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Development and behaviour in Marshall–Smith syndrome: an exploratory study of cognition, phenotype and autism

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Abstract

Background Marshall–Smith syndrome (MSS) is an infrequently described entity characterised by failure to thrive, developmental delay, abnormal bone maturation and a characteristic face. In studying the physical features of a group of patients, we noticed unusual behavioural traits. This urged us to study cognition, behavioural phenotype and autism in six patients.

Methods Information on development, behavioural characteristics, autism symptoms, and adaptive and psychological functioning of six MSS children was collected through in-person examinations, questionnaires, semi-structured interviews of parents and neuropsychological assessments.

Results Participants showed moderate to severe delays in mental age, motor development and adaptive functioning, with several similarities in communication, social interactions and behaviour. There was severe delay of speech and motor milestones, a friendly or happy demeanour and enjoyment of social interactions with familiar others. They exhibited minimal maladaptive behaviours. Deficits in communication and social interactions, lack of reciprocal social communication skills, limited imaginary play and the occurrence of stereotyped, repetitive behaviours were noted during assessments.

Conclusions Systematic collection of developmental and behavioural data in very rare entities such as MSS allows recognition of specific patterns in these qualities. Clinical recognition of physical,developmental and behavioural features is important not only for diagnosis, prognosis and counselling of families, but also increases our understanding of the biological basis of the human physical and behavioural phenotype.

Keywords autism, behavioural phenotype, cognition, intellectual disability, Marshall–Smith syndrome

Introduction

In studying genetic syndromes, clinicians and researchers have described difficulties in examining psychological and behavioural features of the syndromes, and how they might be causally related to

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underlying genetic conditions (Skuse 2000; Cassidy & Morris 2002). Studying syndromes that commonly occur with severe intellectual disability (ID) is further complicated by the lack of adequate instruments to directly measure individual cognitive levels. Although correlations between biological and behavioural variables do not necessarily imply causation, and methodological differences across studies have often limited our ability to draw conclusions, many researchers have recognised the importance of cross-disciplinary collaboration in studying samples of patients with genetic defects in an effort to improve our understanding of normal and abnormal behaviours (Finegan 1998). Careful clinical assessment and description are therefore crucial steps in eventually determining clinical relevance.

Marshall–Smith syndrome (MSS) is an infrequently described malformation syndrome first reported by Marshall *et al.* (1971) and characterised by ID, abnormal bone maturation, failure to thrive, severe respiratory problems and unusual facial features. To date, some 45 cases with this syndrome have been reported internationally in various languages, usually as single case reports or small groups (Marshall *et al.* 1971; Nabrady & Bozalyi 1973; Tipton *et al.* 1973; Visveshwara *et al.* 1974; De Toni *et al.* 1976; Hassan *et al.* 1976; Perrin *et al.* 1976; Iafusco *et al.* 1977; Ferran *et al.* 1978; Flatz & Natzschka 1978; LaPenna & Folger Jr 1982; Johnson *et al.* 1983; Menguy *et al.* 1986; Roodhooft *et al.* 1988; Yoder *et al.* 1988; Smyth *et al.* 1989; Charon *et al.* 1990; Eich *et al.* 1991; Pappas & Rekate 1991; Sperli *et al.* 1993; Sharma *et al.* 1994; Endo *et al.* 1995; Cullen *et al.* 1997; Williams *et al.* 1997; Antila *et al.* 1998; Chatel *et al.* 1998; Dernedde *et al.* 1998; Seidahmed *et al.* 1999; Summers *et al.* 1999; Moon *et al.* 2002; Sumiya *et al.* 2002; Wang 2002; Diab *et al.* 2003; Watanabe *et al.* 2003; Butler 2004; Adam *et al.* 2005; Deshpande *et al.* 2006; Travan *et al.* 2008; Shaw *et al.* 2010).

A recent genetic study reported on mutations in *NFIX* (transcription factor nuclear factor I) resulting in MSS (Malan *et al.* 2010). At present, the specific function of *NFIX* remains unclear, but *NFIX* must have an important role in human brain development and skeletogenesis.

Recently, we reviewed the physical features of a group of 19 patients and compared these to all earlier reported cases (Shaw *et al.* 2010). In addition to medical assessment and clinical examination, personal history and additional information on the patients have been assimilated using an online Wiki. Through this resource, parents and carers had secure access to a lay translation consisting of the general description of the syndrome and medical complications, and could add comments on aspects of the phenotype or natural history, based on their own experiences (Shaw *et al.* 2010). During the study, we noticed unusual behavioural traits in several patients not reported before. Some behavioural features showed resemblance to autism. Earlier reports on children with MSS had described delays in psychomotor development (Sumiya *et al.* 2002; Butler 2004; Adam *et al.* 2005), and absence of speech/language development (Sperli *et al.* 1993), but no other behavioural characteristics. This urged for a more detailed cognitive and behavioural assessment.

Here, we report an exploratory investigation of behavioural and psychological profiles in six children with MSS. Our general aim was to describe their behaviour patterns, development and cognitive abilities, using in-person clinical assessments and a dedicated test battery. A specific aim was to investigate if an autism symptom profile could be part of the syndrome.

Materials and methods

Exploratory study

In accordance with the clinical impression during the study of the natural history in MSS mentioned before (Shaw *et al.* 2010), we wanted to conduct an exploratory study. In this exploratory study, we focused on autism symptomatology and distinctive behavioural features in MSS children at different ages and developmental stages, while at the same time systematically assessing and describing the behaviour and development of the children.

Participants

The total study group of MSS patients participating in the natural history study consisted of 19 children from 11 countries (Belgium, Brazil, Croatia, France, Germany, India, Mexico, the Netherlands, Norway,

UK and USA). Of these, six MSS patients could be assessed: a personal assessment of the other children was impossible, due to a language barrier between children, families and the examiners, death of children, or because of the distance to their country of residence.

The six participating MSS children, three girls and three boys, were born between 1994 and 2006. Three resided in the Netherlands, two in the UK and one in France.

All parents gave written informed consent, and the Medical Review Ethics Committee gave permission to perform the study.

A summary of the major physical characteristics of the six patients compared to those of all known patients with MSS is provided in Table 1. A more detailed description of physical manifestations can be found elsewhere (Shaw *et al.* 2010).

Test instruments

All children in the study were clinically examined by the same child psychiatrist (I. v. B.) and neuropsychologist (P. J. V.). The child psychiatrist was trained in the Netherlands, where she did residencies in paediatrics, genetics, psychiatry and child psychiatry. She has more than 15 years of clinical experience and has expertise in developmental and genetic syndromes. She is certified in the use of standardised assessment instruments for research diagnosis of autism spectrum disorders (Van Balkom *et al.* 1998, 2002, 2009).

One subject (patient 6) could not be fully assessed with the complete test battery due to language problems and geographical distance. Only instruments valid and reliable in studying individuals with limited verbal abilities were chosen to assess cognitive functioning. In-person interviews with parents were used to assess past and current development, and functioning on three major domains: communication (adaptive) behaviour, and social-emotional development. Through standardised questionnaires, additional information was gathered about other symptoms and psychological functions, such as aggression, attention and mood.

Assessment of intellectual capabilities

Mental and motor functioning was assessed using the Dutch version of the Bayley Scales of Infant Development, 2nd Edition (BSID-II; Van der Meulen *et al.* 2002). The mental scale consists of items assessing level of visual and auditive information processing, hand–eye coordination, imitation, language development, memory and problem solving skills. The motor scale assesses level of fine and gross motor development. The BSID-II is considered a reliable and valid instrument (Provost *et al.* 2000, 2004). The raw scores on the motor and mental scale were converted into age equivalents to determine level of motor and mental functioning. The BSID-II was administered according to the manual of the test.

Child psychiatric examination and Autism Diagnostic Interview

An experienced child psychiatrist (I. v. B.) performed psychiatric examinations of each of the children and also interviewed one or both parents of each child with the Autism Diagnostic Interview – Revised (ADI-R) (Lord *et al.* 1994). The ADI-R is considered a reliable and valid instrument (Rutter *et al.* 2003; Cicchetti *et al.* 2008; Le Couteur *et al.* 2008). It is a semi-structured diagnostic interview designed to collect developmental information, a history focused on autism-specific criteria, and information on actual behaviour as it has occurred in the child's daily life, as a basis for a lifetime diagnosis of pervasive developmental disorder. The ADI-R yields individual item scores (normal, possible abnormality, definite abnormality) and domain scores in the areas of social skills and play, communication and behavioural abnormalities. While there were concerns about how level of ID might affect interpretation of the results, we still considered the ADI-R an appropriate standardised instrument to collect data on development given the lack of available measurements for individuals with severe ID (Howlin 2000; De Bildt *et al.* 2004; Bruining *et al.* 2010).

Adaptive functioning

To assess the degree of personal and social self-sufficiency, the Vineland Adaptive Behavior Scales – Survey Form (VABS) was used (Sparrow *et al.* 1984). The VABS supplies measures of the level of adaptive functioning on three domains: communication, daily living skills and socialisation. These mea-

Table 1 Main physical characteristics of the presently studied six patients with Marshall–Smith syndrome compared to those in Marshall–Smith syndrome in general

Patient		1	2	3	4	5	6	Feature reported in literature cases
Epidemiology	Gender	F	F	M	F	M	M	Equal M : F ratio
	Age (years)	14	7	3	8	13	7	0–19
Growth	Birth weight (g)	2990	1590	2975	3630	2000	3230	Term mean 3144
	Gestation	Term	32 weeks	Term	Term	Term	Term	Term
	Weight (kg)	30		15	26	22	21	N/A
	Height (cm)	138	103	100	133	120	120	N/A
	Height centile (SDS if centile <2)	0.2 (−2.90)	7	10	50	<0.4 (−4.9)	30	N/A
Development	Degree of (cognitive) disability	Severe	Severe	Severe	Severe	Severe	Not measured	Moderate–severe
	Walked	4.5 years	–	–	2 years	Never	3 years	Delayed
	First words	48 months	60 months	–	–	None	36 months	Delayed
Typical craniofacial features		+	+	+	+	+	+	+
Eyes	Myopia	–	−12/−9	−14	–	+	–	+
	Glaucoma	–	–	+	–	+	–	N/A
	Optic nerve hypoplasia	–	–	–	+	–	–	N/A
Respiratory problems		+	–	+	+	+	+	+
Neurology	High tone	+	–	–	–	+	–	N/A
	Brisk reflexes	+	–	–	+	+	–	N/A
	Brain MRI	Normal	Normal	Hypoplasia callosal body	Normal	Normal	Normal	N/A
Skeletal	Abnormal bone maturation	+	+	+	+	+	+	+
	Bone fractures	–	–	1	–	–	4	+
	Scoliosis	+	–	–	–	+	+	+
Other	Cardiac defect	–	VSD	–	–	–	–	+
	Hearing loss	–	–	+	–	+	+	+
	Umbilical hernia	–	–	–	–	–	+	+
	Hypertrichosis	–	+	+	+	+	+	+
NFIX mutation found		–	+	+	–	–	+	

F, female; M, male; N/A, not available; SDS, standard deviation score; MRI, magnetic resonance imaging; VSD, ventricular septal defect.

sures provide an overall adaptive composite score, allowing for a classification in adaptive level (in five levels, high to low), and separate composite scores on the three domains. The psychometric properties of the VABS are considered to be good (Sparrow *et al*. 1984). The interview was conducted by two experienced clinicians (P. J. V., M. F.).

Behavioural characteristics

Problem behaviours and competencies of the children were assessed using the Child Behavior Checklist (CBCL; Achenbach 1991a,b). Kostentausta *et al*. have found that the CBCL may be less reliable for those with moderate to severe ID, possibly because many of its items may not reflect problem behaviours in children with ID, and may fail to reveal all psychiatric issues (Kostentausta *et al*. 2004). De Ruiter *et al*. have studied the developmental course of psychopathology in children with and without ID using the CBCL. They found that, while children with ID (ranging from mild to moderate levels of ID) showed increased risk for problem behaviours across all ages when compared to typically developing children, developmental trajectories in both groups were quite similar (De Ruiter *et al*. 2007). The CBCL has previously proven its usefulness in studying populations of children with severe ID, for example, Rubinstein–Taybi syndrome (Hennekam *et al*. 1992), Williams syndrome (Graham *et al*. 2005) and Costello syndrome (Axelrad *et al*. 2004).

The CBCL is completed by the parents or primary caregivers and gives insight into problem behaviours. The questionnaire is informative on eight specific domains and problem behaviours: aggressive behaviour, mood, attention, delinquent rule-breaking behaviour, social problems, somatic complaints, thought problems and withdrawal. Total scores for internalising problem behaviour (withdrawal, somatic complaints and anxious/depressed) and externalising problem behaviour (delinquent rule-breaking behaviour, and aggressive behaviour) are obtained as well as a total problem score by summing all eight specific problem behaviours.

Results

We present first a narrative description of individual clinical assessments and behavioural observations. Subsequently, we present measures of cognition, development, adaptive functioning and behaviour. Because patient 6 could not be assessed with the complete test battery, his findings are included only for those items that could be studied (child psychiatric exam; ADI-R).

Individual child psychiatric assessments, clinical observations of interaction and behaviour

Patient 1

Patient 1 was of middle school age and had a lively, friendly demeanour. She had little initial reserve at first contact, showed no anxiety and immediately tried to actively and spontaneously engage the examiner in play, by running back and forth and talking incessantly or by pulling hands. There was sufficient eye-to-eye gaze during examination; and although reciprocity was limited, she visibly enjoyed the interaction and play with the other. She was able to engage in conversation, but back-and-forth interchange was limited. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient. These observations showed that she had difficulty completing tasks. Probably because she did not understand some of them but also because her attention span was short and she was easily distracted by sounds, movements and her own wishes. She clapped her hands when she was complimented on her efforts in trying to stay on task and during the examination she repeated this action in a ritualised manner. She made her wishes for play clearly and insistently known; she demanded participation while directing the actions of the other, laughing the whole time. There was little joint interactive or collaborative play. She walked independently at age 4, her gait broad-based. Her mood appeared happy; she often smiled without clear cause.

Patient 2

At second examination, patient 2 was of primary school age. She made a friendly, active impression. She was diagnosed with a significant refractive error, but only recently started training to wear glasses at school. There was some eye-to-eye gaze of brief duration and there was little integration of

gaze, facial expression, vocalisation and gesture. When younger she seemed interested in her surroundings, and explored her environment primarily through turning, biting, chewing or licking objects. She had a tendency of staring into lamps. Her mother mentioned that she was sensitive to noises at a young age, she startled easily and would panic and cry loudly, but this behaviour had improved. She would usually cover her ears when her mother vacuumed. Her production of spontaneous language and her comprehension of verbal communication are limited. She had less than 10 words but was able to vocalise sounds in differing intonations. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient. These observations showed that her attention span was short; she was easily distracted by sounds or movements. She enjoyed playing with building blocks, and she was able to slowly stack these or hand them to her mother. Some motor milestones had not been reached, she was not able to walk independently, but would stand and walk holding her parent's hand. Recently, she had started imitating her parents by drinking independently from a mug, although she would do so messily with one hand. Her mood was usually happy; she smiled and laughed often although the cause of it was not always clear. She sometimes smiled while looking at people, but her smiles were generally not reciprocal. Her mother mentioned that she would have difficulty falling asleep, and would cry loudly to be allowed out of bed.

Patient 3

Patient 3 was an alert toddler who had a friendly demeanour. He had marked vision problems and a history of recurrent ear infections. He smiled often without obvious cause and without making eye contact with the examiner. There was little visible reaction to his own name, nor did he respond to the examiner's facial expression, orientation or smiles. His eye-to-eye gaze was limited, and there was little reciprocity or spontaneous initiation of contacting or engaging the other. His parents mentioned that he would put up his arms to be lifted or pull their hand to get attention; he had little response to the examiner's attempts to draw his attention to distant objects. His mother mentioned that he enjoyed playing 'calling on the phone', making prattling sounds but no words. He startled easily at unexpected sounds or movements; and he would become quite upset and start crying by more pronounced sounds as, for example, organ music in church. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was sufficient, although he showed little interest in his surroundings beyond what was right in front of him. He had played with one favourite musical toy for the past year and a half, enjoying its crinkly sounds. He would sometimes reach with open hand for a favourite toy, but did not point to it to indicate a desire to play with it. He could spontaneously initiate a game of peek-a-boo by pulling a cloth over his face and waiting for his father to pull it away. Walking independently had not been achieved yet, but he started crawling at 2.5 years and could pull to standing at 3.5 years. His mood was happy; he would laugh when physical games such as lifting, jumping up-and-down and tickling were initiated by his parents.

Patient 4

Patient 4 was of primary school age and seemed shy and hesitant at first contact; she had a friendly facial expression. At first, eye-to-eye gaze was of brief duration, but this improved during the examination, and there was some integration of gaze, vocalisation and gesture. It was, however, difficult for the examiner to draw her attention to a distant object through eye contact and facial orientation. She made a specific vocalisation, which according to her mother she would always use to indicate the dog. She had no clear words, but would vocalise some sounds in differing intonations. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient. These observations showed that her attention span was short; she was easily distracted by sounds or movements. During the examination she was restless, active and kept moving around the room. Her mother mentioned that she was usually

'on-the-go'. She had difficulty staying on task, even when the task was very structured (such as drawing a shape) and she tended to flit from one thing to the next. She enjoyed playing with her doll, would take it out of a toy buggy and hug it. She would recognise and point to herself in family pictures when invited to do so. When looking at a photo album she was not easily distracted by ringing toys, but persisted in turning the pages to continue looking at pictures. Her mother would find her quite active at home, often imitating play activities initiated by her younger sister. Although she enjoyed imitating play activities she had difficulties initiating and organising new games herself. She was able to walk independently, her gait was broad-based and her gross motor skills were clumsy. Fine motor skills were immature. She walked around the room, pointed out the dog and walked closer to hug him. Her mood was usually happy; she would smile frequently and sometimes put her hand in front of her mouth to indicate surprise.

Patient 5

Patient 5 was of middle school age and had a passive and withdrawn demeanour at first contact; he drooled a bit. He wore a brace and was wheelchair-bound, but able to operate his wheelchair. He was diagnosed with many health problems, which included glaucoma and severe scoliosis. He kept his head down a great deal, and although there was some eye-to-eye gaze, there was little integration of gaze, facial expression and gesture. He had little reciprocal response to the examiner's facial expressions or smiles, and there was no attempt to spontaneously engage in social interaction with the examiner through eye gaze. He vocalised sounds, but had no words. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed. These observations showed that his attention span was sufficient. He did react to being touched by turning his head towards the person, he would smile and laugh when he was tickled, and clearly enjoyed physical interaction and play, inviting the other to continue by re-extending his hands or arms after tickling. He would also extend his hand to grab and would gesture purposively when drumming on a favourite toy drum. He drummed on the plastic side of the toy and not on the drum itself. His mother mentioned that he only wanted this particular toy drum of a certain style and colour, and that he would accept no other replacements. Although his motor skills were limited by his physical disabilities, patient 5 had recently swum small distances in a pool independently from his helper, had walked a small distance in the pool and had shown increasing confidence in the water. He would turn from a sitting position on the sofa and get down from it when verbally requested to do so. His mood was usually happy and stable, but sometimes he would show frustration, for example, when waiting for his food, by throwing things on the floor to get the attention of his helpers.

Patient 6

Patient 6 was a lively, active, primary school age boy at first contact; he was comfortable in the presence of his mother. He wore spectacles and had hearing aids in both ears. Initially, he averted his gaze, but during the continued examination there was intermittent eye-to-eye gaze. There was limited response to the examiner's facial expressions or smiles and little reciprocity in social interaction with the examiner, but he frequently spontaneously engaged with his mother trying to get her attention to help him with tasks and play. His spontaneous language and communication were limited, and although he vocalised sounds there were few discernible words. Some of these were understood by his mother, but not by many others.

For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was short: he was fidgety and had difficulty staying on task, tending to flit from one object or activity to the other. When he was interested in the task or the object, his perseverance improved. When interested in play he would draw his mother's attention primarily through sounds and by pulling her hand towards the object; his mother mentioned that he could be very insistent when trying to have his way. Gross motor skills were sufficient; fine motor skills were immature. His mother mentioned that he was able to ride a bicycle, but was prone to fall and he

would see no dangers. During examination his mood was happy; he enjoyed trying to colour a drawing. He got up just as happily when the examination was finished and rushed to exit the room before his mother. Often his behaviour at home would be challenging, he would tend to be insistent and quite irritable when things would not go as he expected. When irritable he could scream loudly; in general he demanded a lot of attention, and his mother mentioned that it would take a lot of effort to distract and calm him. At night, he used an oxygen mask; he would often be anxious and have difficulty falling asleep.

Cognitive assessment and cognitive function

Bayley Scales of Infant Development

Scores on mental age and motor development can be seen in Fig. 1. In view of their ID combined with the fact that chronological age of most participating children was above that for norms of the BSID-II, we present results in Fig. 1 as age equivalents and omit standard scores. The graph indicates that generally a progression in mental age and motor development can be expected with increasing age, but in a single patient (patient 5) cognitive and motor development remains severely delayed.

Development and autism symptomatology

Autism Diagnostic Interview – Revised

On the three domains of the ADI-R (social skills and play, communication and behavioural abnormalities) all children scored above the cut-off, with the exception of patient 6, who did not score above cut-off on behavioural abnormalities (Table 2).

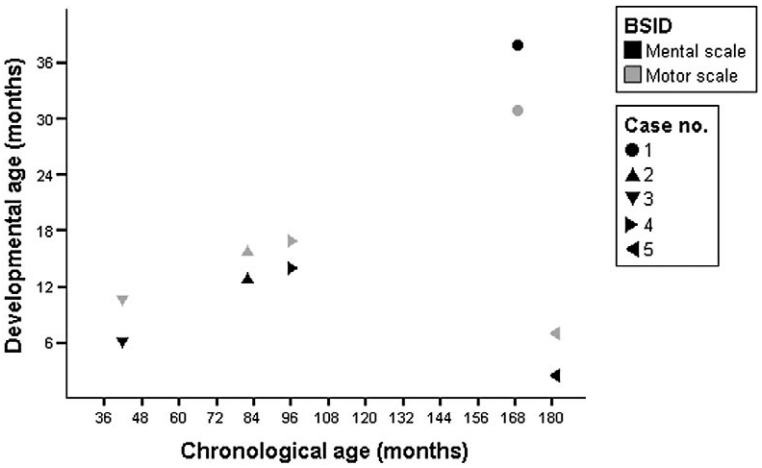

Figure 1 Developmental level of mental and motor functioning, measured by the Bayley Scales of Infant Development (BSID), compared to chronological age.

Table 2 Item scores on the three domains of the Autism Diagnostic Interview – Revised

		Patient #					
Test domain	**Cut-off**	**1**	**2**	**3**	**4**	**5**	**6**
Autism Diagnostic Interview – Revised							
Social skills and play	≥10	14	21	16	16	11	14
Communication (verbal & non-verbal)	≥8	13	NS	NS	NS	NS	14
Communication (non-verbal only)	≥7	NS	10	7	12	8	NS
Behavioural abnormalities	≥3	3	4	3	4	6	2

NS, no score.

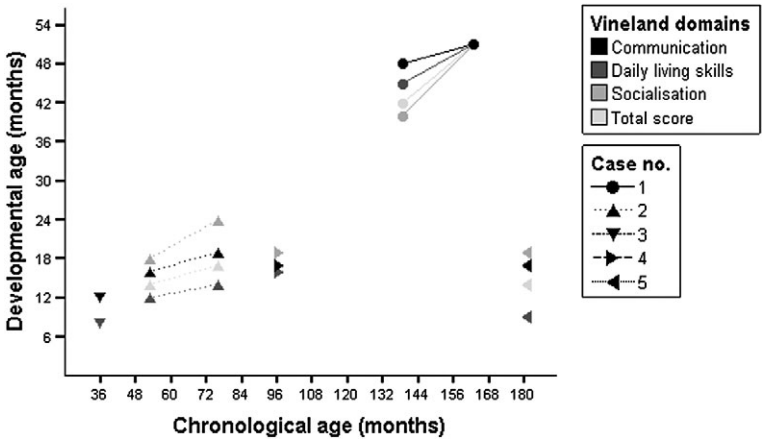

Figure 2 Developmental level on the three domains and total adaptive behaviour score of the Vineland compared to chronological age.

Adaptive functioning

Vineland Adaptive Behavior Scales

Patients 1 and 2 were assessed with the VABS twice during the study, with an interval of 2 years, which allowed for a limited follow-up perspective on their adaptive functioning and development (Fig. 2). For the other subjects, no earlier assessments were available, due either to their young age or to practical considerations, especially a geographical barrier. For these subjects, first measurements are also shown in Fig. 2. The following observations with respect to development, strengths and weaknesses can be made on adaptive functioning based on results of the VABS. First, we see gradual improvements on all adaptive scales of the Vineland over time, when comparing the children with each other (with the exception of patient 5) as well as within themselves (patient 1 and 2). Patient 2 showed progress in all domains at second measurement, although one more gradually than the other, with scores overlapping. This seems to indicate that, although children with MSS are considerably delayed on adaptive functioning, they do have learning potential and seem to follow their own slow developmental trajectory. Second, the domain of socialisation appears to be somewhat better developed, with parents reporting, for example, that their children do show affection to familiar persons, anticipate when they are about to be picked up by their parents or caregivers and imitate simple proceedings of adults. Third, the domain of communication seems to be a weaker domain. Children with MSS score positive on questions like 'understands the meaning of at least 10 words' or 'listening attentively to instructions', but they fail on questions that imply mastering (the beginning of) expressive language like 'has a vocabulary of at least 50 words' or 'uses sentences of at least 4 words'. Fourth, in most children, daily living skills are the weakest domain. This domain contains questions regarding skills such as 'can drink without any help from a cup' or 'alerts the parent that he/she has to go to the toilet'.

Again, results for patient 5 are an exception, as is also visible in Fig. 1 of the BSID scales. Patient 5's somatic condition could partly explain his scores.

Behavioural issues

Child Behavior Checklist

The subjects show hardly any externalising problem behaviour with the exception of patient 2 (Fig. 3), whose externalising problems are the result of scores in the clinical range on attention problems and scores in the borderline range on aggressive behaviour. Three patients scored above the borderline or clinical range on internalising problems: one patient (patient 5) did so because of a high score on somatic complaints (see case description); a second subject (patient 3) scored in the clinical range due to borderline scores on emotionally reactive behaviour and withdrawn behaviour; and the third subject (patient 2) scored in the clinical range on emotionally reactive behaviour.

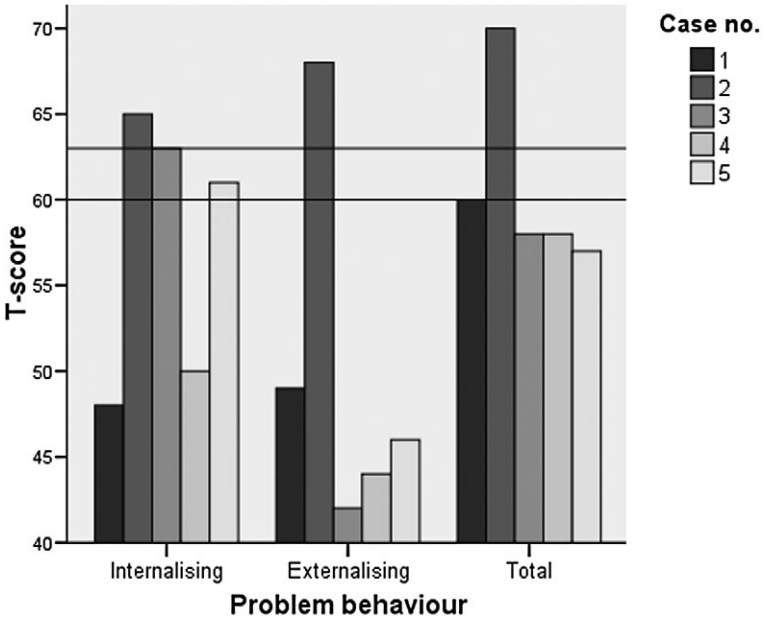

Figure 3 *T*-scores on internalising, externalising and total problem behaviour measured by the Child Behavior Checklist in five patients with Marshall–Smith syndrome.

Discussion

A structured clinical and interdisciplinary approach towards syndrome characterisation and delineation includes the integration of information regarding developmental issues, cognitive skills and behavioural characteristics. Only a limited number of studies of rare syndromes which feature considerable ID have directly assessed cognition and behaviour by examining the child with a structured test battery. More frequently, assessment was performed indirectly by interviewing the parents or based on observations by researcher or clinician. In the present study, we have combined direct evaluation of the child (BSID; psychiatric assessment), with indirect information gathered from parents with structured interviews and questionnaires (VABS; ADI-R; CBCL).

In only a proportion of patients with MSS, a mutation involving the gene *NFIX* is found, suggesting that there may be other factors involved in patients with MSS where the mutation has not been determined. The significance of *NFIX* mutations, however, is still unclear as there is insufficient information on the effects which alterations in the gene may have. Further studies to find other gene(s) involved in the aetiology for MSS are underway at present.

Cognitive and motor functioning in our sample of six cases with MSS is characterised by marked delays in individual development. The chronological age of the present MSS children lies between 42 and 181 months, while the developmental age as assessed by the BSID lies between 7 and 31 months on the mental scale and between 2.5 and 38 months on the motor scale respectively. When examining adaptive functioning, results from the VABS show social functioning as a relative strength and seem to indicate that in the presence of a slow individual development, progress in adaptive functioning, communicative, social and motor skills could be accomplished with increasing age. Decile scores were calculated based on the manual of the Dutch version of the VABS (De Bildt & Kraijer 2003). Likelihood concerning the level of cognitive functioning could not be asserted for one participant due to young age. Within the category of severe ID, two of the participants were categorised as profoundly intellectually disabled, while two others were asserted as having moderate ID.

The children examined in the present study all showed significant delays in the development of speech and language or acquired no language at all. Language and social cognition are closely linked in development (Tecumseh Fitch *et al.*

2010). Language plays an important role in understanding social interactions, which is part of social cognition. Social cognition in turn is necessary to acquire language. Social cognition includes the capacity to follow the other's gaze to objects of interest, imitate the other and understanding the meaning of the other (Frith & Frith 2010; Tecumseh Fitch *et al.* 2010). Communication between humans is determined both by speech and language abilities, and by non-verbal expressions such as eye gaze, joint attention, facial expressions, gestures and postures. Typically developing infants rapidly learn in their first year of life that the gaze and emotional expressions of others provides socially important information (Striano *et al.* 2006). The ability to detect emotional signals from others, interpret their meaning and adjust behaviour accordingly is an important characteristic in social interactions and necessary for the development of social competence. Social competence may be defined as the ability to socially interact and understand others in an effective, responsive and appropriate way, and this is evident in typically developing children even before the onset of spoken language. Examples of socially competent behaviours may be apparent in (developmentally) young children through non-verbal social interactions such as joint attention, smiling, approaching others, imitating another, imaginative play, imaginative play with peers and/or group play. An inability to interact this way may indicate an important deficit in the social domain as can be seen in autism spectrum disorders (Frith & Frith 2008, 2010; Hoehl *et al.* 2009).

There were many similarities in social interactions and behaviour between the children investigated in this study. Most prominent deficits in social interactions were: limited eye-to-eye gaze, lack of either initial reserve or aloofness, lack of reciprocity. Most important behaviours were: inflexibility with or without temper tantrums, repetitive and stereotypical play and limited imaginative play. In contrast to these findings is the determination that socialisation may be a relative strength in MSS, as these children are able to show affection to familiar persons, anticipate when they are about to be picked up by their parents or caregivers and imitate simple proceedings. Scores from assessments and interviews with parents showed that the severe delays in development of speech/language, social skills, and levels of communicative and adaptive functioning may be consistent with autism symptomatology, although social functioning could be considered a relative strength in comparison with other domains of adaptive functioning. Differentiating between deficits related to ID/developmental delay and deficits related to (subtle) autism symptomatology proved too difficult to accomplish with certainty in the small sample of the present study. This is consistent with the difficulties described in other published studies of genetic syndromes with significant ID/developmental delay with autism (Percy *et al.* 1990; Mazzocco *et al.* 1998; Cohen *et al.* 2005).

It is well possible that the autism-like behavioural features found in the present study are influenced by the various significant medical issues. Furthermore, we need to also take into account the higher frequency of repetitive, stereotyped behaviours found in individuals with severe ID reported in various studies (Bodfish *et al.* 2000; Moss *et al.* 2009). Therefore, we hesitate to draw inferences about the association of an autism symptom profile with MSS based on the findings of this first exploratory study of behaviour, cognition and development in the syndrome. Continued careful case descriptions with documentation and long-term follow-up of somatic, behavioural and cognitive phenotypes will eventually help determine their clinical relevance, and increase our understanding of diverse clinical presentations with or without autism symptomatology in this syndrome.

Conclusion

Results from our study make it clear that the children with MSS showed moderate to severe delays in mental age, motor development and adaptive functioning, with several similarities in communication, social interactions and behaviour. Speech and motor milestones were found to be severely delayed. Subjects mostly have a friendly or happy demeanour and seemed to enjoy social interactions that include familiar others, and they exhibited minimal maladaptive behaviours. Deficits in communication, social interactions, lack of reciprocal

social communication skills appropriate for developmental level and stereotyped, repetitive behaviours were noticeable during in-person psychiatric and psychological assessments. There was limited imaginary play; subjects tend to play in a repetitive, stereotypical manner with a favourite toy they are fascinated with. These characteristics may fit the definition of an autism spectrum disorder, but it remains unclear how developmental progress over time might influence this determination.

By using a standardised research protocol through a dedicated test battery and re-examining children with genetic syndromes over time, we improve our ability to detect specific behavioural characteristics of syndromes such as autism or autism-related symptomatology, and gather information on the long-term natural history. Integrating interdisciplinary information contributes significantly to the development of more refined, structured measures of behaviour and cognition in syndromes.

Clinical recognition of both physical and developmental and behavioural manifestations of syndromes is important for diagnosis, prognosis and counselling of the families involved, and coupling this with molecular genetic data will increase our understanding of the biological basis of the human physical and behavioural phenotype.

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