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ORIGINAL PAPER

A Prospective Case Series of High-risk Infants who Developed Autism

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Abstract The present paper documents the development of autism/autistic spectrum disorder in a consecutive series of nine high-risk infants followed prospectively from 6 months of age. Evidence is provided for two broadly defined subgroups: the first subgroup ($n = 6$) showed a decrease in IQ between 12 and 24 or 36 months (from average/near average to severe cognitive impairment), whereas the second subgroup ($n = 3$) continued to obtain average or near average IQs. Signs of autism emerged and/or were more striking earlier in the first subgroup. In all nine children, early impairment in social-communicative development coexisted with atypical sensory and/or motor behaviors, as did a temperamental profile marked by irritability/distress and dysregulated state. Discussion focuses on issues raised by the pattern of findings.

Keywords Autism · Phenotype · Early development · Social · Communication · Cognitive · Sensory · Motor · Temperament · High-risk infants

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Introduction

Major advances have been made in the diagnosis and treatment of children with autism spectrum disorders (ASD). Among the most important are the development and wide implementation of reliable and valid diagnostic instruments (e.g., Lord et al., 2000; Lord, Rutter, & Le Couteur, 1994), and of early autism-specific intervention programs (for reviews, see Bryson, Rogers, & Fombonne, 2003; Dawson & Osterling, 1997; National Research Council, 2001; Rogers, 1998). Evidence that children with ASD benefit from early behavioral intervention has placed the earlier detection and treatment of ASD as a major health care priority (Charman & Howlin, 2003; Filipek et al., 2000; Lord et al., 2005). Diagnoses provided early in life hold real promise for improved child outcomes, and allow parents to take into account recurrence rates in future family planning. However, in the absence of reliable biological markers, such efforts are constrained by our knowledge of the earliest behavioral manifestations of ASD.

Existing evidence on the earliest signs of autism comes largely from retrospective parent reports and early home videotapes. As many as 50% of parents of children with ASD recall abnormalities dating back to the first year of life, including extremes of tempera-

ment and behavior (ranging from marked irritability to alarming passivity), poor eye contact, and lack of responsiveness to parents' voices or attempts to play and interact (e.g., Dahlgren & Gillberg, 1989; De Giacomo & Fombonne, 1998; Ohta, Nagai, Hara, & Sasaki, 1987). Similarly, analyses of home videos have revealed atypicalities in development by 12 months of age in children later diagnosed with ASD (e.g., Adrien et al., 1992; Baranek, 1999; Losche, 1990; Osterling & Dawson, 1994). Relative to typically developing controls, children with ASD are less likely to respond when their names are called, to spontaneously look and smile at others, and may exhibit repetitive behaviors. A few isolated case reports of children with autism, ascertained due to concerns during infancy and followed prospectively, also implicate early social-communicative impairments that may be accompanied by sensorimotor abnormalities (e.g., hyper-sensitivity to sound and touch) and/or atypical motor behaviors (Dawson, Osterling, Meltzoff, & Kuhl, 2000; Klin et al., 2004; Osterling, Dawson, & Munson, 2002). While informative, research to date is limited by several methodological problems, notably the recall biases of retrospective reports, the contextual constraints of videotapes, and the high likelihood that isolated case reports represent the most severe or otherwise atypical cases (Zwaigenbaum et al., 2006).

Ultimately, we need a coherent picture of the early behavioral profiles and developmental trajectories that might distinguish very young children with ASD. For these purposes, prospective longitudinal studies of high-risk infants are ideally suited (Bryson, Zwaigenbaum, & Roberts, 2004; Zwaigenbaum et al., 2006). Infants can be ascertained at or prior to birth based on risk status (i.e., having a sibling with ASD); the methods employed can be standardized across children and over time; and, to the extent that ascertainment is independent of clinical features (i.e., based on risk status alone) and relatively complete within geographically defined regions, findings are likely to be representative of the population with ASD. Many outstanding questions remain about the nature, timing, and patterns of early symptom development, and how the onset and progression of early signs might vary across the diverse group of children who develop an ASD. Prospective research also provides a rich opportunity to more accurately characterize the nature and frequency of developmental regression in ASD (e.g., Lord, Shulman, & DiLavore, 2004).

In an attempt to address these and related questions, we have embarked on a prospective study of high-risk infants with a sibling with ASD (Zwaigenbaum et al., 2005). For this purpose, the Autism Observation Scale for Infants (AOSI; Bryson et al., in press) was developed to systematically monitor the emergence of early signs of autism, as hypothesized from retrospective reports, early home videotapes, case studies, and our collective clinical experience. Our assessments also include measures of cognition, early gestures and language, and temperament. Infants are assessed at 6-month intervals from the age of 6 to 24 months, followed by an independent (blind) gold-standard diagnostic assessment for ASD at 36 months. Preliminary findings indicate that by 12 months of age, infants later diagnosed with autism/ASD are distinguished by elevated scores on the AOSI, temperamental differences, including difficulties disengaging visual attention, and reduced use of gestures that precede the atypical development of language (Mitchell et al., 2006; Zwaigenbaum et al., 2005). Here we provide detailed information on the first, consecutive series of nine infants followed prospectively from 6 months of age and subsequently diagnosed with autism/ASD. In an attempt to identify behavior profiles that might be indicative of ASD early in life, discussion focuses on differences and similarities in the early emergence and timing of signs of autism/ASD across the children.

Methods

Participants

Participants include the first nine children (four females) from our prospective study of infant siblings, who were followed from the age of 6 months and subsequently diagnosed with autism/ASD (Cases 1, 2, 6, and 7 described below also participated in the Loh et al. study in this volume). Diagnoses of the children and their older siblings (probands) were based on ADI-R (Lord et al., 1994) and ADOS (Lord et al., 2000) criteria, and on expert clinical judgment using DSM-IV-TR criteria (APA, 2000). Neither the younger siblings nor the probands had identifiable neurological or genetic conditions, or severe sensory or motor impairments. The children were recruited from three multidisciplinary autism diagnostic and treatment centers in Canada, including McMaster Children's Hospital in Hamilton, The Hospital for Sick Children in Toronto, and the IWK Health Centre in Halifax, and from clinicians in the surrounding regions.

Procedures

Each sibling was enrolled in the study at 6 months of age, and assessed at 6-month intervals from 6 to

24 months. Assessments included measures of ASD symptoms (AOSI; Bryson et al., in press; and/or ADOS; Lord et al., 2000), cognition (Bayley Scales of Infant Development, 2nd ed.; Bayley, 1993; or Mullen Scales of Early Learning; Mullen, 1995), gestural and early language development (MacArthur Communicative Development Inventories-Words and Gestures; Fenson et al., 1993), and temperament (Infant Temperament Scale; Rothbart, 1981; or Toddler Behavior Assessment Questionnaire; Goldsmith, 1996; see Table 1 for assessment protocol). Parents were also surveyed regarding any concerns they had about their child's health (medical conditions, sleeping, and feeding) or development (e.g., interests, sensory, motor, or communicative issues) using a semi-structured interview.

At 36 months of age, and blind to previous assessment results, an independent diagnostic assessment was conducted by an experienced clinician (LZ, WR, or PS) using the ADI-R, ADOS, and DSM-IV-TR. A diagnosis of autistic disorder was restricted to cases given a clinical diagnosis of autism and who exceeded the autism cut-off scores on both the ADOS (the sum of the social and communication domains) and the ADI-R (i.e., for total score, as well as subscale scores for social, communication, and repetitive behavior domains). An ASD diagnosis was assigned to children who did not meet criteria for autism but received a clinical diagnosis of ASD (Pervasive Disorder Not Otherwise Specified or Asperger syndrome), and exceeded the ASD cut-off on the ADOS and that recently proposed for the ADI-R (i.e., exceeded the cut-off score for autism on the social domain and on at least one of the other two domains; Risi et al., 2006).

Based on our ethical considerations, 7 of the 9 children to be described here were given a clinical diagnosis of ASD prior to age 3 years (4 at 24 months and 3 at 30 months) and immediately referred for autism-specific treatment services. Parents of these children were asked not to disclose the clinical diagnoses to the clinician who conducted the independent assessment at 36 months. Our impression is that we have been able to apply clinical best practices in communicating early diagnoses while maintaining blindness of our gold-standard diagnosis. Written informed consent was obtained from parents prior to enrolling the infants in the study.

Table 1 Items in the Autism Observation Scale for Infants (Bryson et al., in press)

1. Visual tracking	9. Reciprocal social smile
2. Disengagement of visual attention	10. Gaze-action co-ordination
3. Orients to name called	11. Reactivity
4. Differential facial emotion	12. Social interest and affect
5. Anticipatory social response	13. Transitions
6. Imitation	14. Motor control/co-ordination
7. Social babbling	15. Atypical motor behavior
8. Eye contact	16. Atypical sensory behavior

Autism Observation Scale for Infants (Bryson et al., in press)

This 16-item interactive play schedule is designed to systematically monitor early putative signs of ASD, including aspects of visual attention, social–communication, play and sensory–motor development (see Table 2). The relative presence or absence of key behaviors is rated on a scale from 0 to 3, where 0 implies normal function, and higher values indicate increasing deviation from the norm; some items are rated from 0 to 2 (disengagement of visual attention, transitions, atypical motor behavior, and atypical sensory behavior), and three items (eye contact, atypical sensory behavior, and atypical motor behavior) do not include a ''1'' rating in order to force a choice between ''atypical'' and typical development. Inter-rater agreement on the total score is excellent: intra-class correlation coefficients (ICCs) at 6, 12, and 18 months are 0.71, 0.90 and 0.92, respectively (Bryson et al., in press). Test–retest reliability (at 12 months) is also good (ICC = 0.63).

Case Descriptions and Analyses

We first present the nine cases. This is followed by an analysis and discussion of the early developmental profiles (cognitive–communicative and behavior–temperament) and recurring patterns across cases. Case descriptions are derived largely from direct standardized observations (AOSI and ADOS); references to ''reported'' observations refer to those made by parents. Summary data on the assessment measures by age assessed are provided in Table 3. As indicated there, an AOSI total score of 9 (or equivalent total marker count of 7) at 12 months has been shown to be predictive at 24 months of the social-communicative impairments diagnostic of autism/ASD on the ADOS (Zwaigenbaum et al., 2005). Note that at 36 months of age seven (two females) of the nine cases received an independent (blind) ''gold-standard'' (ADI-R, ADOS, and DSM-IV-TR) diagnosis of autism or ASD (n = 1; a female). Case 8 (male) received an independent clinical diagnosis of ASD and Case 9 (female) an independent clinical diagnosis of autism; both failed to

Table 2 Measures used at each age assessed

6 months	12 months	18 months	24 months	36 months
AOSI	AOSI	AOSI	ADOS	ADOS
Bayley/Mullen	Bayley/Mullen	ADOS	Mullen	ADI-R
Temperament	MacArthur Communication Temperament	MacArthur Communication	Temperament	DSM-IV-TR
				Mullen
Concerns Form	Concerns Form	Concerns Form	Concerns Form	Concerns Form

strictly meet ADI-R criteria (by 1–2 points), and Case 9 was below the ASD cut-off on the ADOS by 1 point (see Table 3).

Case 1: Male, Diagnosis of Autism at 36 Months

Six months: Placid baby who showed interest/pleasure in and responsiveness to others (e.g., consistent and sustained eye contact; nice social smiling, especially with mom; social anticipation to ''peek-a-boo'' and imitation of raspberries; did not orient to name called but oriented to mom talking; some babbling); oriented to events in his environment, and smooth visual tracking of objects; delayed motor development (floppy, not sitting on own or reaching for toys, and poor motor control).

Twelve months: Limited interest/pleasure in and responsiveness to others (e.g., only brief eye contact and sometimes seemed to look through rather than at others; some social smiling, but more so with physical stimulation such as tickling; no social anticipation to ''peek-a-boo,'' only to physical cause and effect toys, and no anticipatory arm movements to being picked up; inconsistent orienting to name but did orient to voices; equivocal imitation, and delayed if present; and virtually no vocalizations or gestures); also discontinuous visual tracking, and visual fixation on objects (e.g., strings or wheels of a toy car), with distress when removed; little reaching for objects, flailed arms and legs in reaction to toys, and acted on objects without looking at them; atypical sensory behaviors (e.g., visual interest in carpet pattern and feeling with index finger); atypical motor behaviors (hand flapping and finger flicking); marked delay in motor development (generally hypotonic but rigid when standing with assistance); seemed uncomfortable when being held, and easily irritated; reportedly poor sleeper (awake several times/night) and refused food not smooth in consistency.

Fifteen months: As above, although attentive to mom, inconsistent but some sustained eye contact, differential response to change in Examiner's (Ex's) facial emotion, and delayed imitation; no vocalizations other than repeating ''uh'' and ''oh'' when said by mom); also delayed and jerky visual tracking; tentative about touching and little manipulation of toys, and strong startle response to bell and removal of blanket during ''peek-a-boo''; atypical motor behaviors (finger flicking); reportedly no gestures, continues to be very poor sleeper (i.e., up 10–12 times/night), and even more irritable and difficult to settle (vs. passive); 1 month later (at 16 months) mom reported loss of emotional connectedness, with only fleeting eye contact, or looking through others, and virtual absence of smiling and facial expressiveness generally.

Table 3 Descriptive data on cases by age assessed (in months)

Case	AOSI			IQ			ADOS			ADI (36 mos)			36 mos		
	6	12	18	12	24	36	18	24	36	S	C	B	T	GS Dx	C Dx
1	2	14	18	68[a]	<50[a]	50	18	16	17	21	13	5	39	Aut	Aut
2 (F)	4	3	3	90[a]	97	96	10	7	9	11	8	3	22	ASD	ASD
3 (F)	8	15	20	NT	<50	<50	19	19	15	22	14	5	41	Aut	Aut
4	7	13	5	93[a]	52	<50	0	18	20	23	14	8	45	Aut	Aut
5	5	5	13	88[a]	61	<50	13	8	22	19	9	8	36	Aut	Aut
6 (F)	6	2	7	107	79	85	10	0	13	11	12	5	28	Aut	Aut
7	11	9	21	82	<50	<50	19	20	20	22	8	6	36	Aut	Aut
8	NA	1	2	99	86[a]	51	1	5	10	9	13	2	24	Non	ASD
9 (F)	6	10	14	77[a]	80[a]	80	14	11	7	7	12	4	23	ASD	Aut

F female; *AOSI* Autism Observation Scale for infants total score; *ADOS* Autism Diagnostic Observation Schedule total algorithm score; *ADI-R* Autism Diagnostic Interview-Revised Social (S), Communication (C) and Behavior (B) scores; *GS Dx* gold-standard diagnosis; *CDx* clinical diagnosis; *NT* non-testable; *NA* not available

[a] IQ derived from Bayley Scales of Infant Development (2nd ed.); otherwise IQ from Mullen Scales of Early Learning

Eighteen months: As above, although no imitation, avoidant of people and things, very fussy and irritated/upset by virtually all objects introduced (closes eyes, shakes head, and waves arms), and upset by change (e.g., removal of bottle or toys); very poor self-regulation; striking sensory interests (notably strings and round things such as button nose on a clown); not walking independently; reportedly soothed by videos, singing or tickling.

Twenty-four months: ADOS positive for autism; given a clinical diagnosis of autism and referred for services.

Thirty-six months: Independent diagnosis of autism (ADOS algorithm score = 17; ADI subscale scores for Social = 21, Communication = 13, and Repetitive Behavior = 5); global delay (IQ < 50) and no functional speech (only high-pitched moans).

Case 2: Female, Diagnosis of ASD (Aspergers) at 36 Months

Six months: Interest/pleasure in and responsiveness to others (e.g., consistent and sustained eye contact, nice social smiling, differential response to change in Ex's facial expression, social anticipation to ''peek-a-boo,'' and oriented to name called, although equivocal imitation and social babbling, and started to cry during ''peek-a-boo'' for no apparent reason); smooth visual tracking, although limited motor control (e.g., little grasping of objects and some difficulty doing so, and awkward hand movement when swatting an object).

Twelve months: As above, although little social smiling, generally non-expressive facially, and babbling often not directed at others; imitated action on an object, although slow to approach new toys and atypical motor behavior (hand flapping when distressed); reportedly socially reticent, and overwhelmed by and clingy in presence of too many people; over-reactive to certain sounds (hair dryer and toy car), grass on feet (tiptoes), limited food preferences and shivering spells.

Eighteen months: As above, although no orienting to name called, and lack of self-initiated social–communication (e.g., no showing, pointing, or use of eye gaze to share interest); no imaginative play and, while many functional words, echoed others' phrases; visual fixation (bolts in chair and own shoelace), and would not relinquish certain toys, with upset upon removal; reportedly anxious and very clingy around others, and particularly fearful of women with dark hair; upset if door on toy house is open, sensitive to touch, and poor sleeper (up 2–3 times/night).

Twenty-four months: Borderline ADOS positive for ASD (total score of 7; often on ''own agenda'').

Thirty-six months: Independent diagnosis of ASD (Aspergers; ADOS algorithm score = 9; ADI subscale scores for Social = 11, Communication = 8 and Repetitive Behavior = 3); IQ = 96 (Mullen subscale standard scores ranged from 82 for Fine Motor to 106 for Visual Reception).

Case 3: Female, Diagnosis of Autism at 36 Months

Six months: Interest/pleasure in and responsiveness to others (e.g., consistent and sustained eye contact, and nice social smiling, although equivocal social anticipation to ''peek-a-boo'' and some upset afterwards; briefly oriented to other's talking, and some babbling); reaches for, picks up and examines toys; smooth visual tracking but some difficulty disengaging visual attention; not sitting on own; fussed if held by anyone other than mom, and reportedly a bit fussy generally.

Twelve months: Fussy, prolonged distress, with frequent crying, and very difficult to settle (reassessed 1 month later with parallel findings); little interest/pleasure in or responsiveness to others (e.g., infrequent, fleeting eye contact, and seemed to look through rather than at others; no social smiling vs. to toy; no orienting to name vs. to ''sh-sh'' or clap; little babbling but song-like sound and high-pitched squeal of protest); difficulty visually tracking across midline and disengaging visual attention, and poor motor control; tended not to reach for or manipulate toys, although distressed when some were removed; atypical sensory behavior (stared at hands); intolerant of virtually all activities/toys, and strong startle response to some; clings to mom, and touches mom's hair and face when distressed; reportedly engaged by a small set of highly practiced routines, fascinated by bright moving objects, and watches TV for prolonged periods, with upset when turned off; attentive to details (e.g., tiny particles on floor), and distressed by fluorescent lights, sound of running water, noise in stores and by being restrained (e.g., in high chair or stroller); occasionally rolls her eyes back; sleeps well and eats a range of foods, but often fussy and extremely difficult to soothe (sometimes settled with mom's quiet slow singing, tickles or a bottle).

Eighteen months: As above, was very fussy and thus reassessed; at second assessment, some interest/pleasure in and responsiveness to others (e.g., some fleeting eye contact, oriented more readily to name called, smiled to mom playing ''peek-a-boo,'' imitated mom banging a toy on table, and looked back at mom when distressed), although no social-communicative initiations (e.g., no gestures, giving, showing, or social referencing); somewhat less intolerant of/over-reactive

to activities/toys, but remained difficult to engage; actions restricted largely to picking up and dropping objects or rocking on a chair, and distracted by some sounds but unresponsive to others; reportedly distressed by unfamiliar people or situations; has some words (''bye-bye,'' ''mommy,'' and ''daddy''), the latter two of which are used when angry.

Twenty-four months: ADOS positive for autism; given a clinical diagnosis of autism and referred for services.

Thirty-six months: Independent diagnosis of autism (ADOS algorithm score = 15; ADI subscale scores for Social = 22, Communication = 14, and Repetitive Behavior = 5); global delay (IQ < 50); and only a few single functional words.

Case 4: Male, Diagnosis of Autism at 36 Months

Six months: Initially reticent, but interest/pleasure in and responsiveness to others (e.g., consistent and sustained eye contact, nice social smiling, oriented to name called, although equivocal anticipation to ''peek-a-boo''); babbling but jerky visual tracking of objects, limited control of arm movements, and over-reactive to presentation of most toys (tended to tremble and tense body in excitement), followed by intense looking.

Twelve months: Little interest/pleasure in and responsiveness to Ex, although some to mom (e.g., difficult to engage in face-to-face interaction, inconsistent social smiling, equivocal imitation, and did not orient to name or to people talking vs. a bell, although social anticipation to ''peek-a-boo'' and some social babbling); also difficulty engaging his attention in activities/toys, even toys with sounds; tended to look around room, especially at anything moving; wanted to move about on own, and persistent about having certain objects (which would have to be hidden to engage his attention elsewhere); repetitive interest in door stopper; generally under-reactive to toys, people, and people talking.

Eighteen months: Looked better at 18 than at 12 months (AOSI total score of 5 vs. 13 and ADOS negative for autism/ASD at 18 months); interest/pleasure in and responsiveness to others (e.g., good eye contact, social anticipation to ''peek-a-boo,'' imitation of action on object, oriented to name called, and some social babbling, although little social smiling vs. to toys and equivocal differential response to change in Ex's facial expression); drew attention to a poster by pointing and vocalizing, but then repeatedly did the same action to the same poster despite others having already looked; upset/angry when toys removed, startle response (body tensing) to squeaky toy and atypical motor behavior (odd head tilt and hand flapping).

Twenty-four months: ADOS positive for autism; given a clinical diagnosis of autism and referred for services.

Thirty-six months: Independent diagnosis of autism (ADOS algorithm score = 20; ADI subscale scores for Social = 23, Communication = 14, and Repetitive Behavior = 8); global delay (IQ < 50) and only a few single functional words.

Case 5: Male, Diagnosis of Autism at 36 Months

Six months: Interest/pleasure in and responsiveness to others (e.g., consistent and sustained eye contact, nice social smiling, social anticipation and joyful giggling to ''peek-a-boo,'' oriented to name called, and babbling, although not social); smooth visual tracking but somewhat slow and uncoordinated in reaching for toys; reportedly had just started to arch his back when crying, and was becoming more difficult to settle.

Eight and a half months: Seen at mom's request regarding concerns about rocking (e.g., when sitting in high chair or walker, while being held, and when found crying in crib); upset when not held, arching back when upset, and not sleeping through night; otherwise, as above, although little if any enjoyment during ''peek-a-boo,'' and very quiet, with little babbling.

Ten months: As above, and reportedly resists getting dressed and being fed; likes ripping paper and holding (vs. necessarily operating) remote control, even at bedtime.

Twelve months: Interest/pleasure in and responsiveness to others (e.g., good eye contact, nice social smiling, social anticipation to ''peek-a-boo,'' differential response to change in Ex's facial expression, some social babbling, and uses ''mama' and ''dada'' meaningfully, although no imitation); discontinuous visual tracking, and some resistance to giving up particular toys; reportedly lactose intolerant and persistent rocking in crib.

Eighteen months: Some interest/pleasure in and responsiveness to others (e.g., occasionally established eye contact to share enjoyment or for social referencing, and some social smiling, although poor integration of eye contact with other efforts to communicate, inconsistent orienting to name called and limited if any social babbling), and virtually no social-communicative initiations (e.g., no giving or showing to others, or initiation of joint attention, and no distal pointing or other gestures); when upset, turns in to cuddle, but resists contact and difficult to soothe; some functional but no imaginative play, and upset when toys are

removed; atypical sensory behaviors (e.g., running book across his face, and handling of cord on phone) and motor mannerisms (odd finger posturing and some hand flapping); reportedly repetitive interest in vacuum cleaner, wanting to hug it for the vibration; also in plunger, mouthing, and holding or carrying it; afraid of dark, raised voices or yelling, and disrupted sleep; only one word (''mama''), and high-pitched scream when upset.

Twenty-four months: ADOS positive for autism; as above, with inattention, lots of aimless running, and several repetitive behaviors (e.g., counting, lining things up, opening and shutting of doors, and head banging).

Thirty months: Given a clinical diagnosis of autism and referred for services.

Thirty-six months: Independent diagnosis of autism (ADOS algorithm score = 22; ADI subscale scores for Social = 19, Communication = 9, and Repetitive Behavior = 8); global delay (IQ < 50) and only five intelligible single words.

Case 6: Female, Diagnosis of Autism at 36 Months

Six months: Interest/pleasure in and responsive to others (e.g., consistent and sustained eye contact, nice social smiling, differential response to change in Ex's facial expression, oriented to name called and social anticipation to ''peek-a-boo,'' although virtually no babbling); discontinuous visual tracking, and a bit startled during ''peek-a-boo,'' although generally a happy baby; reportedly intense visual examination of objects.

Twelve months: As above, with babbling, and possibly some social babbling, and pointing with index finger (e.g., to pictures in a book), including clear distal point integrated with looking and vocalizations; resistant to giving up toys, but could be redirected by removing them; reportedly had three words (''mama,'' ''dada,'' and ''baby'') and otherwise only a few sounds used indiscriminately; a lot of mouthing, and sometimes reacted negatively to being held (struggles, cries, or screams).

Eighteen months: As above, but poorly modulated eye contact, and few, if any, social-communicative initiations (e.g., no socially directed vocalizations, limited social referencing, and virtually no requesting, giving or sharing of interest in an object/event with others); little manipulation or exploration of toys; discontinuous visual tracking and atypical gait and locomotion (e.g., tentative about taking steps, wavering walking, and falls frequently), although corrective surgery for cross-eyed vision; atypical sensory behaviors (mouths and sniffs objects) and motor mannerisms (hand posturing and tossing of head); does not play unless structured by others, very active, running around with toy in hand, and throws things when frustrated; difficulty with new situations (e.g., screamed with new bubbles in bath), dislikes texture of grass and any dirt on her, and seeks deep pressure (e.g., presses head into her hands); hits self on head and bangs her head on chairs; tantrums frequently and very difficult to soothe; light sleeper (awakened easily by sounds).

Twenty-four months: ADOS negative for ASD.

Thirty months: Given a clinical diagnosis of autism and referred for services.

Thirty-six months: Independent diagnosis of autism (ADOS algorithm score = 13; ADI subscale scores for Social = 11, Communication = 12, and Repetitive Behavior = 5); IQ = 85 and delayed and deviant language development (Mullen subscale standard scores ranged from 76 for Receptive Language to 90 for Visual Reception, 92 for Expressive Language, and 97 for Fine Motor).

Case 7: Male, Diagnosis of Autism at 36 Months

Six months: Interest/pleasure in and responsiveness to others (e.g., sustained eye contact, especially initially; social smiles but his eyes did not appear to be smiling; differential response to change in Ex's facial expression, although no social anticipation to ''peek-a-boo,'' or to bunny or mom kissing him; oriented to voices but not to name called, and some babbling); discontinuous visual tracking, and visual fixation on mom's hands.

Twelve months: Some interest/pleasure in and responsiveness to others (e.g., looking at others in room, and established eye contact, particularly with observer at a distance; social anticipation to ''peek-a-boo,'' although no social smiling (only smiled to tickles), equivocal imitation, and few vocalizations); also discontinuous visual tracking, little manipulation or exploration of toys, and repetitive banging of toy (possibly an imitative response to Ex); atypical motor behavior (shaking head and rolling eyes), and unusual interest in/visual fixation on Ex's hands.

Eighteen months: As above, with no imitation, inconsistent orienting to name called, squeal-like noises, and no social-communicative initiations (e.g., no social referencing, sharing of interests, or socially directed vocalizations); no functional play with or exploration of toys, but rather pushed them away or repetitively picked up and dropped toys; fixated on and resistant to giving up bell (pried out of his hand but not distressed); atypical sensory behaviors (flicked rod in front of his eyes) and motor mannerisms (toe-walking and odd posture in which left hand was splayed open).

Twenty-four months: ADOS positive for autism; given a clinical diagnosis of autism and referred for services.

Thirty-six months: Independent diagnosis of autism (ADOS algorithm score = 22; ADI subscale scores for Social = 22, Communication = 8, and Repetitive Behavior = 6); global delay (IQ < 50) and no functional speech (only hums, whines, or squeals, and 1 sign for ''spoon'').

Case 8: Male, Diagnosis of ASD at 36 Months

Six months: Interest/pleasure in and responsive to others (e.g., consistent and sustained eye contact, social smiling, although particularly with physical play, and social anticipation to ''peek-a-boo,'' but no babbling); smooth visual tracking, interested in and manipulated toys, and good motor control (e.g., reached out for and held several toys); reportedly a fussy baby who ''doesn't have much down time'' and is not readily soothed; tends to look at earrings or hair rather than eyes, and becomes overly stimulated with too many people (i.e., while enjoyable initially, becomes distressed and starts crying); some vocalizations when very happy.

Twelve months: As above, engaged socially and with toys, oriented to name called, and imitated an action on an object, although minimal babbling (only vowel sounds) and no social babbling; reportedly no sleeping or feeding problems.

Eighteen months: As above, with lots of vocalizations and some social babbling, although few intelligible words, fleeting eye contact, difficult to get and sustain his attention, and equivocal imitation; discontinuous visual tracking; difficulty relinquishing certain toys (e.g., ''No(Mine'') and moving on to other activities; reportedly gets upset if he cannot have what he wants, and occasional hand flapping.

Twenty-four months: ADOS negative for ASD. Socially engaged (e.g., good eye contact) and showed interest and pleasure in most of the activities, but did not readily orient to name, and infrequent pointing which was not coordinated with eye gaze; became engrossed in particular activities, and very difficult to get his attention and move it elsewhere; repetitive interest in dinosaurs, and became very angry when doll was removed; atypical motor mannerisms (hand flapping); reportedly has about 50 words but no phrases; grabs parent's hand to request, and some pointing to request but not to show/share interest; easily frustrated, becomes very upset and extremely difficult to redirect or settle him; tends to resist requests, and distinct and limited food preferences (starches, cheese, and fruit).

Thirty months: As above, although reportedly more pointing to request, and starting to label things and to show others things of interest, with some eye contact; waves ''bye,'' shakes head for ''no'' but no nodding for ''yes''; anxious and reserved, particularly with unfamiliar children/adults (e.g., typically non-responsive to their approaches), and very slow to warm up; some hand flapping when excited; diagnosed with language delay (50–75 single words and only a few rote vs. generative phrases).

Thirty-six months: Independent *clinical* (vs. ''gold-standard'') diagnosis of ASD (ADOS algorithm score = 10; ADI subscale scores for Social = 9, Communication = 13, and Repetitive Behavior = 2; 1 point below ADI-R criterion on each of Social and Repetitive Behavior domains); global delay (IQ = 51).

Case 9: Female, Diagnosis of Autism at 36 Months

Six months: Interest/pleasure in and responsive to others (e.g., orients to others, consistent and sustained eye contact, and social anticipation to ''peek-a-boo,'' although inconsistent social smiling vs. to claps or bell ringing, and virtually no vocalizations); interested in different activities and her environment, although occasionally became fixated on a person or toy and difficult to get her attention; smooth visual tracking and good motor control (e.g., reached for objects and transferred objects from one hand to the other).

Twelve months: Some but limited interest/pleasure in and responsiveness to others (eye gaze directed at parent, although less so to Ex, and not sustained; reciprocal social smiling, although smile looks exaggerated; clear change from smiling to neutral expression in response to change in E's facial expression; equivocal social anticipation to ''peek-a-boo'' vs. tickling; few vocalizations and no social babbling; imitation of actions but not vocalizations); visual fixation on particular objects and difficult to get her attention or direct it elsewhere; acts on toys without looking at them; atypical sensory behaviors (sniffing of many objects) and motor mannerisms (hopping and rocking on knees).

Eighteen months: As above, although even less interest/pleasure in and responsiveness to others (e.g., fleeting eye contact and appears to look through versus at people; lack of socially directed affect, did not orient to name called, no vocalizations and at times completely shut out others), and no social-communicative initiations (e.g., no requesting, showing or giving, or asking for help; very active and little sustained attention to anything, and atypical motor behavior (hand flapping when excited); reportedly watches TV and

videos for prolonged periods, has only three single words, and has marked difficulty falling asleep (seeks to feel or suck on mom's arms or legs, or pull her ears), and strong food preferences (e.g., spits out meat and eats fish only if pureed).

Twenty-four months: ADOS positive for autism; referred for language assessment.

Thirty months: Given a clinical diagnosis of autism and referred for services.

Thirty-six months: Independent *clinical* (vs. ''gold-standard'') diagnosis of autism (ADOS algorithm score = 7, 1 point off criterion for ASD; ADI subscale scores for Social = 7, Communication = 12, and Repetitive Behavior = 4; 1 point below Social domain criterion); IQ = 96 (Mullen subscale standard scores ranged from 82 for Fine Motor to 94 for Receptive Language, and 106 for Visual Reception and Expressive Language) and delayed but not clearly deviant language development.

Cognitive and Communicative Assessments

Examination of Table 3 reveals that the present cases can be distinguished from each other by their level of functioning, and by the presence or absence of a developmental change in their measured cognitive abilities. At 12 months, all but two of the infants scored within the average range (68–107; mean = 88) on either the Bayley or Mullen scales (one was untestable due to extreme irritability). However, five of the nine cases (1, 4, 5, 7, and 8; all males) showed a dramatic decrease in IQ with age (range = 19–41 points; mean = 30 points). In all but one child (Case 8), this occurred between the ages of 12 and 24 months, and their relatively low IQs at 24 months remained stable at 36 months. Children with this early change in cognitive development had few communicative gestures at 12 or 18 months and minimal if any functional speech prior to or at 36 months. Case 8 showed a small decrease in IQ between 12 and 24 months (99 and 86, respectively), which was followed by a more major decrement by 36 months (IQ = 51), and associated with less impaired communicative development. At 24 and/or 36 months, all five of these children scored within the severely cognitively impaired range (IQ < 52), as did an additional child (Case 3; a female) who was non-testable at 12 months and showed the same degree of communicative impairment as those with the early change in cognitive development (for a total of six cases).

The remaining three cases (2, 6, and 8; all females) scored within the average or close to average IQ range across all ages. One case (6) showed a decrease in IQ (107 at 12 months vs. 79 and 85 at 24 and 36 months, respectively), although this is largely accounted for by impaired receptive language development (see subscale scores in case description). Thus, the nine children fall broadly into two subgroups: the first consisting of six cases (one female) with severe cognitive impairment, at least four of whom showed a marked decrease in IQ between 12 and 24 and one at 36 months, and the second subgroup consisting of three cases (all females) with average IQs, two with delayed speech and one of the two with impaired receptive language development as well.

Behavior–temperament Profiles

Analysis of the children's early behavior and temperament profiles provides additional evidence for two broadly defined subgroups. The first subgroup (Cases 1, 3, 4, 5, 7, and 8) is distinguished by a marked change in behavior very early in development, which continued and/or was even more evident by 18 months. Notably, with one exception (Case 8), between 6 and 12 months the infants became more difficult to engage socially, showing, for example, less and typically only fleeting eye contact, no or very little social smiling, and little interest or pleasure in interacting with others; interest in and exploration of toys was also minimal, and visual fixation (e.g., on strings, own or others' hands, or on small particles or patterns on a carpet) was striking in all five infants, as was repetitive or otherwise atypical motor behavior (ranging from finger flicking to rolling of the eyes, and repetitive banging of an object). The infants' AOSI scores at 12 months conformed to the pattern predictive of social-communicative impairments at 24 months (Zwaigenbaum et al., 2005): four had a total AOSI score of at least 9 (range: 9–15), and the one exception (Case 5) had a total score of 5. At 18 months, all but one child (Case 4, who interestingly seemed better at 18 than at 12 mos) met ADOS criteria for autism. Concomitant with the behavioral change observed between the ages of 6 and 12 months was an increasing trend, in varying degrees, toward greater irritability, intolerance of intrusions, negative affect/proneness to distress, and marked difficulties with self-regulation, and with being comforted or settled by others.

Case 8 showed a similar but more protracted and in several ways a less severe early manifestation of the disorder. Overall, this child was less socially impaired, showing interest and pleasure in interacting with others (e.g., social smiling and delight in playing ''peek-a-boo'') throughout his first 3 years of life. Symptoms characteristic of autism, most notably

repetitive interest in particular objects (dinosaurs), and difficulties disengaging from and relinquishing objects of interest, became more evident at 18 months, and were associated with the emergence of significant communicative difficulties. His early history was marked by relatively little babbling and few gestures (although eye gaze was used to reference others), and at 18 months, while vocalizing a good deal, he had virtually no intelligible speech. His total AOSI score of 1 at 12 months was well below the cut-off (of 9) predictive of the social-communicative impairments characteristic of autism (Zwaigenbaum et al., 2005), as were his ADOS scores at 18 and 24 compared to 36 months (1, 5, and 10, respectively). Increased irritability, intolerance of requests and intrusions, proneness to distress, and difficulties with self-regulation and with being comforted or settled by others were evident at 18 and particularly by 24 months of age. Interestingly, this child also differed from the other five who were severely cognitively impaired by virtue of not showing a decrease in measured abilities until 36 (vs. 24) months of age, the stability of which remains to be established. Unlike the others, who had a more classic form of autism, Case 8 was subsequently diagnosed with ASD (atypical autism).

The second subgroup (Cases 2, 6, and 9) showed a somewhat different, although variable, pattern of early behavior development. Interestingly, all were females of average measured cognitive abilities. Two were later diagnosed with autism (Cases 6 and 9), both with delays in language development, and one (Case 2) with ASD (Aspergers). Case 9 most closely approximates the early behavior profile described above, although autistic features were particularly evident at 18 (vs. 12) months, including limited social engagement and self-initiated social interactions (e.g., fleeting eye contact, little if any social smiling, at times completely ''shutting out'' others, and virtually no sharing of interests with others), as well as atypical sensory behaviors (e.g., visual fixation and sniffing of objects) and motor mannerisms (hand flapping when excited). Her early behavior was also marked by high and unfocussed motor activity and poor sustained attention, and a relative absence of the irritability, intolerance, and negative affect/distress so characteristic of the infants in the first subgroup. Case 6 was initially a placid child, whose autistic features also became more evident at 18 months, at which time tantrums became frequent (also with delayed as well as deviant language). She showed more interest and pleasure in interacting with others, but did not initiate social interactions (e.g., little social referencing, and virtually no sharing of interests), and, while resistant to giving up certain toys, she was at times relatively easily distracted. This child also showed minimal interest in and exploration of toys or her environment generally. Case 2 was distinguished from the other two females in this subgroup by showing more typical receptive language and speech development. However, like the other two females, symptoms of autism, while evident at 12 months, became more apparent at 18 months. By 18 months, this child had a serious demeanor, showing little positive affect directed at others or otherwise, and, while relatively responsive to others, self-initiated purely social–communication (e.g., showing and sharing interests with others vs. instrumental requests) was rare. She seemed generally content on her own, and was resistant to and even irritated by others' intrusions, and unduly sensitive to various forms of environmental stimulation (e.g., texture of grass). AOSI total scores at 12 months exceeded the score (9) predictive of autism (Zwaigenbaum et al., 2005) in only one of these children (Case 9; total scores of 3 and 2 for Cases 2 and 6, respectively). However, at 18 months all three children exceeded ADOS criteria for autism (Case 9) or ASD (Cases 2 and 6).

Discussion

In the present paper we document the development of autism/ASD in the first case series of high-risk infants followed prospectively from early in life. Overall, evidence is provided for two broadly defined subgroups, each with varying but distinguishable early developmental profiles. The first subgroup is distinguished by the presence of a major change in cognitive development between the ages of 12 and 24 months (or, in one case, by 36 months). While indistinguishable at 12 months (eight of nine cases had average or close to average IQs), by 24 and/or 36 months, six children (one of whom was non-testable at 12 months) scored within the severely cognitively impaired range; the remaining three cases, who formed the second subgroup, continued to obtain average or near average IQs. Signs of autism emerged and/or were more striking earlier (by 12 vs. 18 months) in the subgroup with a decrease in measured IQ (hereafter, ''early onset'' cases). However, all of the children, in varying degrees, showed a combination of impaired social-communicative development (lack of interest/pleasure in, and/or self-initiated contact with, others) and a behavior profile marked by visual fixation, and other atypical sensory and motor mannerisms and/or repetitive behaviors. In all of the children, the emergence of autism was associated, again in varying degrees, with

what can be described as a distinct temperament profile characterized by marked irritability, intolerance of intrusions, proneness to distress/negative affect, and difficulties with self- or other-regulation of state.

The question of whether the particular temperamental profile is associated with, or preceded, the emergence of autistic symptoms is not entirely clear. Some children (notably, Case 1 and possibly Cases 4 and 6) were more passive and content initially, and, with the emergence of autistic symptoms, they changed from being essentially ''easy'' to being readily irritated and distressed, and difficult to console. However, in several of the children (e.g., Cases 2, 3, and 7), there was at least some suggestion of these more difficult temperaments by 6 months of age, which, with the emergence of autistic symptoms, became increasingly striking. In so far as the determinants of temperament, like autism, are largely biological (Kagan, Snidman, Zentner, & Peterson, 1999; Szatmari, 1999), it seems likely that early irritability and proneness to distress both mark and form an inherent part of the behavioral emergence of autism. A temperamental feature observed by us in all nine infants was prolonged visual fixation, the converse of visual disengagement, which has been shown to be impaired in autism (Bryson et al., 2004; Landry & Bryson, 2004; Zwaigenbaum et al., 2005). Such early indices of behavioral inflexibility may be consistent with evidence of executive dysfunction in autism (Russell, 1997). Together with the increase in irritability, it would appear that the children become increasingly ''sensitized'' to various forms of stimulation and that this plays a major, although not necessarily causal, role in their decreased responsiveness to and pleasure in interacting with others. A forthcoming paper will explore these temperamental features and associated behaviors in the larger cohort of infant siblings who do not develop autism.

The striking decrease in IQ evidenced in a subgroup of the of the children between the ages of 12 and 24 months, and in one child by 36 months, is consistent with recent findings reported by Landa and Garrett-Meyer (2006), and raises a number of important questions. Among these is whether there is an actual loss of skills or an arrest in cognitive development. Unfortunately, we are unable to address the issue of skill loss, as most of the children were assessed on different cognitive measures at the two time points (the Bayley at 12 months and the Mullen at 24 months). It also remains unclear whether the change in cognitive development occurred abruptly or more gradually over time (as the IQ scores from Case 8 might suggest). Note further that virtually all of the children showed at least some, if not considerable, loss of social-emotional connectedness. In one child (Case 1) this was particularly marked at 17 months, although evident by at least 12 months. In another (Case 4) there was loss of expressive language, confirmed by us as occurring at 19 months of age (cf. Luyster et al., 2005). Case 4 had approximately ten words between the ages of 12 and 18 months (e.g., dog, car, open, more, and mine), at least some of which were reportedly used functionally but which subsequently were lost; speech gradually began to return at 24 months, but was very limited at 36 months (he used about eight single words, and understood about four single words). In both cases, the ''regression'' was preceded by atypical development characteristic of autism (notably, impoverished social engagement, visual fixation, and/or repetitive interests in particular objects, with distress upon removal), and in Case 1 in particular, by signs of cognitive and motor delay as well.

We are currently following a second cohort of high-risk infants, with more frequent direct assessments between 6 and 24 months. This more comprehensive follow-up will hopefully allow us to more accurately document the nature and timing both of emergent autistic symptoms and of skill loss or arrest in development. In the interim, our working hypothesis, based on the prospective data described here, is that regression, like autism, is a continuous or spectral phenomenon, which in varying degrees is evident across a range of social, cognitive, and/or language functions in those subsequently diagnosed with ASD. Among the outstanding issues is the identification of neuropsychological mechanisms that might explain what appear to be two critical, although presumably related, developmental phenomena observed in this case series. The first of these, between the ages of 6 and 12 months, marks the overt (behavioral) emergence of autism, which was particularly striking in, but not restricted to, our ''early onset'' cases at 12 months. This is precisely the time period during which we have documented a decrement in the ability to disengage visual attention in infants who subsequently show the social-communicative impairments diagnostic of autism (Zwaigenabum et al., 2005). The second critical juncture, between the ages of 12 and 24 months, is the period during which developmental regression has been identified in previous retrospective reports (e.g., Lord et al., 2004; Goldberg et al., 2003) and demonstrated here prospectively in the decreasing IQ scores.

We acknowledge that more subtle abnormalities may be evident at 6 months or even earlier in at least the ''early onset'' subgroup with autism. However, even if abnormalities are evident, the limited and relatively undifferentiated behavioral repertoires of

such young infants may not allow us to distinguish autism from other disorders of development. In any event, increasingly prominent signs of autism between the ages of 6 and 24 months, possibly associated with atypical brain growth (Courchesne, Carper, & Akshoomoff, 2003; Hazlett et al., 2005), would appear to reflect the relative failure to develop functional brain pathways in which the emergence of purposeful or intentional behavior is emotionally and communicatively linked with important others. Mundy's (2003) very thoughtful claims regarding the putative role of the dorsal medial–frontal and anterior cingulate network in the development of autism provides a rich starting point, as does the critically important discovery of the mirror neuron system (Gallese, 2006; Rizzolatti & Craighero, 2004). In the present study, and consistent with previous retrospective parent reports, video and case study data (e.g., Adrien et al., 1992; Dawson et al., 2000; Ohta et al., 1987), the emergence of autism involved both social-communicative impairment and atypical sensory and motor features, as Mundy's analysis would predict. In the meantime, we await more direct evidence to advance understanding of the specific brain networks operative very early in the development of autism.

Finally, while the present findings are preliminary, they form the basis for several hypotheses that can be tested further as data from additional and larger samples of high-risk infants become available. Included here is our initial finding that, among the high-risk infants who developed autism/ASD, males and females are equally represented. While this stands in contrast to the well documented finding that males predominate in autism/ASD (Bryson, 1996, 1997; Fombonne, 1999; Lord, Schopler, & Revicki, 1982; Wing, 1981), firm conclusions are precluded by our small sample size. Our findings also contribute to a growing body of research designed to provide information relevant to the development of autism screens for even younger children, and to the search for biological markers. Ongoing assessment of infants at risk for ASD will allow us to address the important question of recurrence risk, both for autism and for related developmental delays and/or disorders. Efforts aimed in these and related directions promise to further advance both our understanding of autism and its early detection and treatment.

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