affected structures cannot be identified with any certainty with this technique. In high-functioning autism (25), which may not be absolutely discernible from AS, abnormalities in the saccadic eye movements have been shown. Interestingly, the voluntary control of saccades, i.e. rapid eye movements used for quick shifts in visual gaze that are used to look from one object to another, is located in the superior colliculus which is localised within the tectum. The superficial layer of the superior colliculus subserves the visuomotor and visual reflex function and the deeper layers subserve the orientation of the eyes and head to salient stimuli. The pars reticulata of the dopaminergic nucleus substantia nigra, which is also a mesencephalic structure, projects to the superior colliculus. The inferior colliculus, also located in the mesencephalon, on the other hand, is important for hearing and its three main nuclei project to the primary auditory cortex and higher-order auditory areas (26). The mesencephalic region, which was found to be, reduced in size therefore house visual and auditory functions, which appear to relate to the neurophysiological basis of the autism spectrum.

The other part of the substantia nigra, the pars compacta, consists of neurons containing dopamine. It has been speculated that a dopaminergic dysfunction plays an important role in autism (26). Dopamine modulates social behaviour, perception of the outside world, motor activity and attention skills (27,28). The dopaminergic fibres of the pars compacta synapse on neurons in the different parts of the brain, the prefrontal region, cingulate gyrus and amygdala, all of which all are important areas for the development of “theory of mind” skills. A lack of “theory of mind” skills (the ability to attribute mental states to others) is regarded as the basic problem in AS (10,29,30). Mood disorders (depression, anxiety, obsessive-compulsive disorders) (24) are common in patients with AS (3), although it is hard to draw whether the mood disorders are primary or secondary to AS.

The serotonergic system has been implicated in mood disorders and the raphe nucleus partly situated in the mesencephalon is involved in regulating inhibition and anxiety, as well as mediating resilience and enabling a person to cope with ongoing and unavoidable stress. The ascending serotonergic projections of the raphe nu-
culeus synapse on neurons in the amygdala, hippocampus, striatum and cerebral cortex (31). It is therefore not unlikely to assume that the substantia nigra and the raphe nucleus are somehow affected in individuals with Asperger Syndrome and a dysfunction in these nuclei could be compatible with some of the core signs and symptoms of Asperger Syndrome. This is naturally highly speculative and efforts should now be directed towards studying the activation of dopaminergic and serotonergic pathways during specific tests in Asperger individuals in order to determine whether any abnormality can be detected in the mesencephalon.

CONCLUSION
There were no specific structural changes in the brain of individuals with Asperger Syndrome. There is an evident overrepresentation of minor abnormalities. Some of these findings have also been detected in individuals with infantile autism. The most interesting finding was the indication of a slightly reduced size of the mesencephalon in the Asperger group. The significance of this finding remains speculative but calls for both further three-dimensional volumetric and functional neuroimaging analyses.

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REFERENCES
1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed.) Washington DC: American Psychiatric Association (1994)
2. Asperger H. Die autistischen Psychopathen im Kindesalter. Archiv fur Psychiatrie und Nervenkrankheiten 1944:1:76-136
3. Gillberg C. Disorders of empathy: autism and autism spectrum disorders (including childhood onset schizophrenia). In: Clinical Child Neuropsychology. Cambridge: Cambridge University Press, 1995: 54-111
4. World Health Organisation. International classification of diseases (10th ed., chapt. 5). Mental and behavioural disorders. Diagnostic criteria for research. Geneva: Author. (1993)
5. Ehlers S, Gillberg C. The epidemiology of Asperger Syndrome. A total population study. J Child Psychol Psychiatr 1993;34:1327-135
6. Auranen M, Nieminen T, Majuri S, Vanhala R, Peltonen L, Järvelä I. Analysis of autism susceptibility gene loci on chromosome 1q, 4p, 7q, 13q, 15q, 17q, 19q and 22q in Finnish multiplex families. Molecular Psychiatry 2000;5:320-322
7. Philippe A, Martinez M, Gouilloud-Batille M, Gillberg C, Råstam M, Sponheim E et al. Genome-wide scan for autism susceptibility genes. Hum Mol Biol Genet 1999;8:805-812
8. Risch N, Spiker D, Lotspeich L, Nouri N, Hinds D, Hallmayer J et al. A genomic screen of autism: evidence for a multilocus etiology. Am J Hum Genet 1999;65:493-507
9. Vieland V. Results of a genomic screen for autism include strong evidence of linkage to chromosome 13. Am J Hum Genet 1998;63:16
10. Happe F, Ehlers S, Fletcher P, Frith U, Johansson M, Gillberg C et al. Theory of mind in the brain. Evidence from a PET scan study of Asperger Syndrome. Neuroreport 1996;8:197-201
11. Hashimoto T, Tayama M, Miyazaki M, Murakawa K, Sakurama N, Yoshimoto T et al. Reduced midbrain and pons size in children with autism. Tokushima J Exp Med 1991;38:15-18
12. Hashimoto T, Tayama M, Miyazaki M, Murakawa K, Shimakawa S, Yoneda Y et al. Brainstem involvement in high-functioning autistic children. Acta Neurol Scand 1993;88:123-128
13. Schoumistro D, Thompson B. Neuroimaging in autism. Br J Psych 1998;173:299-302
14. Courchesne E, Muller R-A, Saitoh O. Brain weight in autism: Normal in the majority of cases, megalencephalic in rare cases. Neurology 1999;52:1057-105
15. Fonbonne E, Roge B, Claverie J, Courty S, Fremolle J. Microcephaly and Macrocephaly in autism. J Autism Dev Disord 1999;29:113-119
16. Piven J, Bailey J, Ranson BJ, Arndt S. No differences in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J Aut Dev Dis 1998;28:105-110
17. DeLong R. Autism. New data suggests a new hypothesis. Neurology 1999;52:911-916
18. McKelvey R, Lambert R, Mottron L, Shevell M. Right-Hemisphere Dysfunction in Asperger’s Syndrome. J Child Neurol 1995;10:310-314
19. Ehlers S, Gillberg C, Wing L. A screening questionnaire for Asperger Syndrome and other High-Functioning autism spectrum disorders in school age children. J Aut Dev Dis 1999;29:129-141
20. Gillberg IC, Gillberg C. Asperger Syndrome - some epidemiological considerations: a research note. J Child Psychol Psychiatr 1989;30:631-638
21. Laissy P, Patrux B, Duchateau C. Midsagittal MR measurements of the corpus callosum in healthy subjects and diseased patients: A prospective survey. Am J Neurorad 14:145-154,1993
22. Raininko R, Autti T, Vanhanen S-L, Ylikoski A, Erkinjuntti T, Santavuori P. The normal brain stem from infancy to old age. Neuroradiology 1994;36:364-368
23. Ghaziuddin M, Zaccagnini J, Tsai L, Elardo S. Is megalencephaly specific to autism? J Int Dis Res 1999;43:279-282
24. Hashimoto T, Tayama M, Miyazaki M, Murakawa K, Kuroda Y. Brainstem and cerebellar vermis involvement in autistic children. J Child Neurol 1993;8:149-153
25. Minshew N, Luna B, Sweeney J. Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism. Neurology 1999;52:917-922
26. Anderson G. Studies on the neurochemistry of autism. In: Bauman M, Kemper T. The neurobiology of autism. Johns Hopkins University Press, 1994:227-242
27. Ernst M, Zamekkin A, Matzochik J, Pascualcava D, Cohen R. Low medial prefrontal dopaminergic activity in autistic children. Lancet 1997;350:638
28. Martin J H. Neuroanatomy: Text and atlas. MacGraw-Hill, New York, 1996
29. Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M. Another Advanced Test of Theory of Mind: Evidence from Very High Functioning Adults with Autism or Asperger Syndrome. J Child Psychol Psychiatr 1997;38(7):813-822
30. Fletcher PC, Happe F, Frith U, Baker SC, Dolan RJ, Frackowiak RSJ et al. Other minds in the brain: a functional imaging study of “theory of mind” in story comprehension. Cognition 1995;57:109-128
31. Ninan P. The functional anatomy, neurochemistry, and pharmacology of anxiety. J Clin Psychiatry. 1999;60:12-17

Abbreviations

AS Asperger Syndrome
ASDI Asperger Syndrome diagnostic interview
ASSQ Asperger Syndrome screening questionnaire
CSF Cerebral spinal fluid
MRI Magnetic resonance imaging
PET Positron emission tomography

MD Taina Nieminen-von Wendt
Address: HUCH Hospital for Children and Adolescents/Child Neurology
P.O. Box 280, FIN-00029 HYKS, Helsinki, Finland
Phone: +358 9 7572949 or +358 40 5552234
Fax: +358 9 47180688
Taina.Nieminen@sgic.fi