

Regression of language and non-language skills in pervasive developmental disorders

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Abstract

Background As part of the pervasive developmental disorders (PDD), there is a subgroup of individuals reported to have a different onset of symptom appearance consisting of an apparently normal early development, followed by a loss of verbal and/or non-verbal skills prior to 2 years of age. This study aims at comparing the symptomatology of children who displayed a regression and often an associated intellectual disability through investigation of two types of loss, namely language and other skill regression.

Methods This study examined the occurrence of regression in 135 children with PDD, mean age 6.3 years. The sample was composed of 80 (59.4%) children diagnosed with autism, 44 (32.6%) with pervasive developmental disorder-not otherwise specified (PDD-NOS) and 11 (8%) with Asperger syndrome. The Autism Diagnostic Interview Revised (ADI-R) was used to evaluate the type of loss and to characterise associated factors including birth rank, gender and thimerosal exposure through vaccination.

Results A total of 30 (22%) subjects regressed: nine (30%) underwent language regression alone, 17 (57%) lost a skill other than language and four (13%) lost both language and another skill. Significantly higher levels of regression were found in autism (30%) compared with PDD-NOS (14%) and Asperger syndrome (0%). Children who regressed in language skills spoke at a significantly earlier age (\bar{X} = 12 months) than those who did not regress in this domain (\bar{X} = 26 months). Parents and interviewers consistently reported developmental abnormalities prior to the loss. ADI-R domain mean scores indicated a more severe autistic symptomatology profile in children who regressed compared with those who did not, especially in the repetitive behaviour domain. Regression was not associated to thimerosal exposure, indirectly estimated by year of birth.

Conclusions A loss of skill, present in one out of five children with PDD, is associated with a slightly more severe symptomatology as measured by the ADI-R, particularly in the repetitive behaviours domain. Furthermore, although abnormalities are often noticed by the caregivers at the time of regression, the ADI-R reveals that other atypical behaviours were in fact present prior to the onset of regression in most cases. None of the secondary factors investigated were associated with regression. In children unexposed to thimerosal-containing

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vaccines, the rate of regression was similar to that reported in studies of samples exposed to thimerosal, suggesting that thimerosal has no specific association with regressive autism.

Keywords ADI-R, language, PDD, regression, thimerosal, vaccine

Introduction

Pervasive developmental disorders (PDD), also known as autism spectrum disorders (ASD), is a group of neurodevelopmental disorders that comprises autistic disorder, Asperger disorder, PDD-not otherwise specified (NOS) (or atypical autism), childhood disintegrative disorder (CDD) and Rett's syndrome. PDD are categorised by developmental deficits in three domains: language and communication, social reciprocity, and patterns of interests and behaviours. PDD affect individuals worldwide with prevalence rates as high as 60–70/10 000 in recent studies (Fombonne 2005; Fombonne *et al.* 2006; Van Naarden Braun *et al.* 2007). An overrepresentation of the male (male : female = 4.3:1) has been consistently reported (Fombonne & Chakrabarti 2001; Fombonne 2003, 2005). Although the precise aetiology of ASD is still unknown, genetic factors play an important role (Szatmari *et al.* 2007). The significant increased risk of epilepsy (Tuchman & Rapin 2002) and of intellectual disability (Fombonne 2003), along with results from neuroimaging and neuropathological studies (Aylward *et al.* 2002; Courchesne *et al.* 2003; Bauman & Kemper 2005) strongly pointing to a brain disorder of early prenatal development.

A subgroup known as 'regressive autism' has recently received closer attention. Regressive autism affects approximately one-fifth to one-third of children who meet the diagnostic criteria of autistic disorder, and applies to children who lose skills throughout their development. The onset is usually observed between the ages of 15 and 24 months. The variability of the prevalence of regression reflects differences in the definitions used in each study (Table 1). Language regression (LR) occurs at equal rates in children diagnosed with autism or PDD-NOS (Lord *et al.* 2004). This pattern of loss is not found in other groups of children with early developmental delays (e.g. Down syndrome, Fragile

X, etc.) except for a rare group known as epileptic aphasia or Landau-Kleffner syndrome (Mantovani 2000). The close temporal proximity between the age of administration of the measles-mumps-rubella (MMR) vaccine and the age of the onset of regression led to hypotheses of a causal relationship (Wakefield *et al.* 1998). Thimerosal, the organic mercury compound used as a conservatory agent in other childhood vaccines, has also been suspected to be responsible for the appearance of regressive autism. However, the association between autism and MMR and thimerosal-containing vaccines has been investigated in several controlled epidemiological studies and is now largely refuted by the scientific community (Farrington *et al.* 2001; Fombonne & Chakrabarti 2001; Hviid *et al.* 2003; Chen *et al.* 2004; McCormick *et al.* 2004; Parker *et al.* 2004; D'Souza *et al.* 2006; Fombonne *et al.* 2006; Richler *et al.* 2006).

Children with regressive autism exhibit a loss in communicative skills and/or in other skills such as social engagement and responsiveness. Loss of language is most easily noticed by the caregiver; however, it rarely occurs in isolation (Shinnar *et al.* 2001; Goldberg *et al.* 2003; Lord *et al.* 2004). In fact, 76–93% of children who lost language skills had a concomitant loss of another non-language skill (Goldberg *et al.* 2003; Wilson *et al.* 2003 respectively) such as direct gaze, orientation to name, spontaneous imitation or response to social overture.

Possible differences in genetic and environmental risk factors between regressive and non-regressive autism are unknown. Lainhart *et al.* (2002) found that liability to autism, measured by the broader autism phenotype, occurs at the same frequency in relatives of children with regressive or non-regressive autism, suggesting comparable genetic influences in both groups. Similarly, abnormal head circumference growth at the end of the first year of life occurs with comparable frequency in early onset autism and regressive autism (Webb *et al.* 2007), indicative of biological developmental abnormalities much before the loss of skills occurs. In fact, the initial assumption that the loss of skills in regressive autism occurred in children with previously normal development has been increasingly challenged in recent studies (Rogers 2004). Prior to the occurrence of a loss, the

Table 1 Studies of regression in persons with autism or other autism spectrum disorders (ASD)

Author (year)	n (autism/other ASD)	Rates of regression (%)	Domains of regression	Mean age of regression (months)	Definition of regression
Hansen et al. (2008)	333 (ASD group not specified)	41	Language and other skills	N/A	Normal use of skill for at least 3 months (the use of at least five communicative words other than 'mama/dada' is required in the case of language loss) with substantial or complete loss for at least 3 months (coded by the ADI-R)
Richler et al. (2006)	351 (273/78)	N/A	Language	16.94	Word loss: spontaneous use of at least three words other than 'mama/papa' on a daily basis for at least 1 month and had stopped using all words for at least 1 month, prior to 36 months of age or if the child showed a repeated pattern of word gain and loss
Christopher et al. (2004)	82 (82/0)	30	Language	18.96	Note that children with another type of loss was classified in the 'no word loss' group Language regression: loss of consistent use of at least one word used communicatively such as 'mama' or 'juice'
Lord et al. (2004)	96 (68/28)	25	Language	16.63	1. Loss of word: spontaneous use of at least three communicative words other than 'mama/dada' daily for 1 month, followed by 1 month in which the child does not use any recognizable word 2. Fluctuating word loss: used at least three words daily for over a month followed by two periods of no words that lasted at least 1 month
Goldberg et al. (2003)	Non-regressive: 132 (ASD group not specified) Regressive: 44 (37/7)	33	Language and other skills	Verbal: 20.69 Other skill: 18.58	Normal use of skill for at least 3 months (the use of at least five communicative words other than 'mama/dada' is required in the case of language loss) with substantial or complete loss for at least 3 months (coded by the ADI-R)
Wilson et al. (2003)	Regressive: 196 (14 of which were non-ASD)	N/A*	Language	21.20	Any convincing report of loss of previously acquired language skills, whether or not prior language development was considered normal or delayed
Taylor et al. (2002)	473 (278/195)	25	Language and other skills	N/A	Any deterioration in any aspect of the child's development or loss of skills as reported by the parent
Fombonne & Chakrabarti (2001)	194 (98/96)	17	Language and other skills	N/A	Normal use of skill for at least 3 months (the use of at least five communicative words other than 'mama/dada' is required in the case of language loss) with substantial or complete loss for at least 3 months (coded by the ADI-R)
Shinnar et al. (2001)	177 (127 ASD/26 suspected ASD/22 non-ASD)	N/A*	Language	22.80	Any child with language regression was included regardless of if they had other symptoms such as seizures, autistic features, etc.
Tuchman & Rapin (1997)	585 (ASD group not specified)	30	Language	21.00	Communicative use of at least three words followed by a lost of language for at least 3 months

* In this study, the sample was only made up of individuals who underwent a regression therefore the prevalence rates were not obtained. ADI-R, Autism Diagnostic Interview Revised; N/A, not available.

majority of children with regressive autism display subtle developmental abnormalities similar to those exhibited by non-regressive autistic children (Kurita 1985; Goldberg *et al.* 2003; Ozonoff *et al.* 2005) and in the most detailed study of this issue in as many as 72% of regressive autism subjects (Richler *et al.* 2006).

The evidence is less clear concerning the outcome of children with and without regression. Using the Autism Diagnostic Interview Revised (ADI-R; Lord *et al.* 2004) scores, some studies found no difference in autistic symptomatology following the loss (Fombonne & Chakrabarti 2001; Lord *et al.* 2004), whereas a recent larger-scale study found increased social deficit scores in the regressive group indicative of greater social impairment (Richler *et al.* 2006). With respect to intellectual functioning, children with a loss of language tend to have lower verbal IQ scores and appear to be more intellectually disabled, when compared with their non-regressive counterparts, even after regaining speech (Lord *et al.* 2004; Ozonoff *et al.* 2005); Richler *et al.* 2006). In addition, Wilson *et al.* (2003) reported that all children who had experienced LR remained significantly impaired and showed minimal improvement in their expressive language skills following the loss. However, other studies have found few, if any, clinically meaningful differences in the outcome of regressive vs. non-regressive autism (Hansen *et al.* 2008).

The validity of regressive autism as a distinct subgroup of ASD is therefore not strongly established with regard to specific developmental pathways, aetiology, phenotypical features and prognosis. In order to examine this question further, we performed this study with the following aims:

- 1 To compare regressive and non-regressive ASD children for their profile of autistic symptomatology including diagnosis, ADI-R scores and onset of symptomatology;
- 2 To individually describe subgroups of regression: language and other skill regression (OSR), and to compare them on their clinical profile according to age of onset, duration of the loss and attainment of developmental milestones; and
- 3 To identify if regressive autism is associated with secondary factors such as sex, birth rank, illness or thimerosal exposure through vaccination.

Material and methods

Participants

The sample was recruited from the Autism Spectrum Disorder Clinic of the Montreal Children's Hospital (McGill University) as part of ongoing clinical and research activities. All 135 patients included in the study received a clinical diagnosis of PDD following the administration of the ADI-R and a direct clinical examination by the senior author (EF). Diagnoses were derived using the Diagnostic and Statistical Manual of Mental Health (DSM-IV) criteria. Subjects with Rett's syndrome or CDD were excluded from the study. The repartition of diagnoses was 80 (59.4%) with autistic disorder, 44 (32.6%) with PDD-NOS and 11 (8%) with Asperger disorder. The ages at the time of the ADI-R ranged from 1.6 to 22.3 years [\bar{X} = 6.3 years; standard deviation (SD) = 4.1].

Measures

Data from the ADI-R were used to describe clinical profiles of subjects with and without regression. This semi-structured interview has excellent validity and reliability (Fombonne 1992; Lord *et al.* 1994) and yields scores in four domains: social, communication, repetitive behaviours and age of onset. The ADI-R total score combining the score of each domain was used as a global index of severity alongside each specific domain score.

The occurrence of developmental regression is explored in two independent sections of the ADI-R: language skill loss and general skill loss. The definition of loss within the ADI-R is twofold: it requires that any loss be coded only if the skill was initially established for at least 3 months and the loss of skill must last at least 3 months. Each section probes for the specific features of the skill that were lost (see Table 2), the intensity of the loss, the age when the loss was first apparent, the duration of the loss and the association with physical illness. In order to be eligible for a loss of language skills, it must be established that the child has attained sufficient language skills such as the communicative use of at least five words (other than 'dada' and 'mama') on a daily basis.

For analytical purposes, the subjects with regression included in the study were grouped in three

Table 2 Loss of skills (Autism Diagnostic Interview Revised items)

Language skill loss (language regression)	<i>n</i> = 13*
Loss of spontaneous use of at least five meaningful words	10
Loss of communicative intent	10
Loss of syntactical skills (grammar)	5
Loss of articulation (pronunciation)	5
Other skill loss	<i>n</i> = 21*
Loss of purposive hand movement (ability to grip/hold objects)	7
Loss of motor skills (posture, gait, coordination)	5
Loss of self-help skills (feeding, dress, using the bathroom, etc.)	5
Loss of constructive or imaginary play (puzzle, games, make-believe, etc.)	9
Loss of social engagement and responsiveness (social relatedness, interest, involvement)	16

* Note an overlap of four subjects who regressed in both types of skills.

sets: LR, subjects with a loss in language skills affecting any of four features of language (see Table 2); OSR, subjects with a loss of a skill in any of five domains (see Table 2) other than language; any skill regression (ASR), subjects who experienced regression either in language or in other skills.

Regression and thimerosal exposure

As thimerosal was discontinued from common vaccine production in 1996 in Quebec (Fombonne *et al.* 2006), we calculated the proportion of ASR in the subsample of subjects born in or after 1996 who were therefore unexposed to thimerosal. As there were too few subjects born before 1996, this proportion was compared with rates of regression in the published literature of children exposed to thimerosal-containing vaccines.

Statistical analysis

Descriptive statistics according to diagnosis and regression status were computed for the entire sample. The variables that were explored included: the age at referral, the age of first parental concern,

the age of onset of anomalies as coded by the interviewer, the age of first single word/phrase and the age of walking. Mean ADI-R scores were used as measures of the three domains of autistic impairment. Comparisons between the regressive and non-regressive samples were performed using ANOVA for continuous data or chi-squared tests and Fisher's exact test for categorical data. When appropriate, the non-parametric Mann-Whitney test was used for further investigation of the data. Paired *t*-tests were used in comparing the mean age of onset of regression and abnormality onset. A conventional *P*-value of 0.05 was chosen as a criterion for statistical significance. Data were analysed by using SPSS 15.0 statistical software.

Results

Sample characteristics

The sample was made up of 135 individuals diagnosed with PDD. Consistent with other studies, the data show a preponderance of the male (85%), translating into a 5.7:1 male : female ratio. Initial parental concern about development arose when the child was on average 22.9 months (*SD* = 12.65). In 51.1% of cases, problems were noted at or prior to the age of 24 months. Parents noticed a developmental abnormality at a younger age for children with autistic disorder when compared with children with PDD-NOS (19.9 vs. 25.1 months; *P* = 0.028) or Asperger syndrome (19.9 vs. 35.0 months; *P* = 0.001). Children with autistic disorder were also referred at a significantly younger age than children with PDD-NOS or Asperger syndrome (4.0 vs. 7.4 years; *P* < 0.001 and 4.0 vs. 9.8 years; *P* < 0.001 respectively). The mean age of first word for the entire sample was 24.9 months (*SD* = 12.2). The differences according to the diagnostic subgroups were not significant (autistic disorder: 25.0; PDD-NOS: 26.1; Asperger disorder: 18.8; *F* = 1.344, *P* = 0.265) although there was a clear trend for children with Asperger disorder to start speaking at an earlier age.

Descriptive characteristics of the regressive subgroup

The ASR group was composed of 30 subjects, translating into a prevalence rate of regression of

Table 3 Types of regression by diagnosis

	Total <i>n</i>	Regressive*		Non- regressive		Chi-squared <i>P</i> -value	Post hoc test	Fisher's exact <i>P</i> -value
		<i>n</i>	%	<i>n</i>	%			
Any skill regression								
Autism	80	24	30.0	56	70.0	0.024	Autism vs. PDD-NOS	0.050
PDD-NOS	44	6	13.6	38	86.4		PDD-NOS vs. Asperger	0.330
Asperger	11	0	0.0	11	100		Autism vs. Asperger	0.034
Language regression								
Autism	65	9	13.8	56	86.2	0.397	–	–
PDD-NOS	42	4	9.5	38	90.5			
Asperger	11	0	0.0	11	100			
Other skill regression								
Autism	75	19	25.3	56	74.7	0.007	Autism vs. PDD-NOS	0.010
PDD-NOS	40	2	5.0	38	95.0		Autism vs. Asperger	0.108
Asperger	11	0	0.0	11	100		PDD-NOS vs. Asperger	1.000

* There was an overlap of four subjects who regressed in both language and another skill. PDD-NOS, pervasive developmental disorder-not otherwise specified.

22.2% of all subjects with a PDD. A closer investigation of this group revealed that nine (30.0 %) subjects lost language only, 17 (56.7%) lost a skill other than language and four (13.3%) lost both language and another skill. Subjects with autistic disorder were more likely to show ASR than those diagnosed with Asperger syndrome (30.0% vs. 0.0%; $P = 0.034$) and marginally more than those with PDD-NOS (30.0% vs. 13.6 %; $P = 0.050$). The differences between the autistic disorder and PDD-NOS groups were entirely accounted for by a higher proportion of loss of skills other than language in autistic disorder than in PDD-NOS. Language loss occurred otherwise in comparable frequencies in those two groups (Table 3). None of the individuals with Asperger syndrome experienced a regression of skill. This is concordant with the DSM-IV criteria of Asperger syndrome which requires a normal early language development. Therefore, all of the analyses investigating regression-associated factors were subsequently restricted to the autistic disorder and PDD-NOS groups. Following removal of the 11 subjects with Asperger syndrome, the prevalence rate of regression was 24%.

Compared with non-regressive subjects, subjects who exhibited a regression of ASR scored signifi-

cantly higher in the repetitive behaviours domain of the ADI-R (7.4 vs. 5.7; $P = 0.002$) and also had a significantly higher ADI total score (38.5 vs. 33.5; $P = 0.029$) (Table 4). All other ADI-R domain score comparisons were not statistically significant, but a visual inspection of the data indicated consistently higher domain and sub-domain scores in the regressive group compared with the non-regressive group. The mean age of onset of abnormalities, as coded by the ADI-R interviewer, was significantly lower than the mean age of onset of regression [for OSR: 14.45 vs. 31.30 months, $t = 4.08$, degree of freedom (d.f.) = 19, $P = 0.001$ and for LR: 14.67 vs. 24.17 months, $t = 3.68$, d.f. = 11, $P = 0.004$].

Language regression

A total of 13 subjects experienced regression with language skills. Over 75% of them lost either the ability to use words meaningfully and/or the ability to use words with a communicative intent (Table 2). Of the five subjects who had sufficient language, all of them lost syntactic skills. Of the nine children with adequate pronunciation before the loss, five (56%) lost skills in this area. In the LR group, language loss occurred between the ages of 12 and 44 months ($\bar{X} = 24.4$ months; $SD = 9.4$)

Table 4 Autism Diagnostic Interview Revised (ADI-R) sum scores for the three domains for the groups with autistic disorder and pervasive developmental disorder-not otherwise specified

ADI-R domains	Regression \bar{X} (standard deviation)	No regression \bar{X} (standard deviation)	Mann-Whitney test (P-value)
Any skill regression	<i>n</i> = 30	<i>n</i> = 94	
Social	17.9 (5.6)	16.0 (6.5)	0.158
Communication	13.2 (3.4)	11.7 (5.1)	0.138
Repetitive behaviours	7.4 (2.2)	5.7 (2.6)	0.002
Total	38.5 (8.3)	33.5 (11.6)	0.029
Language regression	<i>n</i> = 13	<i>n</i> = 94	
Social	16.2 (6.3)	16.0 (6.5)	0.913
Communication	11.7 (3.2)	11.7 (5.1)	0.989
Repetitive behaviours	6.7 (2.5)	5.7 (2.6)	0.209
Total	34.6 (7.9)	33.5 (11.6)	0.731
Other skill regression	<i>n</i> = 21	<i>n</i> = 94	
Social	19.7 (4.5)	16.0 (6.5)	0.016
Communication	14.3 (3.1)	11.7 (5.1)	0.012
Repetitive behaviours	7.6 (2.3)	5.7 (2.6)	0.002
Total	41.6 (6.9)	33.5 (11.6)	0.003

and lasted between 3 and 41 months (\bar{X} = 20.9 months; SD = 14.9). The language developmental milestones of first word and first phrase were reached within normal age limits by LR subjects but not by the non-regressive subjects (for first word: 11.9 vs. 26.8 months, F = 16.98, P < 0.001; for first phrase: 30.1 vs. 40.8 months, F = 4.11, P = 0.046). As in the non-regressive group, the motor developmental milestone of walking was achieved within the normal age limit (12.5 vs. 14.4 months, F = 1.16, P = 0.28).

Other skill regression

Among the 21 OSR subjects, seven (33.3%) lost purposive hand movements, five (23.8%) lost one or more motor skills, five (23.8%) lost self-help skills, nine (42.8%) lost their ability to play constructively or imaginatively and 16 (76.2%) lost social abilities (Table 2). The age of onset of regression for the OSR group was between 10 and 72 months (\bar{X} = 31.1 months; SD = 18.0) and this loss lasted between 3 and 22 months (\bar{X} = 10.8 months; SD = 6.3). These subjects displayed a pattern of language development similar to that of non-regressive subjects, presenting with a delayed age of first word (25.1 vs. 26.0 months, F = 0.083, P = 0.77) and of first phrase (34.7 vs. 40.8 months,

F = 2.42, P = 0.123). As in the non-regressive group, the motor development milestone of walking was reached within normal age limit by children who regressed in a skill other than language (14.4 vs. 13.2 months, F = 0.76, P = 0.385).

Overlap of language and other skill regression

An overlap is defined as the occurrence of both language and another skill regression for the same subject. In this study, only 4/30 (13.3%) subjects showed an overlap of losses. All of these subjects regressed in their ability to engage in constructive or imaginative play skills, in their social engagement skills and in their spontaneous ability to use meaningful words with a communicative intent. The limited sample size of this group did not allow for further statistical testing.

Comparison of the other skill regression and the language regression groups

A between-group comparison revealed significantly higher ADI-R total scores in the OSR group than in the LR group (41.5 vs. 34.6, F = 5.96, P = 0.021). Although the OSR group had a higher mean score in the repetitive behaviour domain, the difference did not reach statistical significance (8 vs. 6.7,

$F = 2.62$, $P = 0.117$). The LR group said their first word at a significantly younger age than the OSR group (11.9 vs. 28.3 months, $F = 14.76$, $P = 0.001$), and the LR group tended to say their first phrase at a younger age (30.1 vs. 39.7 months, $F = 3.99$, $P = 0.06$). The groups did not differ in their age of onset of regression (LR: 22.6 months vs. OSR: 31.7 months, $F = 1.758$, $P = 0.197$) or in their age of onset of symptoms as coded by the ADI-R interviewer (LR: 14.4 months vs. OSR: 11.9, $F = 1.540$, $P = 0.208$ months).

Other features associated with regressive autism

Sex did not influence the occurrence of regression in the ASR group. The male-to-female ratio was not significantly different in the regressive group than that in the non-regressive group ($\chi^2 = 0.650$, d.f. = 1, $P = 0.420$). Birth rank (first born, second born, etc.) was neither associated with the occurrence of regression ($\chi^2 = 6.06$, d.f. = 4, $P = 0.195$). Likewise, the age of walking, as a reflection of motor development, was not related to the incidence of ASR (13.1 vs. 14.4 months, $F = 1.182$, $P = 0.279$). Moreover, findings indicated that for the majority of cases displaying a loss of any skill regression did not co-occur with illness or with loss of consciousness/epilepsy (OSR: 85.7% and LR: 69.2%). The proportion of regression among children born in or after 1996 and therefore not exposed to thimerosal was 28.7%. This prevalence was not different (and certainly not lower) from that reported in previous studies of thimerosal exposed subjects (Fombonne & Chakrabarti 2001; Taylor *et al.* 2002; Center for Disease Control 2007a,b).

Discussion

Concordant with previous findings, 22% of individuals diagnosed with ASD regressed in verbal and/or nonverbal skills. We found a zero rate of regression in our small Asperger disorder subsample. Regression was therefore specific to other forms of ASD. Dividing the regressive group into language and non-language skill loss subgroups permitted for a closer investigation of distinctive phenotypic profiles. Generally, individuals with

autism were significantly more likely to regress in skills other than language when compared with subjects with PDD-NOS. Findings by Lord *et al.* (2004) were replicated, demonstrating that LR occurred in comparable frequencies in autism and PDD-NOS. However, a particular relationship between regression of non-language skills and autism, a more severe form of PDD, may exist, perhaps suggestive of specific significance of the type of skills lost during regression. As in Hansen *et al.*'s study (2008), we found a higher frequency of non-language loss of skills in our sample, confirming that a regressive developmental course may be more frequent than previously thought if careful attention is paid to loss of skills other than languages.

The severity of the disorder was reflected by ADI final scores, where higher scores indicated more severe symptoms. Overall, subjects with any type of regression scored significantly higher on the ADI-R. More specifically, they displayed significantly more odd/restricted interests and repetitive behaviours. Although differences in mean scores did not reach significance, they also displayed more symptoms in the social and the communication domains. Regression of non-language skills was associated with consistently higher total ADI-R scores than language skill regression, thus reflecting an overall more severe symptomatology. An analysis restricted to the LR group yielded no significant differences on ADI-R domain scores, suggesting that after their loss, this subgroup displayed a manifestation of the disorder similar to that of non-regressive subjects. However, these results should be approached with caution considering the limited sample size of the LR group.

Children with LR said their first word within the normal age range, and in most cases (77%) they had a well-established level of language before the loss occurred. However, mean age of onset analyses revealed the presence of other abnormalities prior to the occurrence of a loss in either domain (OSR or LR). Moreover, the contributory action of regression was unlikely to constitute a possible cause of autism as only a minority of cases reported a co-occurrence with illness. In addition, the proportion of regressive autism in children unexposed to thimerosal-containing vaccines did not differ from that reported in previous thimerosal-exposed

samples (Fombonne & Chakrabarti 2001; Center for Disease Control 2007a,b), suggesting that thimerosal has no specific association with regressive autism. Other factors that were examined in relation to the occurrence of regression such as birth rank and gender were not associated to it in this study.

The overlap of subjects showing a regression of both language and another skill was only 13%. Based on previous studies, this is a much lower prevalence rate than expected (Shinnar *et al.* 2001; Goldberg *et al.* 2003; Wilson *et al.* 2003; Lord *et al.* 2004) and may be explained by differences in skill loss definitions although Hansen *et al.* (2008) recently reported profiles of regression that are comparable to our findings. The skills lost by all four subjects of this subsample were imaginative play, social engagement, communicative intent of their speech and the spontaneous use of a minimum of five meaningful words. ADI-R scores in these subjects compared with those who did not lose multiple skills did not appear different; however, the limited sample size did not allow for statistical testing.

The main limitation of the present study is its limited sample size of 30 subjects with a regressive profile and of the LR and OSR groups. This restricts the generalisation of the results from the LR and OSR group comparison analyses. Second, the data were based on retrospective parental reports. In defence of a possible forward telescopic effect, the ADI-R states its questions with great detail and promotes remembering key life events in order to appropriately time the past behaviour. Another possible limitation was the wide age range of subjects at the time of the interview. This age variability was to some extent controlled for in the ADI-R interview by probing for the most abnormal period of 4–5 years old.

Overall, this study used the ADI-R to investigate differences between individuals diagnosed with PDD who regressed and those who did not. The results document some clinical characteristics distinctive of the regressive subgroup. These children generally say their first words at earlier ages and usually score higher on the ADI-R than non-regressive subjects. A later age of first word along with a greater ADI-R overall score appears to best distinguish individuals who underwent a regression

of non-language skills from those with a regression of language skills. As in other recent studies (Hansen *et al.* 2008), this study did not support the hypothesis that regressive autism is an independent condition distinct from non-regressive autism, as aside from the language development pattern and the severity of ADI-R scores, the general profile of regressive subjects closely matched that of non-regressive individuals. Future studies should further investigate the developmental aspects of language and non-language regressive profiles and target potential neurobiological and/or environmental risk factors. Increased knowledge about the earliest signs associated with regression of skills in autism will allow for a better identification of affected children and improvement of the prognosis of these children.

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