



ORIGINAL ARTICLE

Co-morbid developmental impairments and their co-occurrence in five-year-old boys with autism spectrum disorders



I.A. Kelmanson^{a,b}

^a Department of Children's Diseases, Institute for Medical Education of the V.A. Almazov National Medical Research Centre, Akkuratova Str., 2, St. Petersburg 197341, Russia

^b St. Petersburg State Institute for Psychology and Social Work, Vasilyevsky Ostrov 12th Line, 13-A, St. Petersburg 199178, Russia

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Abstract

Background and objectives: Co-morbid developmental deficits in children with autism spectrum disorders (ASD) are important for both clinical and empirical reasons. This study aimed to measure developmental problems related to motor function, perception, learning, language, and social skills in preschool-aged children with ASD and to look at their possible co-occurrences. **Patients and methods:** The study comprised 18 five-year-old boys with a diagnosis of ASD and 54 typically developing controls. Mothers were approached with the parent version of the Five-to-Fifteen Questionnaire (FTF). To explore possible co-occurrences of developmental problems, a network analysis was performed.

Results: The ASD children presented with higher values (more problems) on the fine motor skills, the perception of forms and figures, the learning, as well as on the social skills. According to the network analysis, co-occurrences of the developmental problems without any obvious mediator variable were characteristic of the typically developing children. Co-occurrences of the developmental problems in the ASD children were more limited and were most prominent between the perception abilities linked with verbal communication, ability to solve problems and fine motor skills. The relation in space had the highest value on the betweenness score thus implying its mediating effect. ASD children presented with a specific constellation of developmental problems reflecting the principle of a nontrivial topology of psychopathological network.

Conclusion: ASD children have co-morbid developmental impairments that co-occur in a specific pattern, and new techniques that can accommodate the complex associations between symptoms present in an individual patient with ASD are needed.

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E-mail address: iakelmanson@hotmail.com

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Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in social and communication skills, restricted and repetitive behaviors.¹ The prevalence of ASD has risen over the past several decades, and ASD is now considered urgent public health concern.² The median ASD prevalence rate for the surveys published in the period 1994–2004 was 12.7 per 10 000, and the male/female sex ratio varied from 1.33 to 16.0, with a mean male/female ratio of 4.3:1.³

Co-morbid developmental deficits in children with ASD are important for both clinical and empirical reasons. However, the specific studies are much recent and yet inconclusive. It has been acknowledged that, in children with ASD, verbal and nonverbal communications are impaired to some degree and that some children never acquire functional speech.⁴ Co-morbidity of ASD and intellectual disability (ID) was shown to increase the complexity and severity of communication deficits.⁵ In addition, children with ID, as well as those with ASD, have significant deficits in social skills used to facilitate interaction with others.⁶ Children with co-morbid ASD and ID present with greater impairments in social skills than those with ASD or ID only.⁷ Recent reports indicate that a strong moderating relationship may exist between motor skill development and social communicative skills.^{8,9} Evidence suggests that contextually inappropriate behaviors such as avoidant, self-injurious, and/or disruptive behaviors may be related to poor fundamental motor skill development.^{9,10} On the other hand, cognitive functioning,¹¹ language development,¹² social communication,⁹ and on-task behaviors¹⁰ are more likely to exist among children with ASD with good motor skill development.

Therefore, co-morbid developmental deficits in ASD are likely to be interrelated, and they can exacerbate ASD symptoms, reduce overall functioning, and result in poorer clinical outcomes over time. However, this issue needs further clarification.

This study aimed to measure parental-reported developmental problems related to motor function, perception, learning, language, and social skills in preschool-aged children with ASD and to look at their possible co-occurrences.

The study

Participants

The study group comprised preschool 5-year-old boys from the community setting with a diagnosis of ASD who attended a special child-rearing center at the time of the study, that is, in 2017. Inclusion criteria were that the children were singletons and lived in the families with appropriate household conditions; they did not have severe co-morbidities, such as seizures, visual and acoustic impairment, orofacial and inner organ malformations. Control group was made up of healthy typically developing normal boys who attended the pre-school daycare centers (case/control ratio: 1/3), matched to the case children for age at study, date of birth and geographical distribution as close as possible. Required information was drawn from the pre-existing medical records stored at the pediatric out-patient centers.

Required sample size computation was performed using G*Power 3.1.5 statistical software.¹³ The study was targeted at determining a large standardized effect size for the differences between two means (Cohen's $d = 0.8$), based on the two-tailed Wilcoxon–Mann–Whitney test, with the α error equal to 0.05, and the power ($1 - \beta$) equal to 0.8. With allocation ratio (cases/controls) equal to 3, this yielded the desired sample sizes in the cases group equal to 18 and in the control group equal to 54 children.

The children who were included in the study were selected from the eligible candidates by chance (a simple random sample). All parents of the recruited children agreed to participate in the study (participation rate of 100%).

Measures

Socio-demographic characteristics

The mothers were asked to complete the questionnaires addressing child, maternal, demographic major characteristics. To ensure reliability and to minimize recall bias, attention was paid to the thorough analysis of pre-existing medical records. The parental educational level was defined as the highest level of completed education and categorized as basic education (elementary school), secondary education (secondary school, college), higher education (institute, academy or university), or incomplete higher education.

Questionnaire for evaluation of developmental deficits

Mothers of the children were approached with the parent version of the Five-to-Fifteen Questionnaire (FTF). The FTF comprises 181 items that can be endorsed as “does not apply” (0), “applies sometimes or to some extent” (1), or “definitely applies” (2). Items are arranged into certain general domains, and this present study accounted for the severity of the problems in the following 5 scales: motor skills, perception, language, learning, and social skills. The domains can be further divided into sub-domains investigating gross and fine motor skills, perception of space, time, and body, as well as visual perception, comprehension, speech, communication skills, reading/writing, math, general learning, coping skills during learning, as well as social skills. The (sub)domain scores are calculated as the mean value of the included domain (sub)domain items as described in the FTF questionnaire instructions, with higher scores representing greater childhood difficulties.¹⁴ The Russian version of the FTF downloaded from the official website (<https://www.5-15.org>) was used in this study.

Data analysis

The methods of descriptive and analytical statistics were used. Statistical significance of the differences between two groups in consideration was evaluated using two-tailed Mann–Whitney U test for continuous variables and χ^2 or Fisher exact test when appropriate for categorical variables.¹⁵

A one-way multivariate analysis of variance (MANOVA) was conducted to test the hypothesis that there would be the overall difference between the child category (ASD vs. controls) and either 5 FTF scales or 13 FTF sub-scales in consideration. The Pillais' Trace multivariate test was used to judge about statistical significance, and the partial eta-squared (η^2) value was used as a measure of the overall effect-size with an η^2 of 0.01, 0.06 and 0.14 referring to small, medium and large effect sizes, respectively.¹⁶

Post hoc comparisons between the values of the 5 global FTS scales and the 13 FTF sub-scales in the ASD and the control children were performed. Statistical significance of the differences between two groups in consideration was evaluated using a two-tailed Mann-Whitney *U* test. To compare the effect sizes of the ASD on different characteristics estimated by the FTF, post hoc evaluations of the standardized effect sizes with 95% confidence intervals were performed. The effect sizes were calculated in terms of the rank-biserial correlations (r_B), with a r_B of <0.1, 0.1, 0.3 and 0.5 referring to trivial, small, medium and large effect sizes, respectively.^{16–18}

The value for significance was set at $p < 0.05$. Statistical analyses were performed using The IBM SPSS Statistics 22 software (Armonk, NY, USA) and JASP 0.9.0.1 software.¹⁹

To explore possible co-occurrences of developmental problems in children from the two groups, a network analysis was performed using JASP 0.9.0.1 software,¹⁹ proved effective in the studies on ASD patients.²⁰ Network analysis is a method for modeling interactions between large numbers of variables. Instead of trying to reduce the structure of the variables to their shared information, as is done in latent variable modeling, it estimates the relationship between all variables directly. To conduct a network analysis in JASP, the 13 FTF sub-scores in consideration were selected as dependent variables. Correlations were used as the estimators to obtain descriptive networks (association network). To control the family-wise error rate, thresholds were set to a Bonferroni method showing edges significant at the 0.05 level with the Bonferroni multiplicity correction.

The nodes of the network were positioned using the Fruchterman-Reingold algorithm that organizes the network based on the strength of the connections between nodes.

A number of conventional statistics (centrality measures) were used in network analysis, including *betweenness* (number of shortest paths that pass through the node of interest), *closeness* (the inverse of the sum of all shortest paths from the node of interest to all other nodes), and *degree* (the sum of the absolute input weights of that node). In general, a higher centrality measure indicates that this node is more central to the network. The estimated network was weighted and not directed. Centrality measures were normalized to ensure each centrality measure has a mean of zero and a variance of one, enabling their comparisons.^{21,22}

Ethical considerations

The study has been approved by the institutional ethics committee. Informed consent for the participation in a scientific study was obtained from all mothers involved, and confidentiality was guaranteed.

Results

The items in consideration were applicable to all respondents, and there were no user-defined missing values. Further analysis did not find any missing data.

Major clinical and demographic characteristics of the two groups in comparison are listed in Table 1. No statistically significant differences were found between two groups for the major demographic characteristics. Children with ASD more frequently had birth trauma, upper respiratory symptoms. These findings are consistent with the known risk factors of ASD. The majority of the ASD children (13 of 18 cases) had an IQ above 70, as measured by the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV).²³

Developmental and behavioral problems

Mothers did not have any difficulties in understanding the language, the meaning of the questions and in selecting appropriate answers within the FTF. The internal consistency of the FTF was quite acceptable: Cronbach's alpha for the specific scales within the questionnaire ranged between 0.72 and 0.85.

A one-way MANOVA analysis was performed to find the possible effect of the child category on the 5 global FTF sores in consideration (motor skills, perception, language and communication, learning skills and social skills). A statistically significant MANOVA effect was obtained, Pillais' Trace = 0.37, $F(5, 66) = 7.83$, $p < 0.001$. The multivariate large effect size was estimated at η^2 equal to 0.37. Another one-way MANOVA was performed to find possible effect of the child category on the 13 FTF sub-scores (gross motor skills, fine motor skills, relation in space, time concept, body perception, perception of forms and figures, comprehension, expressive language skills, verbal communication, reading, spelling, writing, math; ability to solve problems, learning new skills, and social skills). Likewise, there was a statistically significant difference in the FTF sub-scores based on a child category: Pillais' Trace = 0.55, $F(13, 58) = 5.55$, $p < 0.001$. Partial η^2 was equal to 0.55, indicating a large effect size of the difference in the levels of the FTF sub-scores between ASD and typically developing children.

These findings allowed to perform post hoc multiple comparisons for the observed values, and Table 2 is the summary. The findings were that ASD children had statistically significantly higher values (more problems) on the motor skills (specifically, the fine motor skills), the perception of forms and figures, the learning skills (reading, spelling, writing, math; ability to solve problems), as well as on the social skills with moderate to large effect sizes. The largest effect size of the child category was found for the differences in the fine motor skills sub-scale. However, 95% confidence limits around the point estimates of the effect sizes for all mentioned sub-scales were largely overlapping.

To explore possible co-occurrences of the major developmental and behavioral problems in ASD and typically-developing children, a network analysis was performed, in that the nodes of the network were the specific FTF sub-scales, while the edges between the nodes corresponded to

Table 1 Descriptive statistics. Median (minimum–maximum values) or number of cases (%).

Characteristic	ASD children (n = 18)	Control group (n = 54)	p ^a
<i>Birth weight, g</i>	3400 (3125–3800)	3500 (3150–4150)	0.666
<i>Gestational age, weeks</i>	40 (39–40)	40 (36–43)	0.456
<i>Weight at study, kg</i>	18 (17–22)	24 (20–23)	0.356
<i>Birth trauma</i>			0.0013*
No	12 (67)	50 (93)	
Yes	6 (33)	4 (7)	
<i>Perinatal hypoxia</i>			0.099
No	12 (67)	46 (85)	
Yes	6 (33)	8 (15)	
<i>Birth order</i>			0.38
1	10 (56)	38 (70)	
2	8 (44)	15 (28)	
3+	0 (0)	1 (2)	
<i>Low IQ (<70)^b</i>			0.00061*
No	13 (72)	54 (100)	
Yes	5 (28)	0 (0)	
<i>Gastrointestinal symptoms</i>			0.060
No	16 (89)	54 (100)	
Yes	2 (11)	0 (0)	
<i>Upper respiratory symptoms</i>			0.00015*
No	11 (61)	53 (98)	
Yes	7 (39)	1 (2)	
<i>Maternal age at study, years</i>			0.12
<20	0 (0)	1 (2)	
20–24	0 (0)	13 (24)	
25–29	12 (67)	28 (52)	
30+	6 (33)	12 (22)	
<i>Maternal marital status</i>			0.89
Married	9 (50)	28 (52)	
Other	9 (50)	26 (48)	
<i>Maternal education</i>			0.49
Higher	14 (78)	38 (70)	
Incomplete higher	3 (16)	7 (13)	
Secondary	1 (6)	9 (17)	
<i>Father's education</i>			0.36
Higher	15 (83)	38 (70)	
Incomplete higher	0 (0)	5 (9)	
Secondary	3 (17)	11 (21)	

^a Independent-samples Mann–Whitney *U* test for continuous and χ^2 or Fisher exact test for categorical variables.

^b Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV).²³

* Statistically significant *p*-value.

pair-wise statistically significant correlations between the values of the scales.

The findings are presented in Fig. 1, and Table 3 summarizes centrality measures per variable in the ASD and the control groups (z-scores). In both groups, a number of nodes were equal to 13, and only positive correlations between the variables of the FTF sub-scales were found. While the number of the non-zero edges was 78 of 78 in the control group (sparsity=0), the number of the non-zero edges in the ASD group was 8 of 78 (sparsity=0.90), meaning that

co-occurrences of the developmental problems were more characteristic a feature in the typically developing children. In the typically developing children, the highest values on the closeness and the strength centrality measures were found for the social skills, followed by the time concept, the fine motor skills, the expressive language skills, and the perception of form and figures. This implies that the reported problems on any of these sub-scales could well predict another developmental problem. For all the sub-scales in consideration, the values of the betweenness measure

Table 2 Scores on the Five-to-Fifteen Questionnaire.

Scales and sub-scales	ASD (n = 18)			Control group (n = 54)			<i>p</i> ^a	Effect size (Rank-Biserial Correlation)	95% CI for Rank-Biserial Correlation	
	Median	Min	Max	Median	Min	Max			Lower	Upper
Motor skills	1.27	0.90	1.71	0.90	0.00	1.82	0.002*	0.49	0.22	0.69
Gross motor skills	1.01	0.57	1.86	0.87	0.00	1.71	0.076	0.28	−0.02	0.54
Fine motor skills	1.25	0.91	1.80	0.91	0.00	1.90	<.001*	0.54	0.29	0.72
Perception	0.82	0.44	1.67	0.82	0.00	1.78	0.325	0.16	−0.15	0.44
Relation in space	0.80	0.40	1.40	0.80	0.00	1.80	0.974	−0.01	−0.31	0.30
Time concept	1.00	0.75	1.75	1.00	0.00	2.50	0.463	0.12	−0.19	0.40
Body perception	0.70	0.00	1.60	0.70	0.00	2.00	0.885	0.02	−0.28	0.32
Perception of forms and figures	0.63	0.40	1.60	0.63	0.00	1.40	0.012*	0.39	0.11	0.62
Language and communication	0.75	0.48	1.24	0.75	0.00	1.76	0.593	0.09	−0.22	0.38
Comprehension	0.89	0.20	2.00	0.89	0.00	2.40	0.140	0.23	−0.07	0.50
Expressive language skills	0.68	0.00	1.00	0.68	0.00	1.54	0.560	−0.09	−0.38	0.21
Verbal communication	0.85	0.00	2.00	0.93	0.00	2.00	0.195	0.20	−0.11	0.47
Learning skills	1.07	1.07	1.93	1.07	0.07	1.90	0.013*	0.39	0.10	0.62
Reading, spelling, writing, math	1.01	1.01	2.00	1.01	0.00	1.92	0.002*	0.46	0.19	0.67
Learning new skills	1.22	1.00	2.00	1.22	0.00	2.40	0.206	0.20	−0.11	0.47
Ability to solve problems	1.16	1.10	2.00	1.10	0.00	2.10	0.020*	0.37	0.08	0.60
Social skills	0.90	0.59	1.59	0.75	0.00	1.93	0.010*	0.40	0.12	0.63

The FTF global scores in bold.

^a Independent-samples Mann–Whitney *U* test.* Statistically significant *p*-value.

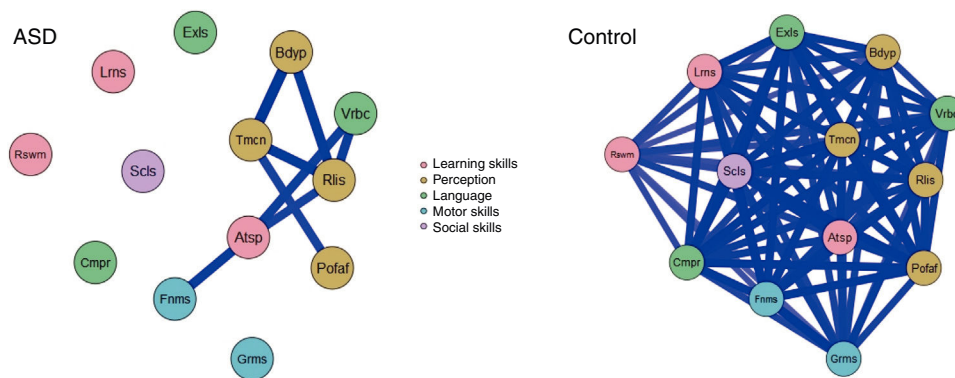


Figure 1 Network plots in the ASD and the typically developing control children. Edges represent positive statistically significant correlations (the Bonferroni correction). The strength of the association is visualized through the thickness of the edge: the stronger the association, the thicker the edge. Bdyp = Body perception; Pofaf = Perception of forms and figures; Tmcn = Time concept; Riis = Relation in space; Grms = Gross motor skills; Fnms = Fine motor skills; Cmpr = Comprehension; Exls = Expressive language skills; Vrbc = Verbal communication; Scls = Social skills; Rswm = Reading, spelling, writing, math; Lrns = Learning new skills; Atsp = Ability to solve problems.

Table 3 Network analysis. Centrality measures per variable.

Variable	ASD			Control		
	Betweenness	Closeness	Strength	Betweenness	Closeness	Strength
Ability to solve problems	1.21	0.00	1.16	0.00	0.15	0.08
Body perception	-0.50	0.00	0.66	0.00	-0.31	-0.27
Comprehension	-0.50	0.00	-0.86	0.00	0.23	0.23
Expressive language skills	-0.50	0.00	-0.86	0.00	0.60	0.59
Fine motor skills	-0.50	0.00	-0.16	0.00	0.81	0.84
Gross motor skills	-0.50	0.00	-0.86	0.00	-1.14	-1.07
Learning new skills	-0.50	0.00	-0.86	0.00	-0.04	-0.09
Perception of forms and figures	-0.50	0.00	-0.22	0.00	0.43	0.47
Reading spelling writing math	-0.50	0.00	-0.86	0.00	-2.65	-2.67
Relation in space	2.57	0.00	1.92	0.00	0.26	0.25
Social skills	-0.50	0.00	-0.86	0.00	1.09	1.07
Time concept	1.21	0.00	1.31	0.00	0.95	0.96
Verbal communication	-0.50	0.00	0.50	0.00	-0.39	-0.40

were equal to zero, meaning that there was no any obvious mediator variable. By contrast, co-occurrences of the developmental problems in the ASD children were more limited. They were most prominent between the sub-scales on child perception abilities, linked with verbal communication, ability to solve problems and fine motor skills. The highest values of the strength centrality measure were found for the relation in space, followed by the time concept, the ability to solve problems, the body perception and verbal communication. The relation in space had the highest value on the betweenness score, followed by the time concept and the ability to solve problems, thus implying the mediating effects of these characteristics.

Discussion

This study was aimed at evaluation of the spectrum of developmental problems in 5-year-old boys with diagnosed ASD

and the examination of the specific co-occurrences of these problems.

The findings were that, compared with typically developing peers, ASD children presented with more parental-reported motor skills problems (especially, related to fine motor abilities), impaired perception of forms and figures, learning skills problems (specifically, reading, spelling, writing, math and ability to solve problems), as well as social skills problems.

Although gross and fine motor delays, as well as problems with the execution of motor skills and tasks, are not an essential or defining characteristic of ASD, it is recognized as a common feature.²⁴ The current researches acknowledge the high levels of co-morbidity of developmental coordination disorder with ASD and their common risk factors.²⁵ The majority of children with ASD present with fine motor and gross motor problems, irrespective of the motor assessment conducted.^{24,26} These findings tend to hold true across the entire autism spectrum and across a wide range of child ages and are independent of gender.^{27,28} These deficits remain

even when intellectual/cognitive development and receptive vocabulary are taken into account,²⁹ and they widen over time in children with ASD.³⁰ Significantly lower motor skills in at-risk infants (siblings of ASD children) were evident from the age of 7 months.³¹ Impaired perception of forms and figures in ASD patients also has been previously reported. Specifically, individuals with autism are impaired at using information from faces, such as gaze, facial expression, and facial speech, to regulate social interaction.¹ One of the earliest symptoms of autism is a lack of attention to faces, followed by deficits in joined attention and deficit in social perception.³² In children with ASD, verbal and nonverbal communications were reported to be impaired to some degree.⁴ As well, ASD children have significant deficits in social skills,⁶ and children with comorbid ASD and ID present with greater impairments.⁷ These deficits also involve adaptive behaviors that include the skills required to support personal and social self-sufficiency.³³ Children with ASD have an overall lower level of adaptive functioning with the social aspect of adaptive behavior being most affected.³⁴ As ASD symptoms increase, the level of adaptive behavior decreases with adaptive skills related to social interaction being most impaired.⁶

An important part of this present study was an attempt to find possible co-occurrences of the developmental impairments in ASD children and their specific features by means of a network analysis. Theoretically, this approach is based on the premises that psychopathological symptoms and signs are not the emerging manifestations of an underlying mental disorder but rather they are networks of symptoms, dynamic complex systems or dynamic constellations of symptoms (and signs) that are causally interrelated.³⁵ There are few publications on a network analysis in ASD patients. In one study, the authors found that autism and obsessive-compulsive disorder emerged as two distinct symptom clusters; obsessions and compulsions showed few direct associations with autism symptoms. Sensory interests were identified as behaviors that may contribute to the link between autism and obsessive-compulsive disorder.³⁶ Other researchers found that, in ASD patients, social satisfaction and societal contribution were the strongest direct paths to happiness, followed by feeling successful and treatment satisfaction. Simultaneously, more physical problems were associated with less reported happiness.³⁷

The network analysis performed in this present study found that, unlike in the typically developing children, ASD children presented with a specific constellation of developmental problems, including impaired perception, verbal communication, ability to solve problems, and fine motor skills. This phenomenon corresponds with the known principle of a nontrivial topology of psychopathological network, which means that mental disorders follow network structure, and some symptoms are more strongly connected than others (e.g., a particular symptom within a mental disorder is more connected to the symptoms of that specific disorder than to the symptoms of other clinical syndromes).³⁸ An important consequence of the above principle is that co-morbidity is an intrinsic feature of mental disorders, including ASD. It is held that fundamental motor skills are generally learned as part of normal growth and development through interaction with others. As the play and social engagement necessary for building these movement

patterns are constrained in children with ASD, it is plausible that the interaction between delayed motor skills and limited social interactions negatively impact each other and lead to greater and greater deficits over time.^{8,28} Weaker motor skills were associated with greater social communicative deficits and poorer future outcomes.^{9,39,40} In addition, when visual-spatial organization and motor coordination abilities are both impaired, ASD symptoms seem to be the most severe.³⁹ Fine motor skills were shown to be associated with learning math skills.⁴¹ The notion of generalized atypical brain development resulted in the concept of co-occurrence of problems related to sensory, motor, and behavioral problems in children. The concept of "DAMP" (deficits in attention, motor control, and perception) was introduced to describe the high rate of co-morbidity between developmental coordination disorders, ADHD, and ASD symptoms.⁴² The growing body of research that links the cerebellum to a number of developmental disorders including autism,⁴³ learning disabilities,⁴⁴ and attention deficit disorders,⁴⁵ suggests investigation of cerebellar dysfunction.

Several limitations of this study should be acknowledged. First, information on child developmental impairments was based on maternal interviews, therefore raising a concern about biased findings. Assessing parental perception for the recognition of a given developmental problem can be important due to the differing tolerance levels among parents regarding their child. Parental perception of a developmental problem is also important as it determines whether people are likely to seek help for the problem. Meanwhile, it seems unlikely that the mothers from the ASD group would systematically provide more unfavorable reports on different aspects of their children's developmental characteristics. Even admitting that in some cases the mothers might have been incorrect in their reports, such misinterpretation was obviously non-differential one, therefore, could not serve as a source of information bias and invalidate the results. Moreover, previous studies confirmed validity of the FTF questionnaire in patients with various neuropsychiatric diagnoses, particularly ASD.^{46,47}

Another limitation of this study is that the ASD group was reasonably small and was made up of 5-year-old boys, most of whom had high functioning forms of ASD. Therefore, the findings cannot be readily expanded across other categories of ASD patients. Expanding the study to a larger population covering children with various types of ASD, including lower IQ, may be of interest and should be the subject of further investigations.

One should also keep in mind that child developmental characteristics are influenced by numerous environmental factors, thus raising concern about their possible confounding effect(s). However, the children from the two groups in comparison did not significantly differ in major demographic characteristics.

Conclusion

Considering all limitations and admitting that further studies in the field are desirable, a conclusion may be drawn that pre-school boys with ASD more commonly have co-morbid impairments in fine motor skills, perception of forms

and figures, learning and social skills. These impairments co-occur in a specific pattern in these patients, and new techniques that can accommodate the complex associations between symptoms present in an individual patient with ASD are needed.

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Conflict of interest

The authors have no conflict of interest to declare.

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