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Autism spectrum conditions in individuals with Möbius sequence, CHARGE syndrome and oculo-auriculo-vertebral spectrum: Diagnostic aspects☆

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ABSTRACT

As part of multidisciplinary surveys of three Behavioural Phenotype Conditions (BPCs); Möbius sequence (Möbius), CHARGE syndrome (CHARGE) and oculo-auriculo-vertebral spectrum (OAV), autism spectrum conditions (ASCs) was diagnosed in 45%, 68% and 42% of the individuals, respectively. Diagnostic difficulties due to additional dysfunctions such as mental retardation (MR), impaired vision, reduced hearing and cranial nerve dysfunction, were experienced in all three BPC groups. The applicability of current autism diagnostic instruments, such as the Autism Diagnostic Interview-Revised (ADI-R), the Childhood Autism Rating Scale (CARS) and the Autistic Behaviour Checklist (ABC), in individuals with ASCs and Möbius/CHARGE/OAV was analysed. Use of an extensive battery of diagnostic instruments, including both observational schedules and parent interviews, and, if possible, independent judgements from two clinicians, is essential in the diagnostics of ASCs in these individuals. Further, in individuals who are deaf and blind the applicability of current autism diagnostic instruments is highly questionable.

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1. Introduction

1.1. Coexisting disabilities in individuals with ASCs

Population-based studies have shown that people with ASCs, diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM) system, often have mental retardation (MR),[1] visual and/or hearing impairment (Steffenburg, 1991). Seventy to 90% of children with autistic disorder (AD) have been reported to have MR (Gillberg & Coleman, 2000). Rosenhall, Nordin, Sandström, Ahlsén, and Gillberg (1999) described hearing problems (including profound hearing loss/deafness) in 10% of Swedish children and adolescents with autism (n=199). Only 31% of Swedish children with AD/autistic-like condition (ALC) (n=45) were found to have normal visual acuity (Steffenburg, 1991).

1.2. ASCs in individuals with sensory deprivation

Conversely, studies of congenitally severely visually impaired children with retinopathy of prematurity (ROP) (Ek, Fernell, Jacobson, & Gillberg, 1998), rubella (Wing, 1969), and Lebers amaurosis (Fazzi, Rossi, Signorini, Bianchi, & Lanzi, 2007) have shown that ASCs are relatively common in certain subgroups, associated with brain damage and neurological disturbances. Brown, Hobson, Lee, and Stevenson (1997) found DSM-III-R autism in 10 out of 24 congenitally blind children with different ophthalmological diseases, and Mukaddes, Kilincaslan, Kucukyazici, Sevketoglu, and Tuncer (2007), reported autism in 30 out of 157 children and adolescents with varying ophthtalmological problems.

Jure, Rapin, and Tuchman (1991) described autism in 46 out of 1150 hearing impaired children (4%). A further 15 excluded children with autism (deaf–blind or inadequate clinical/audiological data), would have brought the total to 5.3%. Donaldson, Heavner, and Zwolan (2004) reported ASCs in eight out of 475 children (1.7%) who had received a cochlear implant, whereas Daneshi and Hassanzadeh (2007) reported autism in as many as four out of 60 (7%) prelingually deaf subjects with cochlear implants.

1.3. Möbius sequence, CHARGE syndrome and oculo-auriculo-vertebral spectrum

Möbius, CHARGE and OAV are congenital conditions involving multiple organs, which all are characterized by craniofacial maldevelopment and cranial nerve palsies. The range of clinical presentations in each of these conditions is wide, some individuals being mildly affected and others very severely (Strömland et al., 2002; Strömland et al., 2005; Strömland et al., 2007). The behavioural phenotype (BP, defined as a characteristic pattern of motor, cognitive, linguistic, social and sensory abnormalities, which is compatible with a biological disorder) in CHARGE has been described by several groups during recent years, while there is less literature addressing the BP's of Möbius and OAV. However, ASCs have been reported in Möbius, as well as in CHARGE and OAV.

1.3.1. Möbius sequence

Cranial nerve palsy of the facial (NVII) and abducens (NVI) nerves is mandatory in Möbius. Limb, oral and ear malformations and dysfunction of facial mimicry, speech, eating, swallowing and hearing difficulties are also characteristic. Visual impairment is more rare (see Strömland et al., 2002 for detailed description of clinical picture). MR has often been estimated to affect 10–15% (Gorlin, Cohen, & Hennekam, 2001), but was found in one third in the survey underlying the present report (Johansson et al., 2001) (Table 1). Both case reports (Gillberg & Winnergård, 1984; Larrandaburu, Schuler, Ehlers, Reis, & Silveira, 1999; Ornitz, Guthrie, & Farley, 1977) and other studies (n=17–37) (Bandim, Ventura, Miller, Almeida, & Costa, 2003; Gillberg & Steffenburg, 1989; Johansson et al., 2001 (n=21; ASCs in 45%) (Table 1); Verzijl, van der Zwaag, Cruysberg, & Padberg, 2003) have reported ASCs in individuals with Möbius. Others have described social emotional and behaviour problems without classifying them as ASCs (Amaya, Walker & Taylor, 1990; Giannini et al., 1984; Meyerson & Foushee, 1978).

[1] K usage: learning disability.

Table 1
ASCs and neurodevelopmental background factors in Möbius CHARGE and OAV groups.

	Möbius		CHARGE		OAV	
	n=25	(Male:female)	*n*=31	(Male:female)	*n*=20	(Male:female)
Total group	*n*=25	(18:7)	*n*=31	(15:16)	*n*=20	(12:8)
Diagnosed re ASC	*n*=21[a]	(16:5)	*n*=25[b]	(11:14)	*n*=19[c]	(11:8)
Total group						
Age range, yrs	1 month–55		1 month–31		8 months–17	
Mean age (S.D.), yrs	12:4 (11:7)		8:11 (6:7)		8:1 (5:3)	
CI, yrs	7:6-17:1		6:6-11:4		5:5-10:4	
Diagnosed						
Age range, yrs	1:11–55		2:4–31		1:11–17	
Mean age (S.D.), yrs	13:11 (11:5)		9:1 (4:11)		8:3 (5:1)	
CI, yrs	8:10–19:0		7:1–11:2		5:10–10:8	
ASC[d,e]	10		17		8	
AD	6 *(MMR 2, SMR 4)*		5 *(MMR 1, PMR 4)*		2 *(MMR 1, SMR 1)*	
ALC	1 *(MMR)*		5 *(NA 1, MMR 1, SMR 1, PMR 2)*		1 *(A)*	
AT	3 *(NA 3)*		7 *(MMR 5, SMR 2)*		5 *(NA 1, MMR 1, SMR 2, PMR 1)*	
AT?	3 *(A 2, NA 1)*		3 *(MMR 1, NA 2)*		3 *(NA 1, MMR 2)*	
No suspicion of ASCs	8 *(A 6, NA 2)*		5 *(A 1, NA 2, MMR 2)*		8 *(A 8)*	
DB			3 *(PMR 3)*		1 *(PMR)*	
Too young	4 *(A 1, SMR 1)*[f]		3[g]			
Cognitive level[h]						
A	9		1		9	
NA	6		5		2	
MMR	3		10		4	
SMR	5		3		3	
PMR			9		2	
Too young	2		3			
Visual impairment[i]	No subjects with PSVI/SVI.		19/31		6/20	
VI	Data on number of subjects with VI not available.		2		4	
PSVI			8			
SVI			9		2	
Hearing impairment[j]	5/19		31/31		16/20	
Bilateral	Data on severity of hearing impairment not available.		31		12	
Minor			7		2	
Moderate			1		5	
Severe			23		5	
Unilateral					4	
Minor					4	

[a] Five out of those 21 diagnosed as regards ASCs were previously reported by Gillberg and Steffenburg (1989).
[b] One out of those diagnosed as regards ASCs was previously reported by Fernell et al. (1999).
[c] One out of those 19 diagnosed as regards ASCs was previously reported by Landgren et al. (1992).
[d] ASCs: autism spectrum conditions; ALC: autistic-like condition; AT: autistic traits; AT?: autistic traits?; DB: deaf–blind.
[e] Cognitive level is given for each individual within each diagnostic category.
[f] Two individuals were too young to be assessed regarding cognitive level.
[g] Three individuals were too young to be assessed regarding cognitive level.
[h] A: average intelligence (IQ ≥ 85); NA: near average intelligence (IQ 70–84); MMR: mild mental retardation (IQ 50–69); SMR: severe mental retardation (Möbius study: IQ < 50, CHARGE/OAV studies: IQ 20–49); PMR: profound mental retardation (IQ < 20).
[i] VI: visual impairment; SVI: severe visual impairment (visual acuity ≤ 0.1 (20/200)); PSVI: probably severe visual impairment, VI visual impairment ≤ 0.3 (20/60).
[j] HI: hearing impairment; classification of hearing impairment referring to better ear when bilateral: deaf, >80 dB; severe HI, 60–80 dB; moderate HI, 40–59 dB; minor HI, 20–39 dB; normal hearing 0–19 dB.

1.3.2. CHARGE syndrome

In CHARGE, malformations of ears, eyes, brain, heart, choanae and retarded growth are common, individuals often being visually impaired or blind, hearing impaired or deaf and suffering from problems with balance, speech, and eating. Strömland et al. (2005) found cranial nerve palsies, most commonly affecting the facial nerve, in about 50%. MR was previously considered to be almost universal, but more recent research reports extremely varying mental functioning (Raqbi et al., 2003). Our group found developmental delay in 82% (Johansson et al., 2006) (Table 1). There have been several case reports of ASCs in CHARGE (Davenport, Hefner, & Mitchell, 1986; Fernell et al., 1999; Jure et al., 1991; Rapin & Ruben, 1976; Simon Harvey, Leaper, & Bankier, 1991; Wiznitzer, Rapin, & Van de Water, 1987). In the study group underlying the present report ASCs were diagnosed in as many as 68% (n=25) (Johansson et al., 2006) (Table 1). During recent years children with CHARGE have been described as frequently exhibiting moderate to severe behaviour difficulties, and often to be diagnosed with obsessive-compulsive disorder, attention-deficit disorder, Tourette syndrome, and autism (Hartshorne & Cypher, 2004). It has been suggested that behavioural difficulties in CHARGE have a compulsive/driven quality, which may be best explained by specific deficits in executive functioning (Nicholas, 2005).

1.3.3. Oculo-auriculo-vertebral spectrum

Individuals with OAV often have ear, ocular, vertebral, cerebral and heart defects, and functional deficits consisting of hearing impairment or deafness, visual impairment or blindness, as well as difficulties with eating and speech (Strömland et al., 2007). Strömland et al. (2007) found cranial nerve palsies, most commonly affecting the facial nerve, in about 50%. In OAV as well as in Möbius, the frequency of MR have often been estimated to be 10–15% (Gorlin et al., 2001), but Johansson et al. (2007) reported MR in 39% (Table 1). Except for the study underlying the present report, in which ASCs were reported in 42% (n=19) (Johansson et al., 2007) (Table 1), previously published work on ASCs in OAV have, to our best knowledge, been case reports (Barton & Volkmar, 1998; Jure et al., 1991; Landgren, Gillberg, & Strömland, 1992; Wiznitzer et al., 1987). Schizophreniform disorder, socially maladaptive behaviour and impaired attention have also been described (Brieger, Bartel-Friedrich, Haring, & Marneros, 1998; Fehlow & Walther, 1990).

1.4. Difficulties in diagnosing ASCs in individuals with MR, sensory deficits and cranial nerve palsy

The problems pertaining to diagnostics of autism in individuals with MR are well known. MR itself often leads to impairments in social and adaptive skills, and the lack of normal adaptation to the demands of daily life is part of the definition of MR. Conversely, diagnostic criteria for ASC may not be met in individuals with MR, because a certain developmental level is needed for some behaviour to emerge.

Autistic-like features in severely sensory deprived individuals are often considered to be explained by visual/hearing impairment per se. In severely visually impaired children, stereotyped behaviours such as body rocking, hand and finger movements, jumping, spinning, repetitive handling of objects, eye pressing and eye poking, light gazing, lying face downwards (Fazzi et al., 2007) are common. These have been attributed to loss of sensory input and secondary difficulties in expressive ability (Fraiberg, 1977), and interpreted as means of increasing the level of stimulation or ways of reducing tension (Fazzi et al., 2007). In addition, communication abnormalities, self-isolation, abnormal play and interpersonal relationships have frequently been described in individuals with severe visual impairment (Carvill & Marston, 2002). Deaf people have been described to more often have behavioural disorders, explosive and labile personalities, and psychiatric disorders such as anxiety disorder (Meadow, 1981; Roberts & Hindley, 1999). Further, there is evidence that development of theory of mind is delayed in both blindness and hearing impairment per se (Hobson, 1993; Peterson & Siegal, 1999).

Palsy of the abducens nerve impairs ocular motility, which may influence the impression of eye contact, and facial nerve palsy causes impaired facial mimicry. Thus, cranial nerve palsies may affect gaze and mimicry in a way reminiscent of impairment of flexible eye contact and facial expressions in ASCs. Considering that recent research indicate brain-stem dysfunction in some cases of autism (Rodier, 2002), the fact that impaired facial mimicry in some individuals with ASCs may be due to cranial nerve palsy per se rather than being a symptom of ASC, merits some attention.

1.5. Use of autism diagnostic instruments in individuals with multiple disabilities—previous research

Current autism and screening diagnostic instruments, including the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), the CARS (Schopler, Reichler, De Vellis, & Daly, 1980) and the ABC (Krug, Arick, & Almond, 1980) have been validated for differentiation of autism from other developmental disorders, especially MR. In the original study by Krug et al. (1980) the total ABC score for the sub-sample of individuals with autism was reliably differentiated from mean scores for severely mentally retarded, deaf, blind, severely emotionally disturbed and, "normal" individuals. Roper, Arnold, and Monteiro (2003) found a somewhat higher, not statistically significant, median ABC score in hearing patients with autism compared to deaf patients with autism. Nordin and Gillberg (1996) suggested lower ABC and CARS cut-off scores in children with multiple disabilities, so as to reduce the number of false negative results. To the best of our knowledge, no study designed to evaluate the psychometric properties of the ADI-R in multiply disabled children has been published, and neither the ADI-R nor the CARS have been validated to differentiate autism from severe sensory deficits.

Hartshorne, Grialou, and Parker (2005) found ABC scores in children with CHARGE to differ from ABC scores in a group of blind children as well as in a group of children with autism. Variance of scores in the CHARGE group was considerably greater, and one in four in the CHARGE group "could be classified as autistic". Difficulties rating ABC items due to additional disabilities were not addressed.

2. Methods

The study was performed as part of a larger prospective multidisciplinary project (including neuropsychiatry) of Möbius, CHARGE and OAV (Johansson et al., 2001, 2006, 2007; Strömland et al., 2002, 2005, 2007). The present study was approved by the Ethical Committee at the Medical Faculty, Göteborg University, Göteborg, Sweden.

The applicability of the ADI-R, the CARS and the ABC in the diagnosis of ASCs in individuals with additional dysfunctions as in Möbius, CHARGE and OAV was analysed. Our aims were to:

(i) estimate the frequency of individual items considered unratable in each of these BPCs,
(ii) compare diagnostic classification of ASCs according to instruments/criteria used,
(iii) analyse the impact of inclusion of omitted items in each BPC.

2.1. Participants

The participants were recruited from all over Sweden and examined at Queen Silvia's Hospital for Children and Adolescents in Göteborg. Criteria for entry into the studies were for Möbius; congenital bilateral or unilateral palsy of cranial nerves VI and VII with or without associated symptoms; for CHARGE, four or more of the six acronym characteristics (ocular coloboma, heart anomaly, atresia of the choanae, retarded growth and/or development, genital hypoplasia, ear anomalies and/or hearing impairment) or three of these plus additional characteristics; and for OAV, malformations in two of the four areas; oro-cranio-facial, ocular, auricular and vertebral. All patients diagnosed with ASCs were 2 years or older, and had hearing and/or vision sufficient to enable some social interaction. The study groups are outlined in Table 1. For further details see Johansson et al. (2001, 2006, 2007).

2.1.1. Neuropsychiatric assessment

ASCs are defined by specific abnormalities in reciprocal social interaction and communication, and a narrow range of interests and behaviours. The focus of the neuropsychiatric assessment was to identify disturbances in these domains. The ADI-R, the CARS, the ABC, the DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association, 1994) autism criteria were utilized (Table 2). All examinations in the multidisciplinary surveys were performed during one day, meaning that the neuropsychiatric examinations had to be constrained in time. Therefore, it was not possible to perform the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000).

Table 2
Neuropsychiatric/neuropsychological instruments used in Möbius, CHARGE and OAV studies.

	Möbius study	CHARGE study	OAV study
Total group in multidisciplinary study	*n*=25	*n*=31	*n*=20
Number of patients diagnosed regarding ASC	*n*=21	*n*=25	*n*=19
Autism diagnostic instruments	ADI-R (*n*=20) CARS (*n*=22) ABC (*n*=23)	ADI-R (*n*=28) CARS (*n*=28) ABC (*n*=28)	ADI-R (*n*=20) CARS (*n*=19) ABC (*n*=19)
Autism diagnostic criteria	DSM-III-R (*n*=22)	DSM-IV (*n*=28) DSM-III-R (*n*=28)	DSM-IV (*n*=19) DSM-III-R (*n*=20)
Measurements of mental development	Wechsler scales (*n*=9) VABS (*n*=19)[a]	Wechsler scales (*n*=12) VABS (*n*=16)	Wechsler scales (*n*=13) Griffith (*n*=1) VABS (*n*=5)

[a] In five individuals with Möbius results from both standardized psychological IQ test and assessment with the VABS were available.

2.1.1.1. The ADI-R. The ADI-R is a semi-structured, investigator-based parental interview, intended to differentiate classic autism from other pervasive developmental disorders. Four sub-domains comprise 84 items, corresponding to the DSM-IV domains; early development, communication, social skills, and restricted repetitive and stereotyped behaviour. Twenty-seven additional items intend to give information for habilitation/educational programs. The ratings for the vast majority of items are numerical codes with a three- or fourfold hierarchy of severity. Most items are scored for current manifestation, manifestation between 4 and 5 years of age, or at any moment during lifetime. The ADI-R provides a diagnostic algorithm with separate thresholds for the sub-domains (Social skills: 10; Communication, verbal individuals: 8; Communication, non-verbal individuals: 7; Restricted repetitive and stereotyped behaviour: 3; Early development 1), which all must be surpassed for a diagnosis of autism. For some items, the ADI-R provides special 'not applicable codes', and instructions for when these should be used. With exception of the item 'undue general sensitivity to noise' these instructions do not appear to have been designed with sensory deficits in mind. The 'not applicable codes' are given the same value as 'not occurring codes' in the algorithm.

2.1.1.2. The CARS. The CARS is one of the most documented and used autism measures. It is a mixture between observation schedule and interview, developed for distinguishing autism from other developmental disabilities. It comprises 15 domains, rated on a nominal scale of 7 classes of severity. It yields a summary score ranging from 15 to 60, scores of 30–36 indicating mild autism, and scores of 37 and above indicating 'severe autism'. The CARS does not give any directions for when specific items should be considered as ''not applicable'' in individuals with other disabilities.

2.1.1.3. The ABC. The ABC is a well-established autism diagnostic instrument, often utilized as a screening device. It was developed for measuring levels of autistic behaviour in individuals with severe autism. It comprises 57 items grouped into five subscales: Sensory, Relating, Body and Object use, Language, and Social and Self-help skills. The items are assigned weighted scores from 1 to 4 depending on their relative power in predicting autism. A total score of 67 or above is considered to indicate autism with 'high probability', and scores in the range of 53–67 to indicate 'suspected autism'. The ABC does not give any directions for when specific items should be considered as 'not applicable' in individuals with other disabilities.

2.1.1.4. Diagnostic process. In the Möbius study one investigator independently completed the ABC, the CARS and the DSM-III-R Checklist for AD, and another investigator the ADI-R. In the CHARGE/OAV groups one investigator independently completed the ABC, the CARS and the DSM-IV Checklist for AD and another investigator the ADI-R and the DSM-III-R criteria for AD. In all studies the ADI-R/CARS/

ABC was performed by interviewing the parents/another principal caregiver. During the CARS and ABC collateral interview, the patient was in the room and was observed by another investigator while playing and/or interacting with the parents/investigator. The DSM-III-R and DSM-IV Checklists were completed after the scoring of the diagnostic interview and the rating scales, on the basis of all available information. In the Möbius study, diagnoses were assigned according to the following; for autism, DSM-III-R symptom criteria for AD and ADI-R algorithm criteria for Childhood Autism CA; for ALC, 6–7 DSM-III-R criteria; for autistic traits (AT) 3–5 DSM-III-R criteria. In the CHARGE and OAV studies criteria as above were required plus the following criteria: for autism, DSM-IV criteria for AD; for ALC, 5 DSM-IV criteria; for autistic traits (AT), 3–4 DSM-IV criteria. In all study groups, cases had to fulfil at least one criterion within the social domain for a diagnosis of ASC.

2.1.1.5. Analysis of ADI-R, CARS and ABC scores. Cut-off scores as recommended by the developers of the instruments (Krug et al., 1980; Lord et al., 1994; Schopler et al., 1980) were applied. In individuals with sign language, items dealing with language were rated in great detail as recommended for spoken language (provided that appropriate education in sign language had been given from the early years). In blind patients, imitation based on non-visual systems, i.e. imitation of sounds and touch was rated.

2.1.1.6. ADI-R. Items assessing use of gesture were excluded in individuals with severe visual impairment, in whom parental information indicated difficulty recognizing non-verbal communication (Table 3). The item concerning eye contact was omitted when severe visual impairment/gaze paresis was deemed to severely affect the impression of eye contact. Items evaluating facial expressions were excluded when facial palsy was deemed to cause a limited range of facial expressions, or when visual impairment was judged to restrict recognition of other peoples' facial expressions. Items concerned with peer interactions were excluded in individuals 'interested in', 'but

Table 3
Omission of ADI-R algorithm items in Möbius, CHARGE and OAV groups.

	Möbius (n=20)	CHARGE (n=28)	OAV (n=20)
Qualitative impairments in reciprocal social interaction			
Failure to use non-verbal behaviours to regulate social interaction			
42. Direct gaze	5 (25%)	6 (21%)	2 (10%)
43. Social smile	8 (40%)	3 (11%)	1 (5%)
52. Range of facial expressions used to communicate	9 (45%)	8 (29%)	2 (10%)
Failure to develop peer relationships			
64. Imaginative play with peers	1 (5%)	3 (11%)	2 (10%)
66. Interest in children	1 (5%)	3 (11%)	1 (5%)
67. Response to other children's approaches	1 (5%)		
68/69. Group play with peers/friends	1 (5%)	5 (18%)	1 (5%)
Lack of socio-emotional reciprocity			
11. Use of other's body to communicate		2 (7%)	1 (5%)
49. Offers comfort		3 (11%)	2 (10%)
51. Quality of social overtures	2 (10%)	6 (21%)	2 (10%)
53. Inappropriate facial expression	1 (5%)	3 (11%)	
Qualitative impairments in reciprocal communication			
Lack of, or delay in, spoken language and failure to compensate through gesture			
30. Pointing to express interest	2 (10%)	2 (7%)	1 (5%)
31. Conventional instrumental gestures	1 (5%)	3 (11%)	2 (10%)
32. Nodding		4 (14%)	3 (15%)
33. Headshaking		6 (21%)	2 (10%)
Lack of varied spontaneous make-believe or social imitative play			
29. Spontaneous imitation of actions	1 (4%)	1 (3%)	1 (5%)
63. Imaginative play		3 (10%)	1 (5%)
65: Imitative social play			1 (5%)
Relative failure to initiate or sustain social interchange			
Inappropriate questions			1 (5%)
Restrictive, repetitive and stereotyped interests and behaviours	–	–	–

prevented from' activities with peers because of sensory impairments/other disabilities. In some patients with both visual and hearing impairment and SMR, the item 'quality of social overtures' (dealing with integration of eye-gaze, vocalizations and gesture in social overtures) was not rated. A large number of items (concerned with eye contact, non-verbal communication, imaginative play, offering of comfort and interaction with peers) were omitted in deaf–blind subjects.

2.1.1.7. CARS. The 'visual response' item was excluded in patients with severe visual impairment, without unusual visual interests, in whom difficulty to recognize facial expressions/gestures/objects was deemed to be a consequence of visual loss (Table 4). The item concerned with listening response was omitted in severely hearing impaired individuals, without oversensitivity to noise, in which hearing impairment was held responsible for the lack of listening responses. The 'verbal communication' item was excluded in subjects with hearing loss, considered to be responsible for lack of/delay in development of language, who did not have repetitive and stereotyped language. The item dealing with 'non-verbal communication', was excluded when facial nerve palsy was deemed to restrict the range of facial expressions.

2.1.1.8. ABC. Most excluded items (Table 5) pertained to the Sensory and Language sub-domains. 'Auditory perception items' were omitted in severely hearing impaired individuals, when hearing loss was judged to account for lack of auditory response. 'Visual perception items' were excluded in the severely visually impaired, when visual loss was deemed to account for absence of visual response or deviant visual perception. 'Speech and language items' were excluded in individuals with insufficient level of spoken language/sign language. In blind/almost blind patients, several items pertaining to the Relating sub-domain were excluded. The item concerned with 'social smile' (included in the Relating sub-domain) was excluded when lack of smile was deemed to be a consequence of facial palsy.

2.1.1.9. Analysis of impact of inclusion of omitted items. For every ADI-R, CARS and ABC Checklist a second 'maximum possible' score was calculated, adding maximum scores for items which in the earlier process had been considered 'not possible to rate' and thus omitted. The number was recorded of individuals in each BPC group, surpassing cut-off scores on the respective instruments when maximum possible scores on omitted items had been added to the rated total scores. ADI-R sub-domains (Social, Communication, Behaviour), CARS and ABC mean scores, before and after inclusion of maximum possible scores on omitted items, were calculated across diagnostic ASC groups in each BPC. The deaf–blind patients were excluded in these comparisons of 'rated' and 'maximum possible' mean scores in the respective BPC groups. Instead, the deaf–blind patients with CHARGE ($n=3$) and OAV ($n=1$) were collapsed into one deaf–blind group. Further, individuals rated as verbal and non-verbal,

Table 4
Omission of CARS items in Möbius, CHARGE and OAV groups.

	Möbius ($n=22$)	CHARGE ($n=28$)	OAV ($n=19$)
1. Relating to people	–	–	–
2. Imitation	–	–	–
3. Emotional response	–	–	–
4. Body use	–	–	–
5. Object use	–	–	–
6. Adaptation to change	–	1 (4%)	–
7. Visual response	–	4 (14%)	1 (5%)
8. Listening response	–	9 (32%)	3 (15%)
9. Taste, smell and touch response and use	–	–	–
10. Fear or nervousness	–	–	–
11. Verbal communication	–	5 (18%)	4 (20%)
12: Non-verbal communication	2 (9%)	–	–
13. Activity level	–	–	–
14. Level and consistency of intellectual response	–	–	–
15. General impression	–	–	–

Table 5
Omission of ABC items in Möbius, CHARGE and OAV groups.

	Möbius (n=23)	CHARGE (n=28)	OAV (n=20)
Sensory			
6. Poor use of visual discrimination when learning		3 (11%)	2 (10%)
10. Seams not to hear	1 (5%)	7 (25%)	6 (30%)
21. Sometimes shows no "startle response" to loud noise		11 (39%)	4 (20%)
34. Often won't blink/light	1 (5%)	2 (7%)	3 (15%)
39. Covers ears at many sounds		8 (29%)	4 (20%)
44. Squints, frowns or covers ears when in the natural light	2 (9%)	5 (18%)	2 (11%)
57. Stares into space for long periods of time			1 (5%)
Relating			
7. Has no social smile	3 (14%)		
17. Not responsive to others' facial expressions/feelings		3 (11%)	1 (5%)
24. Actively avoids eye contact		4 (14%)	2 (10%)
33. Does not imitate other children at play		2 (7%)	1 (5%)
38. Has not developed any friendships		1 (4%)	2 (10%)
47. "Looks through" people		4 (14%)	2 (10%)
Body/object use			
–	–	–	–
Language			
4. Does not follow simple commands given once		1 (4%)	1 (5%)
8. Has pronoun reversal	3 (14%)	12 (43%)	5 (25%)
11. Speech is atonal and arrhythmic	5 (23%)	14 (50%)	6 (30%)
15. Does not respond to own name when called among two others		6 (21%)	2 (10%)
18. Seldom uses "yes" or "I"	3 (14%)	6 (21%)	3 (15%)
20. Does not follow simple commands involving prepositions		1 (4%)	1 (5%)
32. Repeats phrases over and over	3 (14%)	11 (39%)	4 (20%)
37. Cannot point to more than five named objects			1 (5%)
42. Uses 0–5 spontaneous words per day to communicate	3 (14%)	1 (4%)	1 (5%)
46. Repeats sounds and words over and over		2 (7%)	
48. Echoes phrases and statements made by others	3 (14%)	11 (40%)	5 (25%)
56. Uses at least 15 but less than 30 spontaneous phases daily to communicate		1 (4%)	1 (5%)
Social/self-help			
–	–	–	–

respectively, according to the ADI-R algorithm, were collapsed for calculation of Communication sub-domain mean scores.

2.1.2. Neuropsychological assessment

The mental level was assessed with The Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1992), the Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), Griffith's Developmental Scales (Griffiths, 1970), or the Vineland Adaptive Behaviour Scales (Sparrow, Balla, & Ciccheti, 1984) (Table 2).

3. Results

3.1. Discrepancies in diagnostic classification of autism according to DSM-III-R, DSM-IV, ADI-R, CARS and ABC

3.1.1. Möbius group

There was complete concordance as regards 'DSM-III-R, ADI-R and CARS diagnoses of autism', whereas the ABC 'under-diagnosed' autism in three patients as compared with the other instruments.

3.1.2. CHARGE group

Complete concordance as regards diagnoses of AD was not observed between any diagnostic instruments/criteria (Fig. 1). The DSM-III-R criteria were most 'restrictive' and the ADI-R most 'inclusive'. Three individuals, who met algorithm criteria for autism according to the ADI-R did not meet DSM-III-R/DSM-IV criteria for AD, and were diagnosed with ALC ($n=2$) and AT ($n=1$). Two of these had mental ages of about 18 months whereas the third subject had a mental age above this level.

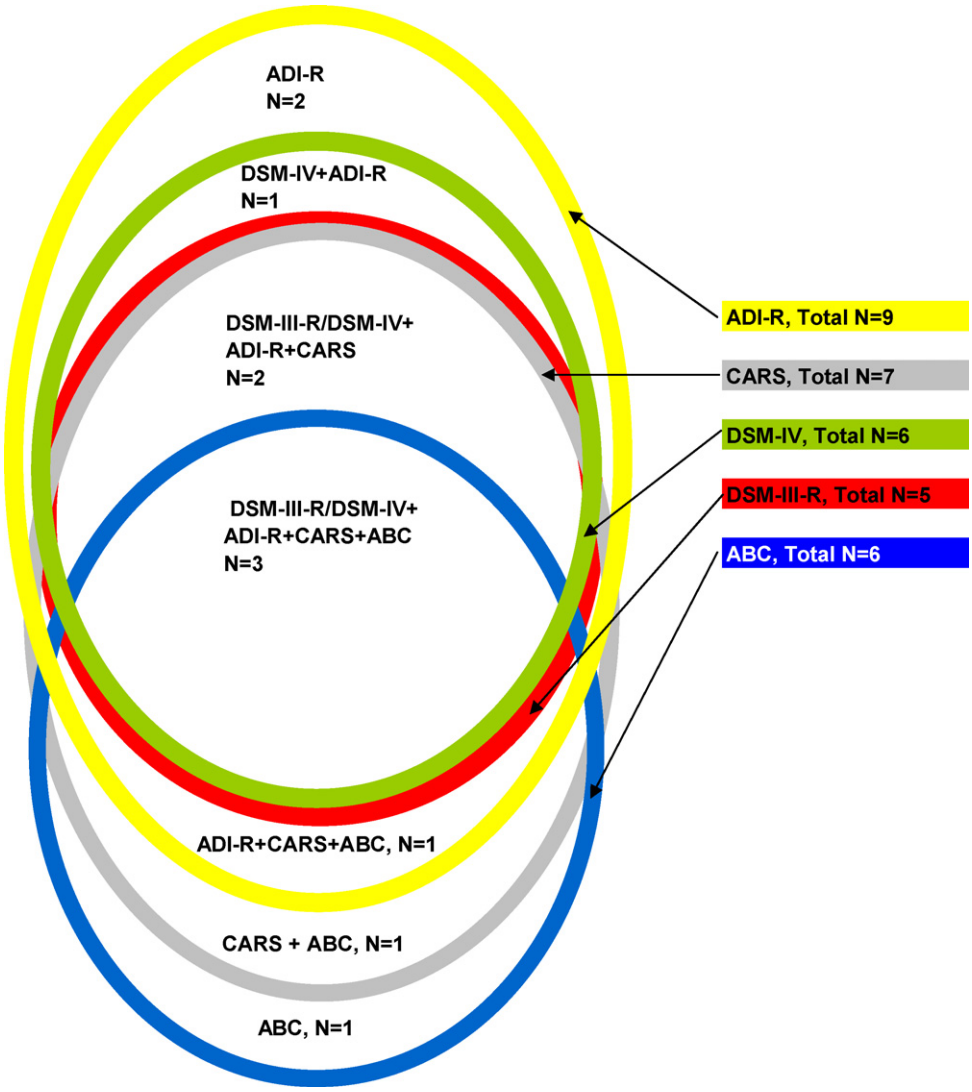

Fig. 1. Discrepancies in diagnostic classification of autism according to DSM-III-R/DSMIV, ADI-R, CARS and ABC in CHARGE group. ADI-R: Autism Diagnostic Interview-Revised; CARS: Childhood Autism Rating Scale; ABC: Autistic Behaviour Checklist; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders Third Edition-Revised; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; CHARGE: CHARGE syndrome (ocular coloboma, heart anomaly, atresia of the choanae, retarded growth and/or development, genital hypoplasia, ear anomalies and/or hearing impairment).

Table 6
Subjects surpassing ADI-R, CARS and ABC cut-off scores after inclusion of maximal scores on omitted items in each BPC.

	Möbius	CHARGE	OAV
ADI-R	–	*N*=3 3 DB	*N*=3 1 ALC, 1 AT, 1 DB
CARS	–	*N*=6 2 ALC, 1 AT, 3 DB	*N*=2 1 AT, 1 DB
ABC	*N*=2 2 AD	*N*=7 1 AD, 2 ALC, 1 AT, 3 DB	*N*=2 1 AT, 1 DB

Diagnostic ASC labels in this table refer to diagnoses assigned during neuropsychiatric study (before inclusion of omitted items).

3.1.3. OAV group

There was complete concordance as regards 'CARS, ABC, DSM-IV and DSM-III-R diagnoses of autism', whereas the ADI-R 'over-diagnosed' one patient with AT and MMR.

3.2. Impact of omitted items on 'ADI-R, CARS, and ABC diagnoses' in individual subjects

Except for the deaf–blind group, only very few subjects surpassed the respective cut-off scores when adding maximal possible scores on omitted items (Table 6). When comparing number of subjects surpassing cut-off scores for each instrument in the three BPC groups collapsed, the ABC cut-off score was surpassed by most subjects and the ADI-R but-off score by the fewest.

3.3. Distribution of sub-domain scores and impact of omitted items across diagnostic ASC groups

There was a general trend for more discrepancy between ABC rated and maximum possible mean scores, as compared to corresponding ADI-R sub-domain mean scores (except for ADI-R Social domain mean scores in the Möbius group and the deaf–blind individuals) and CARS scores. There was less discrepancy between CARS rated and maximum possible scores as compared to corresponding ADI-R as well as the ABC scores.

3.3.1. ADI-R

In comparison between whole BPC groups (Möbius: $n=20$; CHARGE: $n=28$; OAV: $n=20$) the CHARGE group had the highest rated mean scores across all sub-domains. The discrepancy between rated and maximum possible Social domain mean scores was more pronounced in the Möbius group (7.30, S.D.=8.74 versus 10.50, S.D.=9.68), mostly accounted for by omission of the items: 'direct gaze', 'social smile' and 'range of facial expressions used to communicate') (Table 3), than in the CHARGE and OAV groups (11.60, S.D.=10.25 versus 11.96, S.D.=10.35; 6.89, S.D.=6.72 versus 7.89, S.D.=7.28, respectively). In the CHARGE group the discrepancy between rated and maximum possible mean scores was more pronounced in patients with AD than in those with milder autistic symptoms. In the Möbius and OAV groups the corresponding discrepancy was more evenly distributed across the various diagnostic ASC groups.

There was no discrepancy between rated and maximum possible Communication domain mean scores for individuals with AD across the BPCs (Möbius: $n=6$; CHARGE: $n=5$; OAV: $n=2$), nor for the individuals with ALC in the CHARGE group ($n=5$). Almost all of those individuals with AD and ALC were classified as non-verbal according to the ADI-R algorithm.

Across the diagnostic ASC groups in the three BPCs, there were no differences between rated and maximal possible Behaviour sub-domain mean scores (all items included in the Behaviour sub-domain were rated in all individuals, including the deaf–blind group: $n=4$).

In the deaf–blind group ($n=4$), the maximum possible Social domain mean score was more than three times as high as the rated mean score (7.75, S.D.=1.71 versus 26.25, S.D.=1.26), and the maximum possible Communication mean score more than five times as high, as the rated mean score (2.00, S.D.=1.63 versus 11.50, S.D.=1.00).

3.3.2. CARS

When whole BPC groups were compared, the CHARGE group had the highest rated mean score (rated scores; Möbius, $n=22$: 24.14, S.D. = 9.40; CHARGE, $n=28$: 26.16, S.D. = 9.51; OAV, $n=19$: 20.72, S.D. = 5.63). There were only minor discrepancies between rated and maximum possible scores across the three BPC groups (maximum possible scores; Möbius, $n=22$: 24.46, S.D. = 9.24; CHARGE, $n=28$: 27.64, S.D. = 10.30; OAV, $n=19$: 21.72, S.D. = 6.62), as well as for individuals with AD across the BPCs (Möbius, $n=6$: 38.33, S.D. = 3.71 versus 38.33, S.D. = 3.71; CHARGE, $n=5$: 41.10, S.D. = 5.98 versus 41.50, S.D. = 6.04; OAV, $n=2$: 31.50, S.D. = 0.00 versus 33.00, S.D. = 2.12).

There was a considerable discrepancy between rated and maximum possible mean scores in the deaf–blind group ($n=4$, 21.88, S.D. = 3.01 versus 33.38, S.D. = 1.97).

3.3.3. ABC

Comparing the BPCs (Möbius: $n=23$; CHARGE: $n=28$; OAV: $n=19$), the CHARGE group had the highest rated mean scores and the most pronounced discrepancy between rated and maximum possible ABC scores. As regards discrepancy between rated and maximum possible means scores across diagnostic ASC groups, this discrepancy was, in the Möbius and CHARGE groups, more pronounced in patients with severe autistic symptoms than in those with mild or no such symptoms. In the OAV group the corresponding discrepancy was more evenly distributed among various diagnostic ASC groups.

There was a more than twofold discrepancy between rated and maximum possible mean scores in the deaf–blind group ($n=4$: 40.24, S.D. = 21.82 versus 94.50, S.D. = 15.76).

4. Overall summary of findings

Utilizing the ADI-R, the CARS and the ABC in assessment of ASCs in patients with Möbius, CHARGE and OAV presented diagnostic difficulties, which increased with the number and severity of disabilities.

The ADI-R 'over-diagnosed' some individuals, whereas the CARS, and especially the ABC, both 'over- and under-diagnosed' some subjects, as compared with the DSM criteria. There was complete concordance between diagnostic classification of AD according to the DSM criteria and CARS in the Möbius and OAV groups. However, in the present study, the DSM criteria were checked after completion of the ADI-R, CARS and ABC, based on all available information, and should not be taken as 'gold standards'. The rich description of various behaviour, provided by the ADI-R, in combination with the structured clinical observation, was of great value in the estimation of quality and severity of autistic symptoms. The discrepancy between total scores before and after inclusion of maximal possible scores on omitted items was very substantial in the deaf–blind subjects.

5. Discussion

Autism cannot be assumed to be the clinical manifestation of a relatively homogenous neuropathological condition, but rather a behavioural phenotype endpoint of a wide variety of developmental pathways. A number of theories hypothesize that autistic-like phenomena arise out of different forms of neuropsychological deficits. There is no simple way to diagnose ASCs. Constellations of symptoms are tied together conceptually by postulating an underlying disorder. 'The hypothetical construct of ASCs' has to be operationalized into items so as to form the basis for diagnostic instruments, all of which reflect somewhat different underlying theories.

5.1. Limitations

This was not a population-based study and the sample size in each sub-study was relatively small. The mode of recruitment with referrals from habilitation units in many cases may have contributed to overrepresentation of severe cases in each condition.

Statistical analyses with use of control groups, and pooling across BPC groups were not performed. Considering the sample sizes, and the heterogeneity across BPC groups as regards rate of sensory

deficits and cranial nerve dysfunction, as well as of chronological and mental age, such analyses were beyond the scope of this report.

There is an inevitable problem of circularity when analysing the discriminant validity of different autism diagnostic instruments, the present study being no exception in that the DSM Checklists were completed after the completion of the diagnostic interview and the rating scales. However, until there is an independent diagnostic measure for autism this 'circularity problem' cannot be overcome.

5.2. Applicability of instruments and individual items

Symptoms caused by other disabilities than ASCs, e.g. sensory deprivation, and *resembling* symptoms in ASCs may be *misinterpreted as symptoms of ASCs*, and vice versa. Further, since current autism diagnostic instruments assess concepts of behaviour, which in themselves require certain abilities to be present, there is a risk that deviant behaviours in ASCs might not be recognized in individuals with severe dysfunctions (i.e. unusual interest in auditory stimuli in a child with hearing impairment).

The neuropsychiatric assessments were complicated by the fact that the applicability of several ADI-R, CARS and ABC items was in doubt. Furthermore, neither the ADI-R nor the CARS scoring instructions were designed considering of normal/deviant development in individuals with sensory impairments.

Decisions about omission of items were often complicated. None of the instruments used provide clear directions for when specific items should be considered as 'not applicable' in disabilities such as in these BPCs. Neither the CARS nor the ABC provide any bases for distinction between 'not applicable because of disability' and 'not occurring'. Codes for 'not applicable because of disability' and 'not occurring' are given the same numerical values in the ADI-R algorithm. Further, the degree of hearing/visual impairment may be difficult to establish in multiply disabled individuals. Widen and Keener (2003) pointed out the inability of infants (and hence individuals with PMR and autism, our note) to actively participate in providing an audiogram. Jacobsen, Magnussen, and Smith (1997) discovered 'hidden visual capabilities' in deaf–blind multiply disabled people, when visual acuity was measured with a method, not requiring perceptual recognition, language skills or coordinated manual responses. Individuals with colobomas and microcornea (as in CHARGE/OAV, our note) often have better visual function than their clinical appearance suggests, even when the macula is involved (Hornby, Adolph, Gilbert, Dandona, & Foster, 2000). Therefore, decisions about omission of items and applicability of scoring instructions had to be evaluated separately in each case and, to a considerable degree, be based on parental knowledge of the child.

ADI-R and CARS items are dealing with broader concepts than ABC items (for instance several more narrow ABC items under the Sensory sub-section versus only one ADI-R and CARS item, respectively, concerned with unusual reactions to sensory stimuli in general), and there was a trend for ABC items to be more frequently omitted than ADI-R and CARS items (Tables 3–5). Thus, the interviewers were able to consider alternative aspects of the skills/behaviours when scoring ADI-R and CARS items. Further, the ADI-R provides a special algorithm for non-verbal individuals, meaning that ADI-R items dealing with verbal language did not have to be omitted. In contrast, as regards the CARS and ABC, verbal communication items were omitted in several hearing impaired patients. The Language subsection accounted for a major part of omitted ABC items in all the BPC groups. Thus, the ADI-R may be a better instrument in the hearing impaired, who do not have sign language, as well as in other mute individuals. Miranda-Linné and Melin (1997) speculated that ABC items concerned with expressive language might be weighted to heavily in regard to both the Language subscale and the total ABC score, since greater pathology scores are provided to verbal individuals than to mute.

Considering the substantial discrepancy between rated and maximum possible scores in the deaf–blind individuals, it would seem that the applicability of current autism diagnostic instruments is highly questionable in individuals who are deaf and blind.

The rationale for the more frequent omission of ADI-R Social domain items in the Möbius group, as compared to the CHARGE/OAV groups, is probably a more restrictive approach in omission of items dealing with concepts influenced by visual impairment, since vision theoretically may affect all aspects of social interaction, whereas it is possible to define more exactly which items are concerned with concepts which could be affected by facial nerve/gaze paresis.

Conversely, CARS and ABC items had to be omitted more frequently in patients with CHARGE and OAV than in Möbius. The ABC does not comprise any item concerned with facial expressions, and the CARS has only one item dealing with non-verbal communication.

Although previously shown to produce reliable and valid data in individuals without severe sensory impairments, in subjects with such problems, there is no safe way to establish whether autism diagnostic instruments are measuring 'autistic symptoms', i.e. effect indicators of specific neurological disturbances in ASCs, or 'autistic-like features', i.e. causal indicators, defining an 'autistic-like syndrome' rather than being defined by it. Thus, one might argue against the diagnoses of ASCs to describe the patients in our study groups. However, current diagnostic systems (the DSM-IV/ICD-10 criteria) do not provide any criteria for excluding/classifying the diagnoses of ASCs as secondary in the presence of sensory deficits (or other neurological problems).

It may be that perceptual handicaps are not sufficient to explain autistic-like syndromes in the visually/hearing impaired, but nevertheless are important when acting in concert with other factors, such as brain damage. If we extend the problem of diagnosing ASCs in individuals with severe sensory impairments to its most extreme, we end up calling the construct validity of the theoretical model for autism, into question. Under such circumstances, perhaps the most robust way to assess the validity in the diagnostic process would be an empirical approach relying on 'a full descriptive clinical picture'. Structured investigator-based interviews, such as the ADI-R, provides an attempt to merge the advantages of psychometrically sound tests and the full clinical information obtained from conversational interchange with the parents. However, the ADI-R is designed for diagnostics of 'classic autism' according to a categorical conceptualization based on the ICD-10/DSM-IV criteria and provides no cut-off scores for milder ASCs. Nevertheless, the interview yielded rich descriptions of behaviour, which in many instances were compatible with milder ASCs, although the ADI-R cut-off scores were not exceeded.

5.3. Clinical implications

Awareness of the fact that ASCs occurs frequently, at least in some subgroups of children with visual and hearing impairment, is important in the habilitation care of these groups. The parents of several children with sensory impairments in our series, who were diagnosed with ASCs, reported that educational methods, successful with other visually/hearing impaired children, were relatively unsuccessful with their children. We would like to stress that failure to recognize autism in a child with severe sensory impairments frequently results in providing services for that child designed for the hearing/visually impaired. Such services may fail to recognize autistic symptoms masked by communication difficulties related to visual/hearing deficits, which in turn may create a situation where the needs of the child, as they relate to autism, are not met.

6. Conclusions

Since statistical analyses were not performed due to small numbers, our data constitute a descriptive report on difficulties in diagnostics of ASCs in individuals with multiple disabilities, especially sensory impairments and cranial nerve palsies, an area previously practically unexplored. Use of an extensive battery of autism diagnostic instruments, including both observational schedules and parental interviews, and experienced clinicians judgement (preferably two independent clinicians) is essential. There is a need for further development of autism diagnostic instruments, which are rooted in knowledge of normal/deviant development in children with sensory impairments.

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