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Postprint / Postprint

Zeitschriftenartikel / journal article

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Empfohlene Zitierung / Suggested Citation:

Briegel, W., Schimek, M., Kamp-Becker, I., Hofmann, C., & Schwab, K. O. (2009). Autism spectrum disorders in children and adolescents with Moebius sequence. *European Child & Adolescent Psychiatry*, 18(8), 515-519. <https://doi.org/10.1007/s00787-009-0003-1>

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Autism spectrum disorders in children and adolescents with Moebius sequence

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Received: 8 September 2008 / Accepted: 23 January 2009 / Published online: 3 March 2009
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Abstract Moebius sequence is a rare congenital disorder usually defined as a combination of facial weakness with impairment of ocular abduction. A strong association of Moebius sequence with autism spectrum disorders (ASDs) has been suggested in earlier studies with heterogeneous age groups. The primary caregivers of all children and adolescents with Moebius sequence aged 6–17 years known to the German Moebius foundation were anonymously asked to complete two screening measures of ASD [Behavior and Communication Questionnaire (VSK); Marburger Asperger's Syndrome Rating Scale (MBAS)]. For those who reached the cut-off for ASD, well standardized diagnostic instruments (Autism Diagnostic Interview-Revised, Autism Diagnostic Observation Schedule, WISC-III, and Kinder-DIPS) should be administered. Minimal diagnostic criteria for Moebius sequence were congenital facial weakness (uni- or bilateral) and impairment of ocular abduction (uni- or bilateral). Familiar cases should be excluded. The primary caregivers of 35/46 children and adolescents (18 males, 17 females, mean age 11.5 years) sent back completed questionnaires, but only 27 subjects met inclusion criteria. According to the primary caregivers, none of these

subjects showed mental retardation. Two probands (both males 9 and 16 years old) reached the cut-off of the MBAS whereas the results of the VSK did not indicate ASDs in any of the patients. The 9 year old boy could be examined personally and did not meet diagnostic criteria of ASD. ASDs might be not as frequent as reported in previous studies on patients with Moebius sequence, at least not in patients without mental retardation.

Keywords Moebius sequence ·
Autism spectrum disorders · Children and adolescents

Introduction

Moebius syndrome (Online Mendelian Inheritance in Man, no. 157900), or better Moebius sequence, is a non progressive congenital condition with an estimated prevalence of 0.0002–0.002% of births [14, 27]. Etiology and pathogenesis are still not fully understood [6, 15]. The most widely accepted hypothesis, supported by findings of animal experiments [16, 20] and computed tomography/magnetic resonance studies [9, 13], is that of a disruption of the primitive subclavian arteries and their branches before establishment of a sufficient blood supply to the brain stem by the vertebral arteries [2, 23]. This vascular disruption could be caused by various teratogens, e.g. alcohol, chorionic villus sampling, and gestational hyperthermia [10, 19]. Genetic mechanisms seem to play only a minor role with regard to the aetiology of the sequence [6].

In most studies, Moebius sequence has been defined as a congenital facial weakness with congenital impairment of ocular abduction [1, 7, 27, 28].

Disturbances in psychomotor and speech development are said to be very common [24, 27], and mental

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retardation is estimated to occur in 10–15% of patients [14]. So far, four studies with 17–37 Moebius patients [1, 11, 12, 27] showed a markedly increased incidence of autism spectrum disorder (ASD) (5–29 vs. 0.63% in the normal population [8]). Nevertheless, the association of Moebius sequence with ASDs seems to be questionable as some of these studies showed methodological problems, and mental retardation was overrepresented in at least two of them [6].

The aim of this study was to assess the presence of ASDs in a quite homogenous study group of 6–17 year old children and adolescents with the sequence.

Methods

Participants

In a first step, supported by the German Moebius foundation the primary caregivers of all known children and adolescents aged 6–17 years were asked to participate in an anonymous nationwide study. By post, all caregivers received:

- A special questionnaire to compile personal, somatic and psychosocial history of the patients.
- The Behaviour and Social Communication Questionnaire (Fragebogen über Verhalten und soziale Kommunikation, VSK) [4], a German adaptation of the Autism Screening Questionnaire (ASQ) [3]. A cut-off of 17 has been found to have a specificity of 99% and a sensitivity of 92% [4]. Mimic expression (questions no. 9, 27 and 33) was rated as not normal for all probands with a complete bilateral facial paralysis, even if the primary caregiver had not done so.
- The Marburger Asperger's Syndrome Rating Scale (MBAS) (Marburger Beurteilungsskala zum Asperger-Syndrom [21]), a German questionnaire developed for the screening of Asperger's syndrome and high functioning autism. A cut-off of 103 has been found to have a specificity of 89% and a sensitivity of 94% [21]. As for the VSK, in a second step mimic expression (questions no. 10, 11, 13, 41, 42, 44) was re-rated as not normal for all probands with a complete bilateral facial paralysis.

Subjects who, according to their primary caregiver's information, met minimal diagnostic criteria of Moebius sequence, i.e. congenital facial weakness (uni- or bilateral) and impairment of ocular abduction (uni- or bilateral), were included in the further study process. Familiar cases of Moebius sequence should be excluded.

In a second step, subjects who met diagnostic criteria and had been rated at or above the cut-off score on at least

one of the two autism spectrum screening measures were invited for personal examinations with:

- The Kinder-DIPS [26], a structured psychiatric interview for 6–18 year old individuals combining child and parent version. The interview is based on the diagnostic criteria of DSM IV and ICD-10 (research criteria).
- The Autism Diagnostic Interview-Revised [5 (German version), 18].
- The Autism Diagnostic Observation Schedule-Generic [17, 22 (German version)].
- and the Wechsler Intelligence Scale for Children (WISC-III) [25 (German version), 29].

Statistical analysis

Statistical analysis of the results was done using SPSS 15.0.

Results

Forty-six children and adolescents aged 6–17 years were known to the German Moebius foundation. The primary caregivers of 35 patients (17 males and 18 females) with a diagnosis of Moebius sequence (76.1%) completed and returned questionnaires. Subjects were aged 6; 9–17; 0 years (mean 11 years 10 months, standard deviation 3 years 0 month). In most cases, Moebius sequence had been diagnosed by a geneticist or pediatrician. No familial cases were identified.

Three subjects were excluded because of missing information (caregivers did not indicate whether their child was able to abduct one or both eyes), and four subjects because caregivers gave the information that their child showed no impairment of ocular abduction. None of the seven (4 males and 3 females) had reached the cut-off of the VSK or the MBAS. Another male had to be excluded because both VSK and MBAS were missing.

Probands' characteristics

The remaining 27 subjects (15 females, 12 males) were aged 6; 9–17; 0 years (mean 11 years 6 months, standard deviation 2 years 11 months).

Nineteen subjects suffered from bilateral facial paralysis with 11 of them showing complete paralysis. Of 27 subjects, 25 had bilateral impairment of ocular abduction. According to their primary caregivers, 16 subjects had malformations of the extremities: 13 patients showed malformations of feet, especially talipes deformities (11 subjects), and nine had malformations of the hands. Further congenital somatic symptoms were: heart defect (three subjects), arthrogryposis (three subjects), and spastic

paralysis (one subject). Four subjects had Poland syndrome, and two had Pierre–Robin sequence.

According to their primary caregivers' information, five subjects did not speak their first words (except Mum and Dad) before the age of 19 months, and one subject did not speak short sentences of three to four words before the age of 3 years. Eight probands could not walk before the age of 19 months.

All probands went to school, none of them attended a school specialized for children with mental retardation. One primary caregiver estimated the proband's intelligence as below average, but none as mentally retarded.

Screening measures

The VSK

Twenty-seven primary caregivers sent back completed questionnaires; none of the probands reached the cut-off of 17. Even after the above mentioned re-rating, none of the children and adolescents with Moebius sequence could be rated as possibly autistic (mean 7.7; range 2–14).

The MBAS

26 questionnaires could be included (missing 1). One proband (male 16 years, full score 111) was scored above the cut-off before re-rating, another boy (9 years) reached the cut-off after re-rating (full score 103). Results of the subscales (after re-rating) are given in Table 1.

Personal examination

The 9 year old boy was examined with the ADI-R, ADOS-G, Kinder-DIPS, and the WISC-III. He showed a normal Full Scale IQ (98) with a significant higher Verbal IQ (117; Performance IQ: 81). According to the information of his parents, he did not reach any of the cut-offs for aberrant behaviour of the ADI-R, nor did he meet criteria of the ADOS-G for an autism spectrum disorder. Moreover, the Kinder-DIPS did not reveal a current or former psychiatric disorder.

The primary caregivers of the 16 year old boy were contacted three times, but did not answer the invitation for further examinations.

Discussion

Moebius sequence is a rare congenital condition, and therefore most studies included patients of various ages [11, 12, 27]. In this study we focused on children above the age of 5 and adolescents.

Of 46, 35 (76.1%) addressed primary caregivers filled out questionnaires and sent them back, which is a very satisfactory result. Eight subjects had to be excluded as they did not meet minimal diagnostic criteria (seven subjects) or because of missing autism screening questionnaires (one boy).

Compared to the study of Verzijl et al. [27] we found fewer cases of bilateral facial paralysis (70 vs. 92%) and malformations of feet and hands (59 vs. 85%). This might be due to our reliance on parent-reported information while Verzijl and colleagues performed a physical examination. According to estimates by the primary caregivers and judging by the type of school the probands attended, none of the subjects showed evidence of mental retardation. As mental retardation is generally estimated to occur in about 10–15% of individuals with Moebius sequence [11, 12], mental retardation might have been underrepresented in our sample. On the other hand, the true rate might be lower than 10–15% [6].

Earlier studies [1, 11, 12] that focussed on ASDs found 21.7–29.8% of all Moebius patients to be autistic. Nearly all patients with autistic disorder were mentally retarded, and mental retardation was overrepresented in at least two studies [1, 11]. Nevertheless, a strong association of Moebius sequence with autism has been suggested in these studies. As the goal of these studies [1, 11, 12] was to analyze the prevalence of autism spectrum disorders (ASDs) in Moebius sequence, patients with severe and multiple disorders might have been overrepresented. In contrast, fewer children and adolescents with severe grades of the sequence may have participated in our study due to

Table 1 Results of the MBAS: mean (standard deviation), range, and number of subjects who scored at or above the cut-off

MBAS-factors and cut-offs	Mean (standard deviation)	Range	Number of subjects who scored at or above the cut-off
Full scale: (cut-off 103)	57.40 (26.16)	17–113	2
Factor I: theory of mind, social contact and play (cut-off 38)	16.69 (11.34)	0–40	2
Factor II: joint attention, facial expression, gesture (cut-off 21)	21.42 (11.02)	5–36	14
Factor III: stereotyped and inadequate behavior (cut-off 20)	8.46 (6.51)	1–27	1
Factor IV: special interests, conspicuous speech, motor activity (cut-off 16)	10.83 (5.02)	3–20	5

recruitment with the help of the German Moebius foundation.

Verzijl et al. [27] reported in their study comprising 37 subjects with Moebius sequence that only two probands (5.4%), both of them mentally retarded, were autistic. Unfortunately, they did not provide any information about the way the diagnosis of autism had been made. They could not support the above mentioned association between Moebius sequence and ASDs, and suggested an association between mental retardation and autism [28].

Our results are in agreement with the findings of Verzijl et al. [27]. None of our probands seemed to be mentally retarded and only one out of 27 patients might have had ASD, which is a maximum rate of 3.7%. The fact that questions regarding mimic expression were rated as positive for autism in subjects with a complete bilateral facial paralysis, should have minimized the rate of false negative results in our study.

This study has some limitations: lack of objective intelligence assessments on most of our probands, and questionable representativeness. The latter limitation also applies to most earlier studies that focused on ASDs and Moebius sequence [1, 11, 12]. The fact that we used a self-selected sample of subjects clearly limits generalization of our findings.

Conclusion

The results of this study indicate that ASDs might be not as frequent in subjects with Moebius sequence as suggested in earlier studies, at least not in subjects with normal intelligence.

Acknowledgments The authors are very grateful to Moebius Syndrom Deutschland e.V., the German Moebius association, and to all participating families. The authors thank Prof. Regina Bussing, Florida, USA, for help with the manuscript.

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