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The Onset of Autism: Patterns of Symptom Emergence in the First Years of Life

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Abstract

Previous conceptualizations of autism have suggested that symptoms are evident either early in the first year of life or later in the second year, after a loss of previously acquired skills. New research suggests, however, that these two patterns do not capture all the different ways autism can emerge. For example, some children show a developmental plateau marked by failure to progress, while other children display mixed features, with both early delays and later losses evident. This paper reviews the literature on autism onset, discusses problems with the traditional ways in which onset has been conceptualized, and provides recommendations for future research. We suggest that onset is better thought of as a dimensional process rather than dichotomous categories.

Keywords

Onset; regression; infancy; early identification

Introduction

The onset of autism is traditionally described as occurring in one of two patterns. In one onset prototype, children show abnormalities in social and communicative development in the first year or so of life. The most common initial symptom recognized by parents is delayed speech development (De Giacomo & Fombonne, 1998), but a growing body of literature suggests that social and nonverbal communicative delays predate the language abnormalities that typically lead to diagnosis. Behaviors that reliably discriminate between young children with autism, developmental delays, and typical development are orienting to name, looking at the faces of others, joint attention, affect sharing, and imitation (Baranek, 1999; Osterling & Dawson, 1994; Stone et al., 1994, 1999; Werner, Dawson, Osterling, & Dinno, 2000; Wetherby et al., 2004). A few studies suggest that symptoms can be detected before the first birthday in some children (Baranek, 1999; Werner et al., 2000), but these early differences appear to be non-specific (e.g., sleeping, eating, temperament patterns) and do not differentiate children with developmental delays from those with autism (Werner et al., 2005). Group differences are more reliably present and consistently found across studies in the second year of life (Palomo et al., 2006). This so-called “early onset” pattern is thought to occur in the majority of individuals with autism.

In the second pattern of onset, regressive autism, children appear to be developing typically for the first year or two. In the second year of life, they lose skills that they had previously acquired, accompanied by the onset of autistic symptoms. The earliest literature on autism made no mention of this onset pattern. Kanner (1943), for example, did not report any loss

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of previously acquired skills in the 11 cases he described initially. The phenomenon was first reported in the 1970s by researchers in Japan (as cited in Kobayashi & Murata, 1998) and further described in the following decade (Hoshino et al., 1987; Kurita, 1985; Volkmar & Cohen, 1989). The developmental areas most affected by regression are communication and social abilities.

As discussed in more detail below, the way in which regression is defined can have a large impact on study results, making it difficult to summarize a literature that used different methods and instruments across investigations. Furthermore, most studies of onset have been conducted on small, clinic-based samples that may not be representative of the larger population of children with autism. Indeed, prevalence estimates of regression are highly dependent upon both onset definitions (discussed below) and sampling methods. In clinically ascertained samples, regression has been found in as low as 20% (Lord, 1995) and as high as 50% (DeMyer, 1979) of participants, with two moderately sized studies finding rates around 30% (Kurita, 1985; Tuchman & Rapin, 1997). Two recent epidemiological studies found regression in 15.6% (Fombonne & Chakrabarti, 2001) and 27% (Lingam et al., 2003) of large population-based samples. Regression is most often observed between the first and second birthday, with mean ages of regression reported across different samples between 16 and 20 months (Fombonne & Chakrabarti, 2001; Goldberg et al., 2003; Kurita, 1985; Ozonoff et al., 2005; Shinnar et al., 2001).

The mechanisms underlying autistic regression are not known, nor are the relationships of different patterns of onset to etiology, functioning level, or prognosis. Potential etiologic factors or biological correlates of regression that are currently being investigated include accelerated rates of head growth (Webb et al., 2007), genetic and genomic differences (Gregg et al., 2008; Molloy et al., 2005), seizures or other electrophysiological disruptions (e.g., Shinnar et al., 2001), immunizations (Taylor et al., 2002), thimerosal exposure (Verstraeten et al., 2003), gastrointestinal problems (Richler et al., 2006), and immune deficits (Ashwood et al., 2008; Braunschweig et al, 2008; Molloy et al., 2006), but so far none of these factors have been firmly associated with regression.

Despite the progress that has been made in the last half century in describing how autism emerges early in life, a number of difficulties with traditionally held views about onset have become evident with time. One problem is that definitions of regression and methods of describing onset differ across studies and newer research has shown that results can be quite influenced by such measurement differences (Hansen et al., 2008). A second issue is that recent research has not always upheld previous views or clinical intuitions about the central features of and differences between onset types. Therefore, we may need to revise current conceptualizations of how the symptoms of autism first develop. That is the focus of the present review.

Definition and Measurement Issues

Until recently, the only methods to investigate the early autism phenotype and onset patterns have been retrospective. Prospective studies that follow children from infancy through the window of autism susceptibility are relatively new and the bulk of the existing literature is based on retrospective studies. One widely-used retrospective method is the analysis of home movies of children later diagnosed with autism spectrum disorders. While this reduces potential reporting biases of parent interviews, home movie methodology suffers from several biases (Palomo et al., 2006). There is tremendous variability across families in the amount, content, and quality of footage of early development that is captured on video. Many families do not tape their children early in life, so home movie studies are not representative of all children with autism. Many families turn off video cameras when children are not behaving as expected or in a positive manner. Finally, home movie analysis

is a very time-intensive method of collecting information about early development that is not practical for routine research use. Thus, most studies of the early autism phenotype (and clinical practice) have employed parent report, a more efficient method of collecting early history. However, parent report can be biased by knowledge of the child's eventual diagnosis, poor recall, or lack of sensitivity to developmental differences. Retrospective reports are subject to problems of memory and interpretation (Finney, 1981; Robbins, 1963) and need to be used with caution when examining hypotheses that demand precision in estimating event dates and frequencies (Henry et al., 1994). When people are asked to recall particular episodes, they often report them as having occurred more recently than they did, an error called "forward telescoping" (Loftus, & Marburger, 1983). This phenomenon has been described specifically in investigations using parent report to study autism onset (Lord et al., 2004). Thus, it is critical to understand the degree of accuracy in parent reports of regression, particularly since other methods (e.g., video analysis) are labor intensive and require expert training.

One widely used instrument that collects detailed parent recollections of early development is the ADI-R, a "gold standard" research interview used in diagnosis (Lord et al., 1994; Rutter et al., 2003). This instrument has a section of 18 questions that collect detailed information about potential losses, including specific skills lost, duration of losses, and potential factors associated with the losses. The instrument first collects information about language losses (Question 11, "Were you ever concerned that [your child] might have lost language skills during the first years of life?"). If the parent responds affirmatively, the interviewer then probes for the number of words lost, how they were used prior to the loss, the duration of establishment of the skill, and the duration of loss of the skill. To meet ADI-R criteria for loss of language, at least five words must have been used spontaneously, meaningfully, and communicatively for at least three months before being lost for at least three months. If there are losses indicated by the parent that do not meet these criteria (e.g., words lost that fail to meet the quantity or duration criteria or other communicative losses, like loss of babbling or gesture use), they can be recorded on the form, but the child does not meet ADI-R criteria for language regression. There is no consensus in the field yet as to how to handle parent-reported losses that are sub-threshold (e.g., loss of 3 words or loss of 5+ words that had not consistently been in the child's vocabulary for the three months required to meet ADI-R criteria). In most studies, these children would not be included in a language regression group.

A later ADI-R item asks parents about losses in other domains (Question 20, "Has there ever been a period when [your child] seemed to get markedly worse or dropped further behind in his/her development?"). If the parent indicates yes, then possible losses in motor, self-help, play, and social abilities are probed, in that order. If the parent does not endorse other losses, no querying is done nor examples given. This may lead to under-endorsement of losses, particularly in the social domain. In our experience, parents do not as readily regard social behaviors as acquired skills or specific developmental achievements that can be lost. However, when examples are provided, such as asking whether the child got markedly worse in their eye contact or lost interest in interacting with others, parents occasionally recognize this pattern and change their report.

The vast majority of children losing language also lose behaviors indicative of social interest and engagement, such as direct gaze and response to name (Goldberg et al., 2003; Lord, et al., 2004; Ozonoff et al., 2005). The converse is not always true, however. Some children show marked changes only in social development and do not lose spoken language. Hansen et al. (2008) found that only 18% of a large (n=138) sample of children with regression lost language skills alone, while 46% exhibited social losses alone, and 36% had losses in both language and social behaviors. Goldberg et al. (2003) found similar rates (5% language-only

regression, 38% social-only regression, 57% language+social regression). When children experience losses in social development alone, this is typically because they have not acquired language at the time of the regression and therefore have no language to lose (Goldberg et al., 2003; Kurita, 1985; Ozonoff et al., 2005). It is very uncommon for children to retain acquired speech when experiencing a clear loss of social interest and engagement (Ozonoff et al., 2005).

There is debate about whether definitions of regression should require loss of language and how children who only lose social milestones should be classified. Early studies tended to characterize regression as speech loss (Brown & Prelock, 1995; Kurita, 1985; Rogers & DiLalla, 1990) without including loss of social milestones as part of the criteria. In some previous studies, children who experienced social losses without word losses were placed into a no-regression or early onset group (Kurita, 1985; Lainhart et al., 2002). However, recent studies suggest that there are very few differences between children who lose both words and social skills and those who experience losses in social milestones alone (Lord et al., 2004; Luyster et al., 2005). In a multi-site study of children with ASD, Luyster et al. (2005) compared 125 children with word loss to 38 children with non-word loss (regression in areas other than language). They found no differences between the two regression groups. Children with word loss and non-word loss regression lost the same skills (other than words), including pre-speech behaviors, games and routines, social interest, and phrase comprehension, with almost exactly the same frequency (Luyster et al., 2005). Therefore, more recent studies have expanded definitions of regression to include losses in domains other than spoken language (Davidovitch et al., 2000; Fombonne & Chakrabarti, 2001; Kobayashi & Murata, 1998).

Not surprisingly, the prevalence of regression is dependent on the definitions used. When a narrower definition that required language loss was used, only 15% of a large epidemiological sample of children with ASD met criteria for regression, whereas when losses in either language or social behaviors were used to classify onset patterns, 41% were found to have experienced losses (Hansen et al., 2008). Thus, requiring loss of language appears to significantly underestimate the frequency of developmental regression.

There is one published study that reports the test-retest reliability of parent report of regression. Richler et al. (2006) reported data from the multi-site Collaborative Programs of Excellence in Autism (CPEA) sample (n=351). The ADI-R was used initially to determine study eligibility and then later a detailed interview about regression was conducted by telephone. The time lag between administration of these two instruments was not specified in the study, but ranged from several months to several years. Conflicting information about word loss on the ADI-R and regression interview was apparent for 18.9% of the sample, with 12.3% reporting no loss on the ADI-R, but loss on the phone interview and 6.6% demonstrating the opposite pattern.

When reports of onset are inconsistent, it can be difficult to determine which is accurate. Two home movie studies (Goldberg et al., 2008; Werner & Dawson, 2005) have compared parent report with videotape footage and shown that parent report is generally valid, but poorer for reports of social than word loss. Specifically, the Goldberg et al. (2008) study, using a detailed regression interview, found 85% concordance between parent reports and independent video coders' ratings of loss or no loss of spoken language, but only 49% concordance for social losses. Parents were more consistent when reporting no loss than when reporting loss across both language and social domains (Goldberg et al., 2008). As discussed earlier, home video data has its own problems (e.g., heterogeneity of length, content, and quality of video footage; Palomo et al., 2006). Most significantly, parents often do not record difficult moments when their child is behaving in a way they might not wish to

remember. Indeed, a case study that included coded home video footage of a regression noted that taping frequency dropped dramatically during the period of regression, when the parents had far more concerning matters to attend to than video recording (Palomo et al., 2008). Thus, when parent reports are conflicting, home video cannot be counted on to resolve the discrepancy. Neither parent report nor home video analysis can be considered a gold standard method of documenting whether a child displayed early signs of autism or experienced a regression in skills and the respective limitations of each method need to be recognized by researchers.

As we end this section, we provide a few recommendations that may improve the quality of future data acquisition using parent report, the more feasible of the retrospective methods currently in use. First, interviewers need to be well-trained to ask questions fully (with appropriate probes) without being too leading. They should realize that not only may parents have difficulty recalling specific behaviors and their exact timing, but also may not define or conceptualize behaviors in the same way as interviewers. Examples and queries are permitted on the ADI-R, a semi-structured interview that encourages examiners to ask additional questions until they are certain that the parents have understood the behavior being measured and have given a valid response. Parents often do not ask for clarification of questions and it is the interviewer's job to anticipate when this is necessary. Parents may misinterpret failures to progress as regression and this is an additional difficulty that examiners need to be aware of during their queries. It is not uncommon for an initial positive response to questions about regression to change to a negative report of losses after further probing, when it becomes clear that although the child failed to gain anticipated new skills, he did not experience any actual losses of acquired skills. This kind of querying needs to be balanced by recognition that subtle losses of skills are indeed possible.

Evidence for Other Patterns of Loss

A second problem with current definitions of onset is that dichotomous categorical conceptualizations do not capture all the different ways that autism can emerge. The traditional view of regression has been that development is typical prior to the loss of skills. For example, Rogers and DiLalla (1990) reported that parents of children with later onset autism "were emphatic about the normalcy of their children's behavior in the first year of life. The onset of their children's symptoms began with a change in or a loss of the child's previous apparently normal social behavior (p. 866)." Data from recent studies have raised doubt regarding the universality of typical development prior to regression, however. Ozonoff et al. (2005) identified a subset of children who presented abnormalities prior to regression. Of 31 children with regression, 45% were reported by parents to have displayed social and communication delays prior to the onset of the losses. This subset of children were reported by their parents to have never displayed several typical early-developing social behaviors, such as joint attention, showing, and social games (Ozonoff et al., 2005). Another study reported that children with regression displayed significantly fewer communicative, social, and play skills than typically developing children before the age of 24 months (Richler et al., 2006). Kurita (1985) also described a subset of children who showed signs of abnormalities prior to regression. Of the 97 autistic children with speech loss in his study, 78.3% showed some developmental abnormalities before the onset of the speech loss, including lack of stranger anxiety and limited social responsiveness (Kurita, 1985). Goldberg et al. (2003) reported that over two-thirds of their sample with regression were already delayed in their language acquisition prior to the loss of skills. Similarly, Heung (2008) found that two-thirds of subjects with regression had some indication of delayed language or social development prior to the onset of their regression. These studies suggest that mixed onset features, with evidence of both early delays and later losses, are quite common.

Further evidence that traditional onset classifications are insufficient comes from the Childhood Autism Risk from Genetics and Environment (CHARGE) study, a large epidemiological investigation of genetic and environmental risks for autism. Using the Early Development Questionnaire (EDQ; Ozonoff et al., 2005), a measure that asks 45 questions about social and communication development in the first 18 months of life, as well as 25 detailed questions about regression, Hansen and colleagues (2008) demonstrated that some parents who reported no evidence of regression on the ADI-R did report subtle losses of specific skills on the EDQ. Figure 1 displays the distribution of scores on the EDQ as a function of onset subtype. This result is consistent with another study finding that some children whose parents reported no regression on the ADI-R nevertheless demonstrated subtle loss of skills on home video (Werner & Dawson, 2005).

Some parents report neither early signs of autism nor later regression. For example, in one sample, less than a third of parents of children who did not experience a regression reported concerns before the first birthday and, in fewer than half, were these concerns specifically social or autistic-like in nature (De Giacomo & Fombonne, 1998). In another sample, approximately one-third of parents identified only non-specific temperament or physiological patterns (e.g., irritability, passivity, eating or sleeping problems) before the first birthday "which evolved into typical autistic features like stereotypical behavior, aloneness, and a lack of eye contact in the second year of life" (Rogers & DiLalla, 1990, p. 866).

Collectively, these findings suggest that there is an additional pattern of symptom emergence that is characterized by intact early social development and/or non-specific abnormalities that are followed by a failure to progress and gain new skills as expected. It has been hypothesized that this pattern may be due to failures to use intact early dyadic social reciprocity skills to support the typical maturational processes of speech acquisition, intentional communication, and triadic social interactions (Chawarska et al., 2007). In such cases, the intact early behaviors fade away because they are not reinforced by the natural predisposition to seek and communicate with others. What might seem like a loss of skills is simply a failure to progress and transform the basic skills into their more developmentally advanced versions. Klin et al. (2004) used the term "pseudo-regression" to describe this pattern and it has also been referred to as "developmental stagnation" (Siperstein, & Volkmar, 2004) and "developmental plateau" (Hansen et al., 2008). No empirical research has been conducted on this pattern and very little is known about whether it differs from other onset patterns in phenotypic features unrelated to symptom emergence.

Data from two large population-based studies reinforce the notion of additional onset patterns beyond the traditionally defined categories. Byrd et al. (2002) recruited a multi-stage random sample of children with autism from California's Regional Centers, which provide services for persons with developmental disabilities. Two cohorts were studied, one born in 1983-1985 and the other in 1993-1995. The second investigation, the CHARGE study (Hansen et al., 2008)[1], enrolled a large population-based epidemiological sample representing 2 – 5 year olds in the Regional Center system, covering birth years 1998-2004. The ADI-R was employed in both studies. Not only does it collect information about regression, as described above, but also it asks about "onset as perceived with hindsight" (Question 4). Examining the intersection of these questions is informative to onset typology. Traditional definitions of onset suggest that most or all children without regression displayed symptoms early in life, while most or all with regression had typical early development. Thus, there should be very few, if any, subjects in the shaded diagonals of

[1]Hansen et al. (2008) used "traditional" two-category onset classifications. We have reanalyzed their data here using a four-category classification system.

Tables 1 and 2. As is evident, however, almost half of both samples fell in these cells, with the percentages remarkably similar across studies.

In summary, recent research suggests that there may be several different patterns of symptom emergence. Whether these are best characterized as additional onset types or conceptualized in some other way is not yet clear. We will return to this topic after finishing this section with insights from recent prospective studies of autism onset.

Onset as Measured in Prospective Investigations

Prospective investigations are a very helpful method of studying onset, because they reduce errors due to parental recall and biases introduced by selective home videotaping, as well as provide the opportunity to test specific hypotheses through experimental methods. In the past decade, several research groups have instigated prospective investigations that study children at higher risk for autism because they have one or more siblings with the condition. Several infant sibling studies have now been published and thus far all have failed to find differences before the first birthday between children who are later diagnosed with autism and those who develop typically (Landa & Garrett-Mayer, 2006; Nadig et al., 2007; Zwaigenbaum et al., 2005; see also Yirmiya & Ozonoff, 2007 for a summary of this work). Bryson and colleagues (2007), in a consecutive case series of infant siblings followed prospectively from 6 months of age, describe several children whose symptoms are not present at their 6 and 12 month visits, but emerge slowly during the second year of life. Not a single one of the 9 children who developed autism displayed marked limitations in social reciprocity at 6 months. All nine infants were described as interested in social interactions, responsive to others, demonstrating sustained eye contact and social smiles. Most of the children did not experience an explicit loss of previously acquired skills that would meet established definitions of regression either. Two prospective case studies (Dawson et al., 2000; Klin et al., 2004) report on children who were noted to be symptomatic by the first birthday, but who presented with mostly intact social behavior in the first 6-12 months and did not experience a clear regression as symptoms began to emerge. Thus, prospective studies are consistent with retrospective studies in finding that for many, perhaps most, children with autism, symptoms emerge gradually over the first 18 months or so of life.

Conclusions

The research literature reviewed in this paper suggests that signs of autism *emerge* over the first year and a half of life and are not present in most cases from shortly after birth, as once suggested by Kanner (1943). Although it is difficult to compare rates and patterns of onset types across studies that used different methods and instruments, data from both retrospective and prospective studies consistently find that two-category onset classification systems do not fit the empirical data well. There is evidence that the traditionally defined categories of early onset and regressive autism are overly narrow prototypes that may not in fact be very common. There is ample evidence of other ways in which symptoms emerge that are not captured by these prototypes. One possibility is that we need to expand the number of categories used to describe onset. For example, perhaps there are four rather than two categories of onset, adding a plateau and a mixed group. We suggest another possibility, however. We hypothesize that symptom emergence may better be considered as a continuum. The two extremes of this continuum are anchored by the traditionally defined, prototypical early onset and regressive cases, but many intermediate phenotypes containing mixed features and varying degrees of early deficits, subtle diminishments, failures to progress, and frank losses are also possible. We propose that variable combinations and timings of these processes across children lead to symptoms exceeding the threshold for diagnosis at different points in the first 24 months for different children, as also suggested by Landa et al. (2007).

A second insight from the body of research summarized in this paper is that regression may occur more frequently than initially thought. If defined narrowly, in the traditional manner (requiring loss of language, as in the ADI-R criteria), regression is less common (Hansen et al., 2008). If defined more broadly, to include diminishment in social engagement, regression may be the rule rather than the exception. However, losses are subtle, are usually preceded by some early concerns, and are followed by failures to progress in other areas, rather than characterized by typical development followed by catastrophic losses, as traditionally defined.

Thus, it is clear that existing definitions of onset patterns will need to undergo further development as new data emerge from future studies. Investigations using prospective samples may be especially fruitful because they will be less affected by potential videotaping, reporting, and recall biases inherent in retrospective studies. Further research clarifying whether onset is better conceptualized as a categorical (dichotomous) or continuous (dimensional) phenomenon is urgently needed for etiologic studies, which have been hindered already by the tremendous heterogeneity of the autism phenotype.

Future research should strive to find biological markers or underlying processing differences that may predict who will develop autism *prior to the onset of behavioral symptoms*. It is possible that infants who are behaviorally asymptomatic at 6 and 12 months may show differences in lower-level underlying processes that can impact later development. For example, differences in visual attention, such as prolonged visual fixations (Landry & Bryson, 2004), might lead to joint attention deficits or behavioral rigidity a few months later. Deficits in the dorsal stream visual pathway, which is specialized for quick processing of global, low spatial-frequency information, could create a cascade of functional differences in brain regions downstream, such as the amygdala and cortical face processing areas. Recently, McCleery et al. (2007) found high luminance contrast sensitivity in a subgroup of younger siblings of children with autism on a task measuring the integrity of the magnocellular visual pathway (part of the dorsal stream). Two of the infants developed autism, leading the authors to speculate that early abnormalities in the magnocellular pathway might be a risk marker for autism. Thus, research on lower level processes that may signal an affected child prior to the onset of behavioral signs could permit interventions to be applied that might significantly lessen disability.

Finally, this body of work has clinical implications for screening, diagnosis, and intervention. Universal screening has been recommended by the American Academy of Pediatrics at 18 and 24 months (Johnson et al., 2007), but many have hoped that identification even earlier than this might be possible. The research reviewed here suggests that identification of autism prior to the first birthday will be a major challenge and may not possible in many children. In fact, for the large group of infants whose autism emerges through diminishment in skills or frank regression, they may be showing few or no behavioral signs of the disorder at the first birthday. Therefore, screening twice, at both 18 and 24 months, is essential, as many children will be missed at the earlier time point. As universal screening guidelines are implemented in practice, professionals must keep in mind the complexity of determining onset summarized in this paper. Some empirically validated screening methods, like the Modified Checklist for Autism in Toddlers (M-CHAT; Robins et al., 2001), involve more than parents simply completing a form, but require later follow-up from practitioners through a phone call or secondary screening.

Finally, given the gradual and protracted course of symptom emergence, we urge professionals to consider referring children for intervention at the point that there is a suspicion of autism and not wait for a definitive diagnosis. Toward this end, development of

treatments appropriate for infants and young toddlers is an urgent priority (Zwaigenbaum et al., in press).

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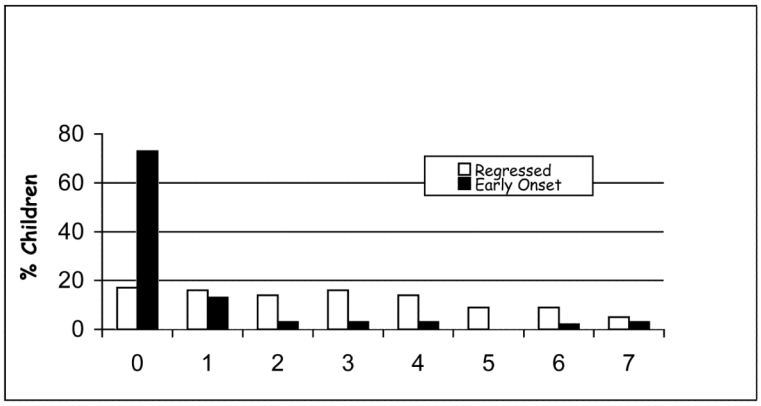

Figure 1.
Number of skills lost in children with and without regression [Hansen et al., 2008].

Table 1

Data from Byrd et al., 2002, n=286

	Loss of Skills (ADI-R Q 11 or 25)	
	No	**Yes**
Symptoms before 1st birthday (ADI-R Q 4)	Early Onset N = 82 28.7%	Mixed N = 34 11.9%
Symptoms after 1stbirthday (ADI-R Q 4)	Plateau N = 96 33.6%	Regression N = 74 25.9%

Table 2

Data from Hansen et al., 2008, n=351

	Loss of Skills (ADI-R Q 11 or 25)	
	No	**Yes**
Symptoms before 1st birthday (ADI-R Q 4)	Early Onset N = 123 35%	Mixed N = 58 17%
Symptoms after 1stbirthday (ADI -R Q 4)	Plateau N = 94 27%	Regression N = 76 22%