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Children with autism spectrum disorders – The importance of medical investigations

Jørn Isaksen [a,*], *Vesna Bryn* [b], *Trond H. Diseth* [c,d], *Arvid Heiberg* [e], *Synnve Schjølberg* [f], *Ola H. Skjeldal* [g]

[a] *Department of Habilitation, Innlandet Hospital Trust, Maihaugveien 4, 2609 Lillehammer, Norway*
[b] *Children's Department, Hospital of Lillehammer, Innlandet Hospital Trust, Norway*
[c] *Department of Clinical Neurosciences for Children, Women and Children's Division, Oslo University Hospital, Norway*
[d] *University of Oslo, Norway*
[e] *Department of Medical Genetics, Oslo University Hospital, Norway*
[f] *Norwegian Institute of Public Health, Division of Mental Health, Norway*
[g] *Women and Children's Clinic, Vestre Viken Hospital Trust, Drammen, Norway*

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ABSTRACT

Background: Considerable knowledge about medical comorbidity in cases of Autism Spectrum Disorders (ASD) is available, still it is not well established how extensive the medical investigations should be in individual cases. The aim is to explore proportions of possible specific medical conditions in ASD.

Methods: 79 subjects went through extensive medical evaluations according to pre-defined procedures, including medical and developmental history, physical and biomedical investigations.

Results: Clinical neurological findings were quite common, and we found a high number of pathological findings in the additional medical investigations. Our study revealed that these pathological deviations occurred more frequently in patients with childhood autism than in the other diagnostic sub-groups, the exception were chromosomal findings which occurred more often in patients not-diagnosed with childhood autism.

Conclusion: Medical and laboratory investigations should still be performed as a consequence of the patient's history, clinical presentations or family history. We should basically continue the use of non-routine and invasive procedures which do not put the patient at some unnecessary risk, in the absence of relevant clinical indications.

1. Introduction

Autism spectrum disorders (ASD) are a group of complex developmental disorders which are heterogeneous both in aetiology, clinical phenotype, outcomes and concurrent comorbidities. They include several subgroups, such as Childhood autism, Atypical autism, Asperger syndrome, Pervasive developmental disorder unspecified, Disintegrative disorders and Rett syndrome.[1] Common characteristics are reduced interest in socialising and/or reduced ability in

* *Corresponding author*. Tel.: +47 48043106.
E-mail addresses: jorn.isaksen@sykehuset-innlandet.no, joisaksen@gmail.com (J. Isaksen).
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communication and to interact verbally, coupled with limited range of interests and/or stereotypic behaviour patterns.[2]

The prevalence of ASD has been reported to be considerably higher the last years compared to numbers reported 10–15 years ago. In a Norwegian study from 1998 the prevalence rate was estimated to 5.3 per 10.000,[3] while a recently conducted Norwegian prevalence study including 31.015 children, aged 6–12, showed a prevalence rate of 51 per 10.000 for the ASD.[4] Several studies outside Norway have demonstrated the same trend.[5] A British cohort study[6] has reported the highest prevalence of ASD in Europe so far – 116 per 10.000, whereas a newly published South-Korean prevalence report estimates the prevalence to 264 per 10.000 (2.64%).[7]

Pre- and perinatal complications are reported more frequently in groups of ASD than in the normal population.[8] Foetal distress and emergency as well as elective caesarean sections are reported more frequently for children with ASD.[9] There are also reported large variations in Apgar scores.[10] Cases with a diagnosis of childhood autism had more complications related to birth than those with other ASD diagnosis.[11,12]

It is commonly accepted that the pathophysiology of ASD is complicated and multifactorial. In most of the patients it is not possible to identify any etiological explanation for the disorder, in spite of extensive medical investigations.[13] However, in about 10% of the patients with ASD a concurrent medical disorder is found[14,15] though the etiological relationship to the ASD group is most often unclear. The medical disorders showing the most convincing evidence being related to autism are Tuberous sclerosis and Fragile X syndrome, although these conditions are only found in a minority of the patients diagnosed with ASD, probably less than 5%, taken together.[16] Other genetic conditions reported as associated with ASD in that the syndrome phenotype may show overlap with ASD are Angelman, Cornelia de Lange, Cri-de Chat, CHARGE syndrome and Myotonic Dystrophy syndromes. Some patients with Down syndrome, Neurofibromatosis type 1, Noonan syndrome, Williams' syndrome, Duchenne muscular dystrophy and Soto syndrome also show symptom overlap with ASD. Metabolic disorders such as untreated Phenylketonuria,[17] Homocystinuria,[18] Ureacyklus disorders,[19] Mucopolysaccharidosis,[20] defects in purine/pyrimidines metabolism[21] and mitochondrial defects[22] are also claimed associated with the ASD group. However, the additional yield of metabolic screening investigations in a group of ASD is low.[13]

The research in later years has brought up an increasing number of different findings of relevance for causal hypothesis like MRI findings, chromosome aberrations and gene locations associated with ASD. As for MRI studies it is important to note that no consistent association between autism and different brain abnormalities have been detected.[23] Different types of radiological methods have been used in patients with ASD, but common to most of these studies is a low rate of detected abnormalities.[24] Corpus callosum abnormalities, temporal lobe abnormalities, hypoplasia of the cerebellar vermis and asymmetry of lateral ventricles have been found in ASD patients. However, these findings have not contributed to any etiological explanation. A potentially more valuable result is that functional MRI during different task challenging comprehension, indicated a lower degree of connectivity and information integration across cortical and other networks involved in language and memory processing as a possible neural basis of disturbed language and brain activity in autism.[25] However, whether these MRI findings lead us to new etiological explanations of ASD remains to be seen.

Furthermore, known chromosome abnormalities are reported to account for approximately 7% of cases of autistic disorder.[26] Microarray studies have consistently pointed to duplications/deletions on chromosomes 2q13, 15q13, 16p11. Linkage association studies have also pointed to possible loci on chromosomes 7, 17, 22 and X,[26] but no specific genes are still consistently identified.

The contribution of these findings for possible etiological explanation and implication is still not clear. The same can be said about the genetic studies done. There is no doubt that autism and autism related disorders to a large extent are of genetic origin. The genetic studies have suggested many different genes contributing to the ASD phenotype. It seems reasonable to believe that both genetic and environmental factors including that of epigenetic influence[27,28] play an important etiological role in ASD. Lately there is suggested a direct link between implicated genes in ASD and molecular pathways involved in immune signalling. The attention to the immune response in previous ASD research has resulted in two prevailing theories[1]: exogenous factor(s) stimulate neuroinflammation during development, and[2] an autoimmune activation causes ASD pathology.[29]

In the context of discussing medical evaluation of patients with autism it is important to note that children with ASD are also more vulnerable to medical associated disturbances such as seizures, sleeping problems and gastrointestinal disorders.[30] Furthermore, many patients with ASD fulfil the criteria for different behavioural disorders, such as anxiety disorders, obsessive compulsive behaviour, ADHD, bipolar disorder with psychotic features, schizophrenia or other psychotic disorders.[31] In a few ASD patients there is as well reported of occurrence of narcolepsy.[32]

However, despite considerable knowledge about medical comorbidity in cases of ASD, it is not well established how extensive the medical investigations should be in individual cases. Experiences from clinics throughout Norway show that the content and thoroughness of medical examinations of children with ASD are characterised by great variability and are not necessarily governed by the patterns of symptoms shown by the patient. Due to this experience the Regional Health Authority in Norway has developed guidelines for diagnosing ASD.[33] All implicated health entities responsible for diagnosing ASD are now supposed to use these guidelines, therefore we used them as basis for this examination.

The purpose of this paper is to descriptive explore the outcome of a recommended, established routine medical examination[33] in a population based cohort of children diagnosed with ASD, according to ICD-10 criteria.[1]

2. Method

2.1. *Subjects*

Subjects presented in this paper were all clinical diagnosed with ASD. Seventy nine children were included, 20 girls and 59

boys, with a mean age 9.1 year at the time of diagnostic assessment (range 5.7 year–12.8 year). IQ below 70 points on Wechsler Intelligence Scale for Children (WISC) were found in 25.3% of the sample and 45.6% were diagnosed with Childhood autism and 24% as Asperger syndrome. See Table 1 for sample characteristics.

Participants in the study were enrolled as part of an epidemiological survey covering two counties in Norway, Oppland and Hedmark,[4] aimed at identifying all children with ASD in the geographical region. In the epidemiological study, children were selected for assessment on the basis of two criteria, a decision of being eligible for special education either documented through the school authorities or the Child Habilitation Services (CHS) combined with reaching a cut-off score on the Social Communication Questionnaire (SCQ). The diagnostic assessment was conducted based on the ADI-R,[34] the ADOS[35] and the ICD-10 criteria[36] of any ASD diagnosis. The cohort is further described in a previous paper.[4] All children who fulfilled diagnostic criteria for ASD and agreed to participate in further investigations were provided medical examination in accordance with the guidelines prepared by Regional Health Authorities.[33]

2.2. *Medical investigations*

All the subjects went through an extensive medical evaluation according to the procedures from Regional Health Authority, including medical and developmental history, physical and biomedical investigation and additional investigations (Fig. 1). The medical examination aimed to identify the proportions of children with ASD having other specific medical conditions and ASD.

2.3. *Medical records*

Information on medical conditions was collected during the medical investigations in this study. In addition, we captured medical information from medical records. Important information and collected data were summarised in medical case summaries, including reports from parents in the form of the returned questionnaires, containing information about medical and developmental aspects of their child.

Table 1 – Clinical characteristics in 79 patients with ASD. Values are reported as *n* (%) unless otherwise stated.

Sample characteristics	N (%)
Sex	
Male	59 (74.6)
Females	20 (25.3)
Age (y); mean, range	9.1 (5.6–12.7)
Mental retardation	
WISC IQ < 70	20 (25.3)
TONI IQ < 70 (Non verbal IQ)	6 (7.6)
ICD-10 diagnosis	
Childhood autism	36 (45.6)
Atypical autism	15 (19)
Asperger syndrome	19 (24)
Rett syndrome	2 (2.5)
Other ASD	7 (8.9)

2.4. *Approvals and ethics*

Information about all aspects of the project was given to parents invited into the study and a written consent was obtained from the parents before children were included in the project. The consent permitted the project to make further contact to ask for further assessment of their children after the initial screening was completed. The Regional Committee for Research Ethics approved the project and procedures. The study was also approved by the Norwegian Data Inspectorate.

3. Results

Birth related characteristics of all 79 children identified with ASD are shown in Table 2.

One third (32.9%) had some anomalies in their birth history; perinatale asphyxia, resuscitation, forceps/vacuum delivery, respiratory distress, meconium-stained fluid, perinatale infections, birth injuries, premature labour (<37 wk), postdates (>42 wk), birth weight <2500 g or >4000 g, congenital malformations. Nearly 20 per cent of the ASD cases were delivered by Caesarean section, planned or emergency. The head circumference in the investigated children did not differ from the norms of 35 cm.

Table 3 displays medical syndromes found among the patients. In 8 (10.1%) of the children a specific medical syndrome were found in addition to ASD.

Furthermore, ADHD were diagnosed in 5%, and Tourettes syndromes were diagnosed in 1.3% of the sample. Neurological findings such as brain nerve pathology, motor disturbances, nystagmus, cerebellar pathology and sensory dysfunction were relatively common among the patients with ASD, and especially in the childhood autism group (21.4%). Dysmorphic findings were detected in 20.6% of the patients. Café au lait spots, were observed in 6 patients (7.8%).

EEG findings are reviewed in Table 4, and of the 16 patients (20.2%) with pathological findings, 9 have a clinical diagnosis of epilepsy according to ICD-10 criteria and were treated with different kinds of anti-epileptic medication.

Genetic findings (chromosome aberrations or gene mutations) were found in 25 of 79 (31.6%) of the ASD cases. Different chromosome aberrations or DNA changes were found in 25 cases whereas only 18 (22.8%) were considered as associated with ASD, either by findings in literature or through careful clinical genetic examination of each case. All genetic findings and findings from Array CGH, were discussed with a specialist in clinical genetics, and are presented in Table 5. Only findings earlier reported as associated with ASD and positive reports after genetic evaluation are classified as associated findings.

Pathology on CT or MRI was found in 22.8% of the cases. The specified findings from the neuroimaging investigations are shown in Table 6. Microcephali were seen in 11.4% of the patients and 8.9% were classified as macrocephalic when the diagnostic definition used is head circumference under 10 percentile and above 90 percentile, according to Norwegian norms.

Of concurrent behavioural disorders, obsessive compulsive behaviour were reported by parent in 56.7% of the cases,

Medical and developmental history

- Medical history specially with emphasis on birth, medical comorbid symptoms and family history, early development and characteristics of development, age and nature of symptom onset
- Sleep anamnesis
- Assess natural functions, eating pattern / feeding anamnesis and gastrointestinal symptoms
- Identify existing psychiatric disorders (comorbidity)
- Provide an assessment in relation to psychomotor development, attention functions and contacts capability

Physical investigation

- Assessing somatic problems in each child
- General status (height, weight, head circumference, vision, complete hearing examination, organ status)
- Neurological examination (stigmata, skin phenomena, gross and fine motor skills, coordination, reflexes, soft signs)

Additional investigation

- Blood tests (iron, liver status, thyroid function, allergies, immunology screening, haematology, celiac disease)
- Chromosome investigation (Array CGH) and specific investigations for Fragile X and 22q 11 and other known chromosomal conditions. Implemented for all patients when the clinical picture at Fragile X is difficult to separate from the ASD, especially in the early childhood.
- Metabolic screening of urine
- Genetic testing taken on suspicion of other syndromes, as example Retts syndrome by MECP 2 and Angelman syndrome by DNA
- EEG were taken of all children with autism, when possible supplemented with sleep deprivation EEG
- Complete eye exams
- Broader metabolic tests, including cerebrospinal fluid examination.
- Woods Lamp inspection for suspected tuberous sclerosis (TS)
- Other genetic investigations carried out on clinical indication
- Cerebral MRI done on specific indication and in some cases substituted by CT.

Fig. 1 – The protocol of medical investigation (Regional Health Authorities).[33]

Table 2 – Birth related characteristics. Values are reported as *n* (%) unless otherwise stated.

Characteristics	
Birth weight in gram; mean, (range)	3362 (1274–4920)
Birth length in cm; mean, (range)	49 (37–56)
Birth complications	26 (32.9)
Elective caesarean section	15 (19.0)
Emergency caesarean section	8 (10.1)
Apgar score: mean, (range)	
1 min	8.21 (3–10)
5 min	9.03 (6–10)

gastrointestinal manifestations were reported in 46.8%, sleep disturbances in 39.2% and feeding disturbances in 32.9%. Two children were identified with narcolepsy included in the 31 (39.2%) of the children already reported as having any kind of sleeping disorder.

4. Discussion

This study reveals that medical disorders or manifestations are highly prevalent in children and adolescents diagnosed with ASD. Abnormal clinical neurological findings were quite common, and we found a high degree of pathology as a result of the additional medical investigations. Even though the

Table 3 – Medical syndromes found in the ASD cases.

Diagnostic label	Medical syndromes	(N)
F84.0	Kabuki syndrome	1
	Down syndrome/CHARGE syndrome	1
	Down syndrome	1
F84.1	Neurofibromatosis	1
F84.2	Rett syndrome	2
F84.5	Klinefelter syndrome	1
F84.9	Klinefelter syndrome	1

sample size does not allow us to determine the true association between a specific medical condition and ASD, we found that pathological deviations occurred more frequently in patients with Childhood autism than in the other diagnostic sub-groups, the exception were abnormal chromosomal findings (Array CGH) which occurred more often in ASD patients not-diagnosed with childhood autism. In contrast to Miller and Wu,[37] we did not find the reported correlation between degree of mental retardation and the occurrence of chromosome deviations.

4.1. *Birth complications*

Whereas as many as 29.1% of the children were delivered by caesarean sections, the prevalence of caesarean section, including emergency caesarean sections, in the general population of the area is reported to be about 17%.[38] Furthermore, in 32.9% (Table 2) some kinds of birth complications were noted. This is consistent with previous reports showing that children with autism spectrum disorders have higher rates of birth complications than unaffected children.[39] Autism is unlikely to be caused by a single obstetric factor. The increased prevalence of obstetric complications among autism cases is most likely due to the underlying genetic factors or an interaction of these factors with the environment. Findings from our study, are supported by the general hypothesis that systemic problems at the prenatal stage may form a distinct dimension of risk associated with autism.[12] Thus, it is important to underscore the need to obtain a thorough medical history in each child, focussing on circumstances before, during and after birth.

4.2. *Medical conditions/syndromes*

For some ASD associated syndromes and conditions no or limited epidemiological data exits, due to their rarity. We identified one case of Down syndrome (1.3%). The reported prevalence of Down syndrome in ASD in other studies varies from 0 to 16.7%, but most studies report prevalence rates of 1–2%.[12,15] We did not identify any cases of Fragile-X syndrome, tuberous sclerosis or Angelman syndrome. The reported prevalence of Fragile X syndrome is reported to be 2.1%[40] and Tuberous sclerosis is reported to occur in 0–3.8% of ASD cases.[26,40] The prevalence of Angelman syndrome in ASD cases is reported to be 1%.[41] It is reasonable to explain the low identification of these groups with low sample sizes and small populations.

Klinefelter syndrome occurs in 1 of 500 in the population.[42] In our ASD population the prevalence were 2.6% which is higher than what is expected in a normal population. Autistic features may be more common in persons with Klinefelter syndrome than generally believed.

The condition, Chiari type 1 malformation was found in two of the 79 patients, even though only the children with a suspected brain dysfunction had been to MR imaging. Compared to Chiari type 1 malformation discovered with routine use of MR imaging in the general population with a prevalence rate of 0.1–0.5%,[43] there are reasons to believe that autistic features is more common among patients with Chiari malformation. Surgery may be an appropriate treatment in these patients. Individuals with Chiari type 1 malformation and ASD, or vice versa, have improved functioning and shown less autistic symptoms after treatment.

Table 4 – Results of medical investigations in 79 patients with ASD. Values are reported as *n* (%).

Characteristics	Childhood autism	Asperger	Other ASD
Neuroimaging pathology	8 (10.1)	5 (3.8)	2 (2.6)
Chromosome aberrations	8 (8.9)	6 (5)	6 (5)
EEG	11 (13.9)	2 (1.3)	3 (6.3)

4.3. *Clinical symptoms*

Medical conditions investigated in this study encompass a range of disorders, from common child diseases to more ASD related conditions. ASD related conditions refer to conditions earlier described in literature as associated with autism spectrum disorders. Association with metabolic disorders have been reported. Untreated phenylketonuria, classical homocystinuria and Sanfilippo disease are among the conditions which have been reported associated with ASD. Screening for metabolic disorders was performed in all our ASD patients, involving abnormalities in metabolism of urinary purines and pyrimidines, urinary organic acids and plasma amino acids. Furthermore, all our patients underwent tests for the peroxysomal and mitochondrial disorders. On the basis of these investigations we have no evidence to believe that any of the patients have a metabolic disease. This is in accordance with a recent report by Schiff et al.,[13] who investigated 273 patients with ASD without finding any cases with metabolic disorder. In our opinion this indicates that undiscovered classical metabolic disorders are rare among patients with ASD. A much larger sample size will be needed to determine any association between ASD and metabolic disorders.

4.4. *Neuroimaging*

Some of our patients showed abnormalities on MRI and CT scan. The abnormalities found (Table 6) were unspecific and they did not indicate any kind of a specific medical disorder. If MR and CT are considered the potential risks of these investigations must be evaluated and balanced against the probability of diagnostic yields from the examination. There must always be considered whether an investigation could lead to

Table 5 – Findings from Array-CGH.

ASD subgroup	Patient ID	Description of findings, as reported from the clinical geneticist, at department of genetics..	Associated/ non associated (+/−) *
F84.0	12	Duplication 8q11.21	+
	17	Deletion16p11.2 (previously reported)	+
	13	Duplication 6q24.1 (500Kb)	+
	37	Deletion 4q32.2	–
		Duplication 15q11.2 and 2q13.2 (8 Mb)	+
	5	1p36.22 p36.21	+
	53	Balanced translocation: 46xx, t (7,19) (p10q10)	+
	26	16p11.2 Micro deletion (400Mb)	+
	19	Deletion 7q31.33	+
		Duplication 1p13.2(chromosomal rearrangement)	+
F84.1	21	7q31.1	–
	5	Deletion 2q22.3-q23.1 (900Kb)	+
	47	18q11.2	–
	39	Duplication 16p13.11 (800Kb)	+
F84.2	79	MECP 2	+
		Heterozygote S134C	+
		Heterozygote S166F	–
	29	MECP 2 Heterozygote 1156del44 bp	+
F84.5	3	Duplication 16q.11.2 (320 Kb)	+
	27	Duplication 1p36.33 (150Kb)	+
	46	Deletion 16p11.2 (500Kb)	+
	71	Duplication 7q22.1 / (240 kb)	+
		Duplication 9q34.3	–
	60	Deletion 18p11.2	+
	6	Klinefelter syndrome, (47) xyy	+
		Duplication: Xq13.1 (90Kb)	–
	71	Deletion: 10q23.33	–
F84.9	22	Deletion 15q13.1/ q13.3 (4Mb)	+
	2	Klinefelter syndrome (47,xyy)	+
	7	Duplication 1q25.2	–

The sizes of the aberrations are presented, if reported from the genetic laboratory.
* Possible causally related to ASD.

Table 6 – Neuroimaging.

ASD label	Description
F84.0	Enlarged temporal horn and hippocampus asymmetry Temporal lobe cyst Hypoplasia of right frontal lobe Hypoplasia of right cerebral hemisphere Enlarged perivascular space on subcortical frontal area Large cisterna magna, enlarged subarachnoidal spaces around brainstem. Focal enlarged spaces in sulcus cerebellaris Corpus pineale cyst Thin corpus callosum and lateral ventricular dilatation, right side (intrauterine vascular insult) Dilated third and lateral ventricles Mega cisterna magna
F84.1	Hydrocephalus
F84.2	Neuroepithelial cyst in thalamus 3 × 3 mm
F84.4	Chiari type 1 malformation
F84.5	Chiari type 1 malformation Abnormal signal in white matter, subcortical and periventricular Abnormal signal in white matter subependmal on the right side (periventricular leukomalacia)
F84.9	Retrocerebellar cyst

some form of treatment, unless the examination may be unnecessary. It is possible that some non-routine procedures which do not put the patient at unnecessary risk should be used, in the absence of relevant clinical indications.

4.5. EEG

In our study we identified 17 cases (20.2%) with irregularities on EEG, of these cases 9 were diagnosed with epilepsy. Increased rates of epilepsy have long been reported in ASD, but prevalence estimates vary from as little as 5% to as much as 46%.[44] The occurrence of epilepsy and EEG pathology found in this study compares to other studies with low/medium incidence. Due to a broadened spectrum of autistic disorders, and specially the increase in cases diagnosed with Asperger syndrome, it is reasonable that the percentage of epilepsy in ASD in total is decreasing. Our study finds that the occurrence of epilepsy is higher among children with childhood autism than in all the other subgroups taken together.

4.6. Chromosomal findings

Array CGH identified a spectre of different deletions, duplications and other cytogenetic malformations. Since the

sample is so small, we report only those findings that have previously been documented in larger studies with larger samples. In addition, positive reports from genetic evaluation including sampling parents, are classified as associated findings. Several chromosomal abnormalities are associated with childhood autism.[45] A striking finding in our study was the high frequency of chromosome deviations in children with relatively high functioning, low degree of dysmorphology and being in other subgroups than Childhood autism.

4.7. *Parent reported behavioural conditions*

Of parental reported conditions, obsessive compulsive behaviour, sleeping disorders and feeding disorders were the most common. The reported occurrence of obsessive compulsive behaviours in 57% of the cases, even in the absence of high scores on compulsive and repetitive behaviour as assessed in the ADI and SCQ, are significantly higher than the occurrence in the normal population and compared to reports for most other developmental disorders. The high occurrence could also be the result of misinterpreting core ASD features (e.g. fixated interests, adherence to routines) or of the idiosyncratic nature of the subject sample. Whereas the findings of sleeping disorders (39.2%) and feeding disorders (32.9%) are comparable with findings in other studies.[46] These findings underscore the need to obtain a thorough developmental and medical history, so that these difficulties can be treated at an early stage. The need for sleep and food must be seen as fundamental factors in child development and should be taken seriously.

4.8. *How necessary is the supplemental medical investigations in children with ASD?*

There have been various findings in the literature concerning the prevalence of diagnosable medical conditions in people diagnosed with ASD and the arguments used to implicate each as relevant in the causal processes for ASD have also varied (16; 48). One of the major difficulties in identifying precise estimates of the association is due to that the findings are influenced both by the nature of the samples investigated and the thoroughness of the medical investigations undertaken. However, a reasonable estimate would be that 10–20% of individuals with ASD have some potentially relevant identifiable somatic disease or disorder. This means that an appropriately extensive medical assessment is essential in all cases.

An appropriate clinical evaluation of all clinical signs is crucial; such a medical practice appears to be more reasonable and cost effective than a systematic medical/laboratory work-up based on a schedule. The general consensus would be that this should include careful medical examination, including the use of Wood's light, in order to detect tuberous sclerosis; that karyotyping should be routinely undertaken, but also that this should include the use of DNA methods to diagnose the Fragile X anomaly as well as an array CGH.

4.9. *Strengths and limitations of the study*

The ASD group evaluated in this study was clinically well diagnosed, and, as a part of our investigation, all had their diagnosis verified by the use of gold standard instruments, (ADI-R, ADOS) of certified professionals. They all underwent a thoroughly medical evaluation, done by highly qualified paediatricians and standardised guidelines were followed.[33]

When generalisability are evaluated, the sample size ($n = 79$) must be taken into account. With a larger sample we could to do more accurate estimation of the association of rare medical conditions to ASD.[41]

5. Conclusions

The findings of this study, despite a small sample, are largely in line with existing literature in the field. The new and most interesting finding in this study are the chromosome aberrations, that are detected in individuals with ASD and relatively high functioning. This is not reported in other studies, as far as we know.

Clinically, it is important to provide children with ASD the correct adequate treatment and support, because we know that this is essential for their further development and well being. Treatment of comorbid medical conditions may result in a substantial improvement of quality of life both of the child and their parents. What investigations should be implemented can vary both within the autism spectrum and individually.

It appears to us that medical and laboratory investigations should still be performed as a consequence of the patient's history, clinical presentations or family history.[18,24] We should basically continue the use of non-routine and invasive procedures which do not put the patient at some unnecessary risk, in the absence of relevant clinical indications for such a procedure. There must be considered whether an investigation could lead to some form of appropriate treatment, unless the examination may be unnecessary and cause the patient an unnecessary risk. Comorbidity is to be expected in autism spectrum disorders – directly or indirectly. Comorbid conditions may be markers for underlying pathophysiology and request a more varied treatment approach. There is a great need for in-depth research into this area, meaning that the exclusion criteria, of current diagnostic manuals, i.e. those that rule out a diagnosis of autism in some disorders, and a diagnosis of certain other disorders in autism may have to be revised.

Contributors

All authors contributed to all parts of this work, including the design, writing, editing and integration of editing as suggested from co-supervisors.

Conflicts of interest

We declare that we have no conflicts of interest.

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