Article

Screening for autism spectrum disorder in young children with trisomy 21

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Abstract

Children with trisomy 21 are at increased risk for autism spectrum disorder. A prevalence between 9 and 42% is reported in the literature. Early diagnosis of autism spectrum disorder has multiple potential benefits for the child and its environment.

Several screening tools have been developed for children with intellectual disabilities. The PDD-MRS scale (Pervasive Developmental Disorder in Mentally Retarded Persons Scale) was originally designed and validated in Dutch. We aimed to evaluate the accuracy of this scale as screening test in our trisomy 21 clinic.

Method:

22 children (11 girls, 11 boys) with trisomy 21, aged 24-84 months (mean 56,2 months) were included and screened with the PDD-MRS. After screening all children completed a comprehensive multidisciplinary diagnostic evaluation at the Centre for Developmental Disorders. The results of the PDD-MRS screening test and the full multidisciplinary evaluation were compared.

Results:

Autism spectrum disorder was diagnosed with multidisciplinary diagnostic evaluation in 59% of our population. The PDD-MRS results in two outcome scores: a clean points score based on the parents' answers to the questionnaire and a clinical score based on both the answers and the observation of the child's behaviour by the examiner. The sensitivity and specificity of PDD-MRS were as follows: clean points score: sensitivity 0.69, specificity 0.56; clinical score: sensitivity 0.92, specificity 0.67. The feasibility of the PDD-MRS was good.

Conclusion:

In our population, the accuracy of the PDD-MRS scale as screening test is moderate. The sensitivity of the clinical score, combining parents' answers and functional observation, is clearly better than the clean score, but that might be determined by the examiner's experience.

Introduction

Trisomy 21 (Down syndrome) is the most common genetic cause of intellectual disability worldwide. As life expectancy of people with trisomy 21 has increased to an average of 60 years, they represent an important population (1). Trisomy 21 is characterized by intellectual disability and the occurrence of several additional problems such as congenital and acquired health disorders, specific difficulties with language and autism spectrum disorder (2-4). The reported prevalence of autism spectrum disorder in trisomy 21 varies as widely as 9 to 42%, the higher prevalence being reported in recent studies (4-9).

Diagnosis of autism spectrum disorder is always challenging but even more so in children with trisomy 21 because of a certain overlap of symptoms. Stubborn behaviour and difficulties in adjusting to change are often regarded as a typical behavioural feature of trisomy 21, but they can also be a sign of autism spectrum disorder. Language development is delayed in trisomy 21 and can be delayed in autism spectrum disorder but is even more hampered in children with both conditions. This overlap in symptoms is one of the reasons for under- and over-diagnosis of autism spectrum disorder in children with trisomy 21 (10-14).

Timely diagnosis of autism spectrum disorder is important as it allows for early intervention, prevention of regression and secondary behavioural problems, and additional support for children and their families. For parents it can be a relief to understand why their child is different from other children with trisomy 21 (15-18). In order to enable early diagnosis and intervention, the Council on Children with Disabilities of the American Academy of Pediatrics issued in 2020 an update of the 2007 recommendation to screen all children for symptoms of autism spectrum disorder through a combination of developmental surveillance and standardised autism-specific screening tests at 18 and 24 months of age (19, 20).

Several screening tools for autism spectrum disorder have been used in children with intellectual disability. The Scale of Pervasive Developmental Disorder in Mentally Retarded Persons (PDD-MRS) was developed in the Netherlands by Kraijer et al. for individuals with intellectual disability from 2 to 70 years. Kraijer reports a has a high sensitivity and specificity, both 92.4%, based on testing of 254 persons with trisomy 21, both children and adults. The scale has been validated from the age of 24 months (21).

Another screening test is the Modified Checklist for Autism in Toddlers (M-CHAT) validated for children 16-30 months old. The test consists of 23 yes/no questions with 6 critical questions. DiGiuseppi et al. reported a sensitivity of 81.8% (95% CI: 55-96.4%) and a specificity of 46.8% (95%CI: 33.2-60.7%) for the diagnosis of autism spectrum disorder in young children with trisomy 21(6). The M-CHAT was improved in 2014 by Robins et al. (22). The new version is named M-CHAT-R/F (M-CHAT-Revised with Follow-up), a 2 stage screening test with an improved accuracy in comparison to the M-CHAT. The first stage consists of 20 yes/no questions after which a child is classified as low, medium or high risk. For low risk children no other evaluation is planned, high risk children are immediately referred for

diagnostic evaluation; in medium risk children the follow-up questionnaire (20 questions) is administered to determine whether referral is necessary. We did not find any publication reporting the use of the M-CHAT-R/F in children with trisomy 21.

The Social Communication Questionnaire is another screening test with 40 yes/no questions. This test requires more developed language skills and can therefore be used for children with DS from the age of 4 years old. Sensitivity is 0.85 - 0.88 and specificity is 0.72 - 0.75 in both children and adults with trisomy 21 (23).

Because the PDD-MRS was designed and validated in Dutch (which is the language in which we communicate with our patients in our hospital), we wanted to evaluate whether we could use this test to screen children with trisomy 21 for autism spectrum disorder in our hospital's trisomy 21 clinic.

Methods

Children with trisomy 21 aged 24 to 84 months from the Antwerp University Hospital trisomy 21 clinic were invited by letter to participate in the study. The only exclusion criterion was previous diagnostic testing for autism spectrum disorder. The parents had the possibility, without obligation, to mention why they accepted or refused participation. The study was approved by the Ethical Committee of the University Hospital of Antwerp (Belgian registration number B300201215833).

After informed consent given by one of the parents, the PDD-MRS was administered by a senior speech therapist, trained in the administration of the PDD-MRS, who is experienced in intellectual disability and autism spectrum disorder, and is also a staff member of the trisomy 21 clinic. The PDD-MRS consists of 19 questions in 12 categories all answered by a caregiver of the child. Categories are 1) quality of contact with an adult, 2) contact with age-related peers, 3) no active language, 4) language and speech with deviant content, 5) language and speech with deviant production, 6) obsessive interests, 7) stereotypical manipulations of objects, 8) stereotypical handling of own body, 9) patterns and rituals, 10) self-injury, 11) unpredictable behaviour and 12) unusual fears. It takes approximately 1 hour to perform the test.

The PDD-MRS results in 2 scores, a clean points score based on the answers to the questionnaire and a clinical score based on both the answers to the questions and the observation of the child's behaviour by the examiner. Both scores result in 3 possible outcomes: 'pervasive development disorder' (PDD), 'possible PDD' and 'no PDD'. The results of the screening test were not communicated yet to the parents, nor to the staff of the Centre for Developmental Disorders.

After conducting the PDD-MRS in the trisomy 21 clinic, the children were referred to our Centre for Developmental Disorders for a full multidisciplinary functional evaluation, including the administration of the Autism Diagnostic Observation Schedule test (15), evaluation of intellectual development by a child psychologist, of receptive and expressive language skills, speech development and communication by a speech therapist, of gross and fine motor development and coordination by a physiotherapist and clinical evaluation by a child neurologist. The final diagnosis was made at the Centre for Developmental Disorders and communicated to the parents.

Birth date, gender, age at time of PDD-MRS, the PDD-MRS scores, diagnosis at the Centre for Developmental Disorders, severity of intellectual disability, behavioural problems as mentioned by parents, suspicion of autism spectrum disorder by parents and the presence of a first degree relative with autism spectrum disorder were entered into a SPSS 21 database. Furthermore, medical records were checked for any additional data, in particular a history or presence of epilepsy, as a higher prevalence of seizures has been described in children with trisomy 21 and autism spectrum disorder (13).

Variables were analysed by frequency and, if applicable, minimum and maximum. Prevalence of variables was calculated with 95% confidence interval (CI). Prevalence of autism spectrum disorder was calculated on the basis of the results of the full diagnosis at the Centre for Developmental Disorders. Sensitivity and specificity of the PDD-MRS questionnaire score, the PDD-MRS clinical score and the combination of both were calculated in comparison to the final diagnosis at the Centre for Developmental Disorders. A logistic regression analysis was done to evaluate the relationship between the additional variables and the result of the PDD-MRS.

Results

Parents of 99 children, aged 24 – 84 months, were invited to participate. We received a response from 36. 11 chose not to participate. Reasons for non-participation were given by 8: distance to specialty clinic [1], too many doctor visits [2], feeling sure that their child has no autism spectrum disorder [2], fear of diagnosis [1], already tested on autism spectrum disorder [1]. Two parents indicated that suspicion of autism spectrum disorder was the motivation to participate in the study. 25 gave informed consent; 3 children were excluded from analysis because they did not complete both the PDD-MRS screening test and the diagnostic test at the Centre for Developmental Disorders.

22 children were included in our analysis, 11 girls and 11 boys. The age range was 28 tot 79 months (mean 56,2 months, median 53 months, 9 children ≤ 48 months, 13 children > 48 months).

The diagnosis of autism spectrum disorder was made in 13/22 (59%) children after full diagnostic evaluation. As described above, the PDD-MRS results in 2 outcome scores: a clean points score and a clinical score given by the examiner. The outcomes of both scores can be: 'negative', 'doubtful' and 'positive' for autism spectrum disorder. The result of the PDD-MRS, the comparison with the result of the full diagnostic test, the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios of the PDD-MRS score (considering doubtful tests as positive, as this would be an indication for referral) are shown in table 1 for the clean points score and in table 2 for the clinical score.

Epilepsy was present in 4/22 (18%). Two had a first degree relative with autism spectrum disorder. Behavioural problems were reported by parents in 8 children (36%). Categories of intellectual disability were as follows: 4 children mild (IQ 55-80), 13 moderate (IQ 30-55), 4 severe (IQ 15-30), 1 profound (IQ <15). With logistic regression analysis none of these associated features, i.e. epilepsy, behavioural problems and degree of disability, were found to be a significant predictor of a correct result of the PDD-MRS.

In the 2 children, whose parents had indicated that they suspected autism spectrum disorder, this diagnosis was not confirmed.

Table1: results of the clean points score of the PDD-MRS screening test as compared to the full diagnostic standard for autism spectrum disorder

Negative		Diagnostic standard for autism spectrum disorder	
		Positive	
PDD-MRS screening test	Negative	5	4
	Doubtful	1	2
	Positive	3	7
Total	22	9	13
Sensitivity	0.69	95% CI 0.39-0.91	
Specificity	0.56	95% CI 0.21-0.81	
PPV	0.69		
NPV	0.56		
LR +	1.56		
LR -	0.55		

PPV= positive predictive value; NPV = negative predictive value; LR+ = likelihood ratio for a positive result; LR- = likelihood ratio for a negative result

Table2: results of the clinical score of the PDD-MRS screening test as compared to the full diagnostic standard for autism spectrum disorder

Negative		Diagnostic standard for autism spectrum disorder	
		Positive	
PDD-MRS screening test	Negative	6	1
	Doubtful	3	1
	Positive	0	11
Total	22	9	13
Sensitivity	0.92	95% CI 0.64-1.0	
Specificity	0.67	95% CI 0.30-0.93	
PPV	0.80		
NPV	0.86		
LR +	2.77		
LR -	0.12		

PPV= positive predictive value; NPV = negative predictive value; LR+ = likelihood ratio for a positive result; LR- = likelihood ratio for a negative result

Discussion

A significant number of children with trisomy 21 have autism spectrum disorder. The prevalence as described in the literature varies from 9 to 42% (4, 6, 7, 24, 25). We found a prevalence of 59% which is still a lot higher than the 42% described by Oxelgren et al. A probable explanation is selection bias. As our study included a full diagnostic evaluation at the Centre for Developmental Disorders, parents who had doubt or suspicion about the diagnosis of autism spectrum disorder could have been more motivated to participate. Nonetheless, we believe that there is a significant proportion of people with trisomy 21 who have autism spectrum disorder and that early recognition should be included in routine health supervision.

As described in the introduction, several screening tests for detection of autism spectrum disorder in young children with disabilities have been developed (21, 23, 26). Moreover, children at risk for autism spectrum disorder can also be identified by an approach within a functional framework, particularly evaluating cognitive function, language development, communication, and reciprocal social interaction (27, 28). Additionally, a functional framework provides the opportunity to take action to improve specific areas of functioning. We believe that there is no conflict between screening tests and functional approach. Routine implementation of a screening test in the health supervision schedule could be a helpful tool to address certain problems in development and behaviour that would not be discussed otherwise and to evaluate if additional interventions and support would be desirable, even if there is no suspicion of autism spectrum disorder.

Whatever the approach, one should always keep in mind that behaviour in children with trisomy 21 could also be influenced by different organic problems.

What ultimately counts is that children with suspected autism spectrum disorder, whether based on a functional approach, a screening test or both, are referred for a comprehensive diagnostic evaluation. In addition, it is our experience that a formal diagnosis of autism spectrum disorder is necessary to initiate specialised counselling, support and therapy. Although the diagnosis is a relief for some parents, others may be dumbfounded by the burden of a double diagnosis. The diagnosis should be communicated to parents in a sensitive manner, with emphasis on the fact that while it does not change their child, it can change the way their child is approached for the better.

In our study we have evaluated the PDD-MRS as screening test for autism spectrum disorder in children with trisomy 21. We have not experienced any problem with regard to the feasibility of the test. Regarding the accuracy, the sensitivity (0,69) and specificity (0,56) of the clean points PDD-MRS score are significantly lower in our population than in the original study of Kraijer et al. (sensitivity and specificity both 0,92) (21). The sensitivity and specificity are also lower compared to the M-CHAT used by Wong et al. (sensitivity 0,93, specificity 0,77) (26). However, the clinical score, obtained via observational interpretation by the examiner, results in a remarkable increase in sensitivity (0,92) and small increase in specificity (0,67). This discrepancy is due to the fact that in the clean points score the researcher has to quote the answers of the parents as indicated by them, even if there is a clear difference with the observed behaviour. That also indicates that the critical reflection of a well-trained clinical observer contributes significantly to the accuracy of the test, meaning that the test should be done by an experienced practitioner. Even then, a false positive result must be taken into account in about 1/3 and a false negative result in 1/10.

Apart from the value as screening test in itself, administering the test also offers the opportunity to raise issues that are more difficult to address in a regular consultation.

Limitations of our study are the low number of responders and participants.

Conclusion

We have evaluated the accuracy of the PDD-MRS scale as screening test for autism spectrum disorder in children with trisomy 21, aged 24 - 84 months. The sensitivity and specificity of the clean points score are low (respectively 0,69 and 0,56) but increase remarkably in the clinical score, obtained by observational interpretation of the examiner (sensitivity 0,92, specificity 0,67). Thus, the accuracy may also depend on the experience of the examiner. The test is well feasible for young children in the setting of a trisomy 21 clinic to select children for comprehensive, multidisciplinary diagnostic testing, but cannot replace it.

The results of our study are consistent with reports in literature about the increased prevalence of autism spectrum disorder in children with trisomy 21. Systematic evaluation within a functional framework and/or with a screening test should be implemented in the routine health supervision of young children with trisomy 21, aged 24-84 months, to identify these children who should be referred for comprehensive diagnostic evaluation.

Different screening tools for autism spectrum disorder in young children have been described but little research has been done in children with trisomy 21. More research would be welcome.

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