Published in final edited form as:

J Autism Dev Disord. 2011 December ; 41(12): 1727–1732. doi:10.1007/s10803-011-1203-3.

Brief Report: Symptom Onset Patterns and Functional Outcomes in Young Children with Autism Spectrum Disorders

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Abstract

This study examined the relationship between onset status and current functioning using a recently proposed onset classification system in 272 young children with autism spectrum disorder (ASD). Participants were classified into one of the following groups, based on parent report using the Autism Diagnostic Interview – Revised: Early Onset (symptoms by 12 months, no loss), Delay +Regression (symptoms by 12 months plus loss), Plateau (no early symptoms or loss), and Regression (no early symptoms, followed by loss). Findings indicate that current functioning does not differ according to onset pattern, calling into question the use of onset categorizations for prognostic purposes in children with ASD.

Keywords

autism; regression; onset; symptom; outcomes

Studies of symptom onset in children with autism spectrum disorders (ASD) generally suggest one of two patterns: early onset, in which symptoms emerge in the first year or so of life without a clear indication of decline in functioning, and regressive onset, in which a loss of previously acquired skills is reported after a period of mostly normal development. Multiple previous studies have examined the correlates of these two onset patterns to determine whether there are differences in clinical phenotype, etiology, or outcome. To date, the results of such studies have been inconclusive (Stefanatos, 2008).

One area of particular contention has been the relationship between onset and later functional outcome. While it is generally thought that children with ASD who experienced a regression are more impaired (e.g., Bernabei, Cerquiglini, Cortesi, & D'Ardia, 2007; Kalb, Law, Landa & Law, 2010; Parr et al., 2010), a review of this literature is less conclusive. Some studies have reported poorer developmental outcomes and/or worse autism symptomatology in children with a history of regression (Bernabei, et al., 2007; Kalb et al., 2010; Richler, et al., 2006; Rogers & DiLalla, 1990), while others have found no group differences in cognitive level or symptom severity (Hansen et al., 2008; Jones & Campbell, 2010; Short & Schopler, 1988; Werner, Dawson, Munson, & Osterling, 2005) or even higher skills in children with regression (Davidovitch, et al., 2000). In most studies, the findings are mixed, with one or two scores indicating poorer functioning (usually in the regression group) but overall no group differences on most variables (Brown & Prelock, 1995; Kobayashi & Murata, 1998; Meilleur & Fombonne, 2009; Richler et al., 2006; Wiggins, Rice & Baio, 2009).

Recent studies have suggested that a dichotomous view of onset does not adequately capture the complexity of ASD symptom emergence. A stagnation or plateau pattern characterized by intact early skills, but failure to progress to higher developmental achievements such as gesture use, language, and joint attention, has been described in several recent studies (Hansen, et al., 2008; Jones & Campbell, 2010; Kalb et al., 2010; Siperstein & Volkmar, 2004). Abnormalities prior to regression have been found in studies using retrospective videotapes (Maestro, et al., 2006; Werner & Dawson, 2005) and parent report (Goldberg, et al., 2003; Ozonoff, Williams, & Landa, 2005; Richler, et al., 2006), suggesting an additional group that experiences aspects of both early onset and regression. To account for these additional patterns, a more differentiated classification system for subtyping onset patterns has recently been proposed (Ozonoff et al., 2008). The current study is the first to empirically examine this method of onset classification. Using a large multi-site sample, we explored whether these newly proposed categories demonstrate meaningful ways to examine phenotype differences, focusing in particular on current functional outcomes. Following Ozonoff et al. (2008), this study used parent report of both early development and loss of skills from the Autism Diagnostic Interview-Revised (ADI-R; Le Couteur, Lord, & Rutter, 2003) to characterize and operationalize four onset patterns (see Figure 1): (a) an **Early Onset** group in which signs of ASD were reported in the first year but there is no indication of later skill loss, (b) a **Delay+Regression** group with parent-reported early symptoms as well as loss of language and/or social skills, (c) a **Plateau** group that has neither symptoms reported in the first year nor later loss, and (d) a **Regression** group in which there were no early signs of ASD but a loss of language and/or social skills.

The purposes of this study were two-fold: 1) to examine whether a meaningful proportion of children with ASD fall outside the traditionally conceptualized “early onset” and “regression” categories (that is, demonstrate features of a “delay + regression” and a “plateau” pattern), and 2) to evaluate whether a more differentiated system of classifying onset patterns reveals differences in current functioning that may have been obscured in previous studies that used a dichotomous definition of onset.

Method

Participants and Procedures

This study included 272 children from two sites collecting data as part of the Autism Phenome Project, a study aimed at defining subtypes of ASD. As shown in Table 1, there were 166 participants recruited at the National Institute of Mental Health (NIMH; age range 20–84 months), which specifically recruited children who met DSM-IV-TR criteria for Autistic Disorder, and 106 participants from the M.I.N.D. Institute (age range 25–59 months). Due to differing enrollment criteria, participants at the NIMH were significantly older than the M.I.N.D. Institute site [$t(270) = 9.91, p = .000$]. There were no other site differences.

All participants completed a diagnostic evaluation. Diagnosis was determined by best estimate clinical judgment of doctoral-level clinicians, using DSM-IV-TR criteria and cutoff scores for autism and PDD-NOS (Risi et al., 2006)¹ on the ADI-R and Autism Diagnostic Observation Schedule (ADOS; Lord, et al., 2000). Two hundred thirty five children were classified as autism and 37 as PDD-NOS.

Measures

Autism Diagnostic Interview-Revised (Le Couteur, et al., 2003)—The ADI-R is a semi-structured, standardized instrument that includes questions about the attainment of milestones, loss of skills, and the onset of symptoms, including symptom onset as perceived with hindsight. A Toddler version of the ADI-R (Lord, et al., 2004) was used in children under 4 years at the NIMH site ($n=87$).

Mullen Scales of Early Learning (Mullen, 1995)—The Mullen Scales of Early Learning is a standardized developmental test for children birth to 5 years, 8 months. Due to floor effects and children out of age range, Developmental Quotients (DQ) were calculated based on age equivalent/chronological age $\times 100$. Nonverbal DQ was calculated from the average of the Fine Motor and Visual Reception scales, and Verbal DQ from the average of the Receptive and Expressive Language scales.

Autism Diagnostic Observation Schedule (Lord, et al., 2000)—The ADOS is a semi-structured observational instrument used in diagnostic evaluations for ASD. ADOS algorithms that include social affect and restricted, repetitive behaviors domains (Gotham, Risi, Pickles, & Lord, 2007), as well as newly developed ADOS severity scores (Gotham, Pickles, & Lord, 2009; Lord, et al., 2000) were employed in the present study.

Vineland Adaptive Behavior Scales-2nd Edition (Sparrow, Cicchetti, & Balla, 2005)—This is a semi-structured caregiver interview designed to evaluate adaptive functioning in four domains: Communication, Daily Living Skills, Socialization, and Motor Skills. Standard scores are provided for each domain and for an overall Adaptive Behavior Composite.

Data Analysis

Differences in current functioning were examined using a series of one-way analyses of variance (ANOVA) for comparison of means across the four groups. The analysis plan included Tukey's HSD post-hoc comparisons between all four classification groups for significant findings from omnibus tests. Following comparison of the four groups, post-hoc

¹Fell within one point on ADI-R social and communication domains, or met ADI-R autism cutoff on one domain and fell within two points on the other.

contrasts were conducted to examine differences between the more traditional dichotomy of broader “regression” (i.e., Delay+Regression and Regression groups; $n=133$) and “no regression” (i.e., Early Onset and Plateau groups; $n=139$). A Bonferroni correction was used to adjust for the number of outcome measures (i.e., 12) examined in each analysis. Thus, with an overall significance threshold of $p<.05$, two-tailed, Bonferroni correction for multiple comparisons provided a threshold of $p<.004$. Given the site difference in age, we reviewed the correlations between age and outcome measures across sites. The patterns were similar across sites, so age was not included as a covariate in the analyses.

Results

Descriptive characteristics of the four onset groups are shown in Table 2. The four groups were not significantly different in age [$F(3, 268) = 1.49, p = .218$], diagnosis ($\chi^2 = 1.39, df = 3, p = .709$), or gender ($\chi^2 = 5.73, df = 3, p = .125$). As expected based on group definitions, age of first concern was significantly earlier in both the Early Onset and the Delay +Regression groups compared to the Plateau and Regression groups [$F(3, 260) = 27.06, p < .001$]. Age of earliest loss was not significantly different between the two groups that experienced regression [$t(130) = -1.45, p = .151$]. In both the Delay+Regression and the Regression groups, the vast majority of the sample experienced losses in the social domain, either with or without word loss; very few children lost words only.

Table 3 shows means and standard deviations for current functioning variables. Results of a series of one-way ANOVAs that corrected for multiple comparisons indicated that, contrary to our hypothesis, the four groups were not significantly different on any measure of current functioning (see Table 3 for F statistics and p values). Post-hoc contrasts conducted to compare two groups of broader “regression” (i.e., Delay+Regression and Regression) and “no regression” (i.e., Early Onset and Plateau) revealed no significant differences in current functioning after correcting for multiple comparisons.

Discussion

To date, most studies examining regression as a phenotype have employed a dichotomous framework (i.e., regression, no regression) without regard to the presence of early symptoms or the normality of development prior to loss of skills. Given the mixed findings across studies on how a history of regression affects later functioning, the current study sought to resolve prior inconsistent findings by using a more differentiated onset classification system. For example, it has been suggested that children with a “plateau” pattern of onset may show a different profile than children with other onset patterns (Jones & Campbell, 2010). If this is the case, then combining plateau and early onset cases into a single category, as a dichotomous system does (e.g., “no regression”), would obscure such meaningful differences. However, our findings indicate that the current functioning of young children with ASD does not differ across onset patterns. Specifically, no significant differences were found in current functioning from cognitive, adaptive behavior, or autism symptom measures among the four groups. We also examined whether there were group differences using the more traditional dichotomy of regression/no regression and again found none. Given the large sample sizes and the range of functional domains examined, the lack of group differences does not appear to be due to inadequate power. Rather, these results suggest that the manner in which symptoms emerge early in life has very limited value in predicting prognosis a few years post-onset.

Findings from this study provide information about symptom onset in ASD. Nearly two-thirds of the children (62%) were reported to have symptoms present in the first year of life, consistent with previous studies revealing symptom onset in the first year based on parent

report (Luyster, et al., 2005; Richler, et al., 2006). The present study provides further support that a portion of children with behavioral signs noted before 12 months also lose skills (Ozonoff et al., 2005; Richler, et al., 2006; Werner & Dawson, 2005), indicating that “early onset” does not preclude loss in onset pattern. Findings also provide further evidence of a developmental plateau onset pattern, in which even with hindsight, parents reported no developmental concerns prior to the child’s first birthday as well as no loss of skills. Continued prospective studies are needed to investigate the social communication development of this group of children (plateau) in the first two years of life, to examine the presence of early behaviors as well as the timing and behaviors that appear to fade away or not progress/transition into more developmentally advanced skills. Findings from the present study also add to literature showing that social losses may actually be more common than language loss. Thus, studies that measure loss of language only may significantly underestimate the frequency of regression (Hansen, et al., 2008; Meilleur & Fombonne, 2009).

While this is the first large-scale study to examine a recently proposed classification system that uses both early development and loss of skills to characterize onset (Ozonoff, et al., 2008), a limitation of this study (along with most studies of regression) is reliance purely on parent report to classify onset. We utilized a sample with a relatively young age to reduce recall bias; however, recent prospective studies have suggested that parent report may not always match observational evidence of a decline in skills (Ozonoff et al., 2010). Prospective studies will thus provide another type of empirical data to test whether “regression” (defined observationally) relates to later outcomes.

The present study did not find any onset group differences in current functional outcomes, indicating that onset pattern is not useful for prognosis of behavioral outcomes in preschool children with ASD. However, the lack of differential outcomes could indicate that onset may be represented by even more finely tuned categories or a continuum rather than a dichotomy or four groupings (Ozonoff, et al., 2010). Further study will be needed to understand how best to characterize onset patterns in autism. In addition, age at outcome in this sample was relatively young (mean = 43.7 months) and it is possible that differences emerge over time, as children age. The current study also did not examine other domains in which meaningful differences might be apparent. Future studies should examine whether use of a more differentiated onset classification system, such as the one employed here, may reveal differences in medical or etiological variables.

Acknowledgments

This research was supported by the Intramural Program of the National Institute of Mental Health (NIMH), National Institutes of Health (NIH), NIH Grants MH 07-080, 1R01MH089626, and by the M.I.N.D. Institute. The views expressed in this article do not necessarily represent the views of the NIMH, NIH, HHS, or the United States Government. The authors thank Drs. David Black, Christine Golden Williams, Lisa Joseph, and David Luckenbaugh for their helpful assistance and suggestions throughout this project. In addition, we extend our gratitude to the children and their families who volunteered their time and efforts during these research protocols.

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	Loss of Skills	
	NO	YES
<p>Early Symptoms</p> <p>(symptoms before 1st birthday)</p>	<p>Early Onset (Early delays, no loss)</p> <p>Hindsight of symptoms in first 12 months (Q4=0) and No loss of language (Q11=0) and No loss of social engagement/responsiveness (Q25=0)</p>	<p>Delay+Regression (Some delays before loss)</p> <p>Hindsight of symptoms in first 12 months (Q4=0) and Loss of language (Q11=1) and/or Loss of social engagement/responsiveness (Q25≥1)</p>
<p>No Early Symptoms</p> <p>(symptoms NOT present before 1st birthday)</p>	<p>Plateau (No early delays, no loss)</p> <p>Hindsight of NO symptoms in first 12 months (Q4≥1) and No loss of language (Q11=0) and No loss of social engagement/responsiveness (Q25=0)</p>	<p>Regression (No delays before clear loss)</p> <p>Hindsight of NO symptoms in first 12 months (Q4≥1) and Loss of language (Q11=1) and/or Loss of social engagement/responsiveness (Q25≥1)</p>

Figure 1.
Onset pattern groupings: Operationalized by ADI-R items

Table 1

Summary of Participant Characteristics

	NIMH	MIND	Combined Sample
N	166	106	272
Age at ADI (M, SD)	49.08 (16.33)	35.26 (6.00)	43.70 (14.90)
ASD Grouping			
Autism (n, %)	140 (84.3%)	95 (89.6%)	235 (86.4%)
PDD-NOS (n, %)	26 (15.7%)	11 (10.4%)	37 (13.6%)
Males (n, %)	139 (83.7%)	89 (84.0%)	228 (83.8%)

Table 2

Participant Descriptors According to Onset Categories

	Early Onset	Delay+Regression	Plateau	Regression
Sample size (n, %)	96 (35.3%)	72 (26.5%)	43 (15.8%)	61 (22.4%)
Age at ADI (M, SD)	42.60 (15.11)	41.72 (14.16)	46.00 (16.63)	46.13 (13.91)
Diagnostic Group				
Autism (n, %)	80 (83.3%)	64 (88.9%)	37 (86.0%)	54 (88.5%)
PDD-NOS (n, %)	16 (16.7%)	8 (11.1%)	6 (14.0%)	7 (11.5%)
Males (n, %)	81 (84.4%)	55 (76.4%)	40 (93.0%)	52 (85.2%)
Age First Concern (M,SD)	11.34 (7.58)	13.85 (6.37)	20.00 (6.47)	19.92 (6.56)
Age Earliest Loss (M, SD)		17.75 (6.21)		19.44 (7.16)
Loss Type (n, %)				
Word Loss Only		6 (8.3%)		1 (1.6%)
Social Loss Only		40 (55.6%)		25 (41.0%)
Word + Social Loss		26 (36.1%)		35 (57.4%)

Table 3

Current Functioning According to Onset Categories

	Early Onset	Delay+ Regression	Plateau	Regression	F value	p value
ADI-R Domains (M, SD)						
Social	17.47 (4.52)	18.72 (4.34)	17.60 (4.46)	17.66 (4.78)	1.20	.311
Communication	11.94 (3.09)	11.72 (3.17)	13.21 (4.26)	11.64 (3.50)	2.20	.089
RRB	5.01 (1.73)	5.24 (1.72)	4.70 (1.95)	4.59 (1.63)	1.85	.139
Vineland (M, SD)						
Communication	72.22 (14.89)	67.14 (15.41)	68.90 (11.56)	71.15 (14.86)	1.81	.146
Socialization	70.40 (9.42)	67.74 (9.42)	68.45 (7.92)	70.18 (10.57)	1.33	.266
Composite	70.49 (10.24)	67.77 (10.90)	69.95 (7.99)	71.13 (11.83)	1.33	.265
Mullen (M, SD)						
Nonverbal DQ	67.21 (22.46)	62.49 (18.72)	66.17 (16.47)	63.50 (18.07)	0.93	.429
Verbal DQ	55.01 (28.64)	45.54 (22.25)	49.82 (20.36)	46.82 (21.17)	2.41	.067
ADOS (M, SD)						
Social Affect	13.22 (4.15)	14.25 (3.54)	13.44 (2.89)	13.70 (3.53)	1.13	.338
RRB	4.81 (1.81)	4.54 (1.89)	4.98 (1.60)	5.10 (1.79)	1.17	.320
Total	18.03 (4.85)	18.79 (4.16)	18.42 (3.60)	18.80 (4.20)	0.58	.629
Severity Score	7.62 (1.81)	7.54 (1.67)	7.30 (1.49)	7.66 (1.52)	0.45	.717