Autism and Early Neurodevelopmental Milestones

Autismo e Marcadores Precoces do Neurodesenvolvimento

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ABSTRACT

Introduction: Autism spectrum disorder, also referred to in this study as autism, is a neurodevelopmental chronic disease that manifests early in childhood by impairment in social interaction, communication and repetitive behavior. Since there are no specific biomarkers available, the diagnosis is based exclusively on clinical criteria. The purpose of the present study is to determine which are the early psychomotor development or neurodevelopmental milestones that present a significant correlation with the severity of the main symptoms of autism, development quotients, and adaptive function.

Material and Methods: We performed a retrospective study on a sample of 1572 individuals with a diagnosis of autism that were monitored at Hospital Pediátrico do Centro Hospitalar e Universitário de Coimbra, in the Neurodevelopment and Autism Unit. We analyzed six early psychomotor developmental milestones: age of acquisition of 'walking', 'first words', 'first phrases', 'daytime control of bladder sphincter', 'night-time control of bladder sphincter', and age of first complaints. Afterwards, we divided the sample in three subgroups regarding clinical severity, according to the Childhood Autism Rating Scale, and we analyzed significant differences among each other concerning the six milestones established beforehand.

Results: The milestone 'age of first phrases' was, from the six milestones, the one with a stronger correlation with the variables of clinical manifestations of autism, development/intelligence quotients, and adaptive function. In division of the sample into subgroups of clinical severity, it was the most severe that showed later ages of acquisition of the neurodevelopmental milestones and earlier ages of first complaints.

Discussion: This study proves the clinical utility to know the age of achievement of early psychomotor developmental skills, since they act as predictors of clinical severity of autism, cognition, and adaptive function of a wide population with autism. Therefore, this data contribute for prognostic and prediction of autism progression.

Conclusion: Taking into account the results of this study, it is strongly recommended to all clinicians who have contact with autistic children, to record the ´age of acquisition of first phrases´.

Keywords: Autistic Disorder; Child Development; Developmental Disabilities; Prognosis.

RESUMO

Introdução: A perturbação do espectro do autismo, neste texto também designada por autismo, é uma patologia crónica do neurodesenvolvimento, que se manifesta precocemente na infância por alterações da interação social, comunicação e comportamento repetitivo. Não estando disponíveis biomarcadores específicos, o diagnóstico baseia-se exclusivamente na avaliação clínica. O objetivo deste estudo é verificar quais os marcadores precoces do desenvolvimento psicomotor ou neurodesenvolvimento, que se correlacionam significativamente com a gravidade da clínica central do autismo, quocientes de desenvolvimento e com a função adaptativa.

Material e Métodos: Procedemos ao estudo retrospetivo de uma população de 1 572 indivíduos com o diagnóstico de autismo seguidos na Unidade de Neurodesenvolvimento e Autismo do Centro de Desenvolvimento da Criança do Hospital Pediátrico do Centro Hospitalar e Universitário de Coimbra. Analisámos seis marcadores precoces do desenvolvimento psicomotor: idades de aquisição 'da marcha', 'das primeiras palavras', 'das primeiras frases', 'do controlo de esfíncter vesical diurno', 'do controlo de esfíncter vesical noturno' e de início das primeiras queixas. Posteriormente dividimos a amostra em três subgrupos de gravidade clínica segundo a escala Childhood Autism Rating Scale e pesquisamos diferenças significativas entre os três subgrupos relativamente aos seis marcadores definidos.

Resultados: O marcador 'idade de aquisição das primeiras frases' foi, de entre os seis, aquele que se correlacionou mais fortemente com as variáveis da clínica de autismo, quocientes de desenvolvimento/inteligência e comportamento ou função adaptativa. Na divisão da amostra em subgrupos de gravidade clínica, foi o de maior gravidade que mostrou idades de aquisição dos marcadores do neurodesenvolvimento mais tardias e idades mais precoces de manifestação das primeiras queixas.

Discussão: Este estudo vem demonstrar a utilidade clinica dos marcadores precoces do desenvolvimento psicomotor nos primeiros anos de vida, como preditores da gravidade da clinica de autismo, cognição e função adaptativa duma vasta população com autismo. Deste modo, estes dados vêm contribuir, em associação com outros, para o prognóstico e previsão da história natural do autismo.

Conclusão: Tendo em conta os resultados deste estudo, recomenda-se fortemente o registo da ´idade de aquisição das primeiras frases´ a todos os clínicos que tenham contacto com crianças com autismo.

Palavras-chave: Desenvolvimento da Criança; Perturbação Autística; Perturbações do Desenvolvimento; Prognóstico.

INTRODUCTION

The concept of autism was for the first time used by Eugen Bleuler to describe one of major clinical symptoms of schizophrenia, by the second decade of the 20th century.[1] He used the Greek term *autós*[2], which means

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'self or by oneself,'[3] involving social interaction deficits as major signs in autism. Autism was subsequently described as a childhood-presentation clinical/nosological entity, by Leo Kanner in 1943[4] and by Hans Asperger, one year later.[2,5] It is currently considered as a chronic and complex neurodevelopmental disorder, related to a multifactorial brain disorder which is undetermined in approximately 80% of cases.[6] Typical semiology of autism includes social interaction, verbal and non-verbal communication deficits, as well as restricted, repetitive patterns of behaviour, interests or activities. It has variable clinical severity and was therefore identified in the 5th Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013)[7] as autism spectrum disorder (ASD). Other symptoms of neurological disorder, such as intellectual disability (68%)[8], epilepsy (up to 26%)[9], sensory processing dysfunctions (95%)[10] and disruptive behaviour (23.3%)[7,11,12], among other comorbidities, are frequently associated to primary presentation.[13] Presentation usually occurs within the first years of life and is considered as one of the most frequent neurodevelopmental disorders, with an estimated prevalence of around one per 1,000 school-age children in Portugal.[14,15]

Autism has a relevant impact on individual's daily functioning and its current therapy is based on tailored and intensive educational and behavioural approach.[5,16,17] Diagnosis remains strictly based on clinical evaluation as there no biomarkers; regardless of the underlying severity of each case, outcome[18] also depends on an early and high-quality intervention.[14,19-21] The identification of a neurodevelopmental model in early ages has a very relevant clinical role in order to adapt the intervention and future expectations to each patient, allowing for an estimated outcome[18,22] in terms of severity and therefore the needs of each child and his/her family.

Our study aimed to determine whether early neurodevelopmental milestones (brain maturity) and early signs of autism are associated to severity, to global development as well as to adaptive functioning. The analysis of longitudinal follow-up of a large group of patients with autism attending the Children's Hospital of the *Centro Hospitalar e Universitário de Coimbra* was carried out.

MATERIAL AND METHODS

In total, 1,572 patients diagnosed with autism and attending the Neurodevelopment and Autism Unit of the *Serviço do Centro de Desenvolvimento da Criança do Hospital Pediátrico* (a tertiary referral hospital) at the *Centro Hospitalar e Universitário de Coimbra* were included in the study. Diagnosis was confirmed by a specialized neurodevelopmental multidisciplinary team and was based on gold standard instruments in this area (Portuguese version of the semi-structured interview - Autism Diagnostic Interview™-Revised [ADI-R])[14] and on clinical evaluation. Social interaction deficits were analysed using the score of social interaction area of the ADI-R (0-30 range) and the higher the score, the higher the social interaction impairment.

Global clinical severity of autism was assessed using the Portuguese version of the Childhood Autism Rating Scale (CARS)[14] (15-60 range) and the higher the score, the more severe the autism. Three subgroups of severity of autism global clinical presentation were developed, according to CARS score (mild: < 30, moderate: ≥ 30 ≤ 36, severe: ≥ 37).

Global developmental quotient (GDQ) and subquotients in different dimensions (hearing and language [*QDL*], eye and hand coordination [*QDOM*], personal-social [*QDPS*] and performance [*QDR*]) were obtained using the Ruth Griffiths developmental scale[23] and was applied by psychologists experienced in autism and in other neurodevelopmental disorders. A subgroup of 227 patients were assessed regarding these parameters at pre-school and at school age. Normal GDQ and subquotients is 100 ± 15; the higher the score, the better the level of child's global development.

Adaptive behaviour (daily life activities) was assessed by Vineland Adaptive Behaviour Scale[24] and standard global score and domains (communication, socialization and daily living skills) were used. Normal score is 100 ± 15; the higher the score, the better the individual adaptive level.

Apart from this multimodal assessment usually carried out for every patient, a comprehensive and systematic clinical history was obtained by a paediatrician specialized in neurodevelopment and recorded on a digital database (authorized by the Portuguese *Comissão Nacional de Proteção de Dados*).

Apart from the variables related to diagnosis and clinical severity, as well as to the different sub-domains of GDQ and adaptive behaviour, information regarding patient's age of onset (in months of age) of early neurodevelopmental milestones, described by caregivers, such as: walking (first unsupported gait), first meaningful words apart from 'mom' and 'dad', first phrases (composed of two or more words, one word being a verb, routinely used), daytime and night-time bladder control. Early clinical manifestations of autism were also analysed through age of onset (in months) of the first signs detected by caregivers or by healthcare or education professionals.

Statistical Package for the Social Sciences (SPSS, Chicago, IL, EUA), Microsoft Windows® version was used in statistical analysis.

Kolmogorov-Smirnov-Lilliefors test was used to test for the normal distribution of the different variables and, as most patients showed deviation from normality, non-parametric statistical tests were used. Spearman's correlation coefficient was used for the analysis of linear association between two quantitative variables and a significance level (α) = 0.05 ($p < 0.05$) was considered. Finally, Kruskall-Wallis test, followed by Mann-Whitney's test, were used for the analysis of significant differences between the three subgroups of clinical severity.

RESULTS

Our study involved 1,572 patients (81.4%, male), with a 4.4:1 male : female ratio. Clinical characteristics are shown

in Table 1 and functional characteristics in Table 2.

Correlations

Spearman's correlation coefficient was used for the analysis of the correlation between two quantitative variables. Only Spearman's coefficient values (S coef) of 0.30 and above were presented, regardless of whether the sign is positive or negative, based on Cohen's criteria.[25] According to these criteria, S coef between 0.30 and 0.49 show a moderate correlation and those between 0.5 and 1 a strong correlation. The sign of S coef does not interfere with its value, only showing the direction of correlation as direct (+) or reverse (-).

The early neurodevelopmental milestone 'age for onset of walking' significantly correlated ($p < 0.05$) with all the variables for clinical assessment of autism, developmental quotient (DQ) and level of adaptive function, although the highest values of S coef were obtained for GDQ (-0.33), *QDOM* (-0.33) and *QDR* (-0.35), where a moderate negative association was found.

Table 1 - Clinical characteristics of the group of patients with autism (n = 1,572)

	n	Median	Interquartile range (IQR)
Age for onset of the first signs (months)	1,341	24	12
Age for onset of walking (months)	1,77	14	6
Age for onset of the first words (months)	1,309	24	22
Age for onset of the first phrases (months)	1,007	40	18
Age for onset of daytime bladder control (months)	949	36	18
Age for onset of night-time bladder control (months)	750	36	12
CARS assessment age (years)	1,169	2.5	1
CARS score	1,162	34	10
ADI-R assessment age (years)	1,224	4.8	4
ADI-R score – Social interaction	1,367	20	11

ADI-R: Autism Diagnostic Interview™-Revised; CARS: Childhood Autism Rating Scale; IQR-Interquartile range.

Table 2 - Psychomotor development of patients with autism (n = 1,572)

	n	Median	Interquartile range (IQR)
Age of the first DQ assessment (years)	1,104	5.1	3.8
GDQ	1,275	68	42
QDL score	1,099	49	48
QDOM score	1,101	65	41
QDPS score	1,101	63	40
QDR score	1,101	73	48
Age of DQ reassessment (years)	227	7.3	1.8
Reassessed GDQ (reas)	227	79	39
Reas *QDL*	227	76	51
Reas *QDOM*	226	84	42
Reas *QDPS*	227	71	32
Reas *QDR*	227	84	38
Age of assessment of adaptive behaviour (years)	1,348	9.3	6.5
Adaptive behaviour – global score	725	59	26
Adaptive behaviour – autonomy score	726	62	25
Adaptive behaviour – communication score	726	62	33
Adaptive behaviour – socialization score	726	66	22

IQR: Interquartile range; DQ: Developmental quotient; GDQ: Global development quotient; *QDL*: Language development quotient; *QDOM*: Eye and hand coordination development quotient; *QDPS*: Personal-social development quotient; *QDR*: Performance development quotient; Reas: reassessment.

The 'age for onset of the first words' significantly correlated ($p < 0.05$) with all the variables for clinical assessment of autism, DQ and adaptive function, even though never beyond a 0.3 S coef.

Instead, the 'age for onset of first phrases' significantly correlated with ($p < 0.05$) all the variables for clinical assessment of autism, DQ and adaptive function. The values of S coef were over 0.3 and a negative association with GDQ (-0.35), *QDL* (-0.42) and adaptive function (communication [-0.41], socialization [-0.31] and global [-0.38]) was found. A positive association with clinical severity assessed by social interaction impairment in ADI-R (+0.33) and CARS total score (+0.30) was found.

Moderate and strong negative associations between the age for onset of first phrases and DQ at school age were found in the subgroup with reassessed DQ at school age, namely: reassessed (reas) GDQ (-0.52), reas *QDL* (-0.61), reas *QDOM* (-0.42), reas *QDPS* (-0.47) and reas *QDR* (-0.38).

The 'age for onset of daytime bladder control' significantly correlated ($p < 0.05$) with all the variables for clinical assessment of autism, DQ and the level of adaptive function, even though the highest values of S coef were obtained in a negative association with *QDOM* (-0.31) and *QDPS* (-0.31).

The 'age for onset of night-time bladder control' significantly correlated ($p < 0.05$) with all the variables for clinical assessment of autism, DQ and the level of adaptive function, except with reas *QDOM* ($p = 0.08$), reas *QDPS* ($p = 0.06$) and reas *QDR* ($p = 0.15$). Nevertheless, no value of S coef above 0.3 was found.

The 'age for onset of the first signs', significantly correlated ($p < 0.05$) with all the variables of clinical assessment of autism, DQ and adaptive function, except with reas GDQ ($p = 0.05$), reas *QDOM* ($p = 0.12$), reas *QDPS* ($p = 0.06$) and reas *QDR* ($p = 0.10$). Values of S coef over 0.3 were obtained in a negative association with CARS (-0.38) and positive with QDG (+0.34), *QDL* (+0.31), *QDOM* (+0.32) and *QDPS* (+0.30).

Subgroups of clinical severity of autism

Kruskall-Wallis test was used for the analysis of six early neurodevelopmental milestones in the three subgroups of autism according to total CARS (mild, moderate and severe autism). The analysis of the results allowed for the conclusion that at least one subgroup of severity was significantly different from the other two (Table 3).

As Kruskall-Wallis test rejected the null hypothesis, Mann-Whitney's test was used between the three subgroups of severity regarding the age for onset of each early neurodevelopmental milestone, in order to determine whether only one subgroup is significantly different from the remaining two or all subgroups show significant differences between them.

As regards 'age for onset of walking', 'age for onset of the first phrases' and 'age for onset of daytime bladder control', the subgroups showed significant differences between them ($p = 0.00$, for all the subgroups). Mean ranks for the subgroups are shown in Table 4 and allows for the conclusion that severe autism subgroup showed delayed onset of neurodevelopmental milestones, followed by moderate-severity subgroup and then by mild-severity subgroup showing earlier onset of milestones for brain maturity.

As regards the 'age for onset of the first words', the subgroups showed significant differences between them ($p = 0.00$ between mild and moderate-severity subgroups and between mild and severe subgroups; $p = 0.022$ between moderate and severe subgroups). Mean ranks are shown in Table 4 and allow for the conclusion that severe subgroup showed delayed onset of the first words, followed by moderate and by mild-severity subgroup showing earlier onset of this neurodevelopmental milestone.

Regarding the 'age for onset of night-time bladder control', mild and moderate-severity and mild and severe subgroups showed to be significantly different ($p = 0.00$). Instead, moderate and severe subgroups did not show significant differences ($p = 0.087$). Mean ranks are shown in Table 4 and allow for the conclusion that severe, moderate and mild-severity subgroups show progressively lower ages for onset of night-time bladder control.

The 'age for onset of the first signs', the comparisons between mild and moderate, mild and severe, moderate and severe subgroups showed to be significantly different ($p = 0.00$, for all comparisons). Mean ranks showed earlier onset of the first signs in the severe subgroup, followed by moderate and by mild-severity subgroups.

DISCUSSION

Autism or ASD is a neurodevelopmental chronic disorder with early clinical manifestations mostly presenting before the age of two.

Onset of motor skills, which classically did not associate with cognitive development, has proved to be affected in patients with autism.[22] In fact, onset of independent walking was delayed in toddlers with autism when compared to those with the same age and a typical development, in whom onset of walking occurs at the age of 12 months, on

Table 3 - Early neurodevelopmental milestones in the three severity subgroups of autism

	Age for onset of walking	Age for onset of the first words	Age for onset of the first phrases	Age for onset of daytime bladder control	Age for onset of night-time bladder control	Age for onset of the first signs
χ^2	55.588	30.745	58.876	50.988	27.056	125.687
p	0.000	0.000	0.000	0.000	0.000	0.000

Table 4 - Mean ranks of ages for onset of each milestone within each subgroup

	Autism severity	n	Mean rank
Age for onset of walking	Mild	205	430.30
	Moderate	481	517.98
	Grave	391	621.85
	Total	1,077	
Age for onset of the first words	Mild	201	386.60
	Moderate	460	478.43
	Severe	283	523.86
	Total	944	
Age for onset of the first phrases	Mild	187	291.95
	Moderate	395	376.87
	Severe	169	466.98
	Total	751	
Age for onset of daytime bladder control	Mild	159	265.29
	Moderate	348	358.47
	Severe	199	415.28
	Total	706	
Age for night-time bladder control	Mild	134	220.95
	Moderate	277	289.64
	Severe	148	315.42
	Total	559	
Age for onset of the first signs	Mild	194	641.76
	Moderate	442	568.94
	Severe	395	394.99
	Total	1,031	

average.[26]

An approximately 13-month (12.59) average age for onset of walking was found in toddlers with autism, according to the study by Iverson and Wozniak,[27] compared to 11.61 months in the control group. The onset of this milestone occurred at a median 14 months of age in our group of patients with autism. In fact, we may reach the conclusion that delayed onset of walking is associated with lower non-verbal intellectual skills, shown by the development of 'performance' and 'eye and hand coordination' sub-dimensions in our study, where a negative -0.35 and-0.33 S coef were found, respectively.

The age for onset of the first words in our group of patients showed scarce clinical relevance, unlike the age for onset of the first phrases, according to caregivers, that significantly correlated with all clinical variables of autism, psychomotor development and adaptive function. In fact, the delayed onset of first phrases was associated with higher autism severity, when assessed either by ADI-R's social interaction area (0.33) or by CARS score (0.30). Delayed talking showed as a moderate predictor of lower functioning in global adaptive behaviour (-0.37), autonomy (-0.30), communication (-0.41) and socialization (-0.31). In line with our results, Yang and Jong[28] found that lack of speech in children with autism and six years of age predicts a severe restriction in adaptive function in adulthood. These authors also found that cognitive and communication skills in children with autism at school age are the most valuable outcome variables. In a follow-up study with a population of patients with autism, Howlin *et al.*[29] found that the association of autism with language impairment showed worse outcome in adulthood.

The age for onset of first phrases was also shown as an early milestone of intellectual skill in pre-school age. In fact, the association between the age at which children use two-word sentences and the future verbal and non-verbal intellectual skills, assessed through GDQ and sub-dimensions of language, eye and hand coordination, personal-social and performance, showed moderate negative correlations in pre-school age and strong

correlations in school age. The conclusion that delayed onset of first phrases is associated with lower verbal and non-verbal intellectual skills in pre-school and mainly in school age became a very relevant information in clinical history (Fig. 1 and 2). Johnson *et al.*[30] found similar results in a group of 244 patients, where delayed onset of talking in early ages were associated with cognitive impairment in adulthood.

The age for onset of daytime bladder control showed to be a clinically useful milestone. We found that delayed onset of daytime bladder control is associated with lower intellectual skills. Some studies[31,32] in children with autism associated the successful onset of sphincter control (daytime and night-time bowel and bladder control) with the intellectual skills and reached similar conclusions.

Unlike the previous milestone, the age for onset of night-time bladder control, even though significantly correlated with almost all studied variables, did not show as a clinical data with outcome value. Dalrymple and Ruble[32] compared the age for onset of night-time bladder control by dividing the group of patients into subgroups based on cognitive and language skills and found that patients with lower cognitive levels and lower verbal skills had significantly delayed onset of this milestone.

In autism, as in other neurodevelopmental disorders, the more severe forms have earlier onset. The age for onset of the first signs showed a moderate negative correlation with global severity of autism, showing that the more severe presentations have earlier onset, allowing for an easy identification by patient's caregivers.

The age in which autism presentation is obvious for caregivers relates with child's cognitive skills. In fact, we found a positive correlation between the age for onset of the first signs and the GDQ values (0.34) and sub-dimensions of language (0.31), eye and hand coordination (0.32) and personal-social (0.30), showing that the earlier the onset, the lower the cognitive skills. De Giacomo and Fombonne[33] reached the same conclusion in a study showing that cognitive skills strongly correlates with the age for onset of first signs. Baghdadli *et al.*[34] also found a statistically significant correlation between cognitive skills and the age for onset of the first signs.

Based on CARS scores of clinical severity, the three subgroups in which we divided our group of patients were significantly different as regards the age for onset of psychomotor basic developmental skills, as well as regarding early onset of the disease. Children in the higher severity subgroup had delayed onset of walking, talking and sphincter control, unlike those in mild severity subgroup; those in moderate severity subgroup were between these two extreme ranges (Fig. 3).

As expected, the 'age for onset of first signs' occurred earlier in the severe subgroup (15-month median age) and was delayed in the mild subgroup (24-month median age). These results are in line with the study by Baghdadli *et al.*[34] in which the group of patients with autism was split into two subgroups (first signs before and after the age of 18 months) and found that those with the onset of the first signs before the age of 18 months were associated with lower cognitive skills and adaptive behaviour and higher clinical severity of autism.

CONCLUSION

Our study enhances the relevance of careful clinical records as regards the age for onset of psychomotor developmental milestones as crucial elements for natural history of autism, as these are associated with the specific clinical presentation of autism, as well as with cognitive skills and adaptive functioning, mainly in school ages. We may therefore reach the conclusion that the age for onset of the first sentences is a very relevant clinical milestone in children diagnosed with autism. Therefore, even though traditionally less valued and used than the age for onset of the first words, we strongly recommend to all healthcare professionals dealing with these children the additional record of the age for onset of the first sentences. In fact,

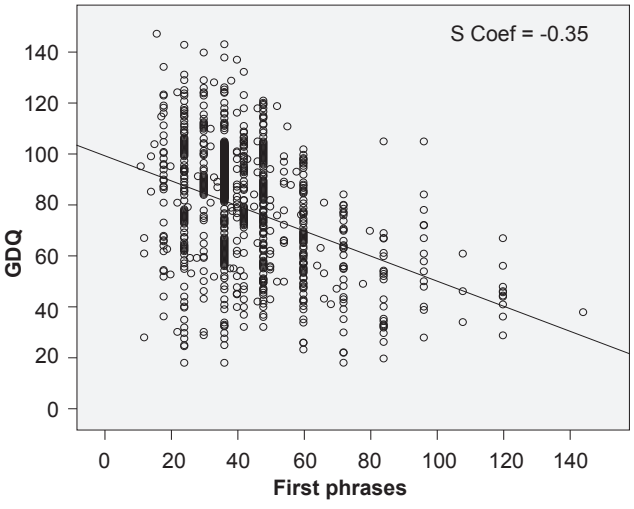

Figure 1 - Linear relationship between the age for onset of the first phrases and GDQ assessment in pre-school age.

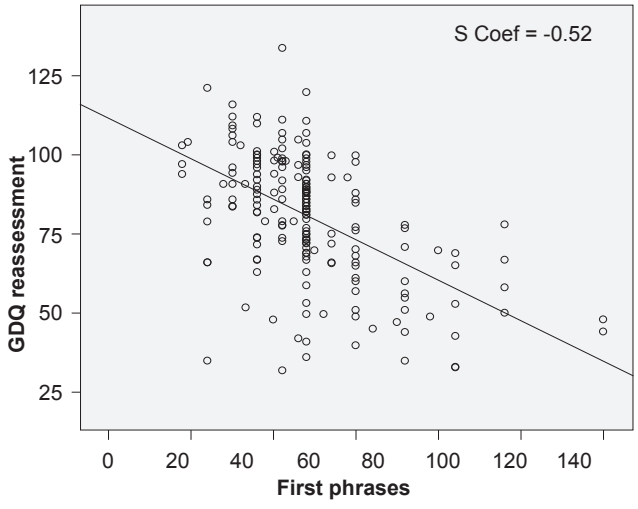

Figure 2 - Linear relationship between the age for onset of the first phrases and GDQ reassessment at school age.

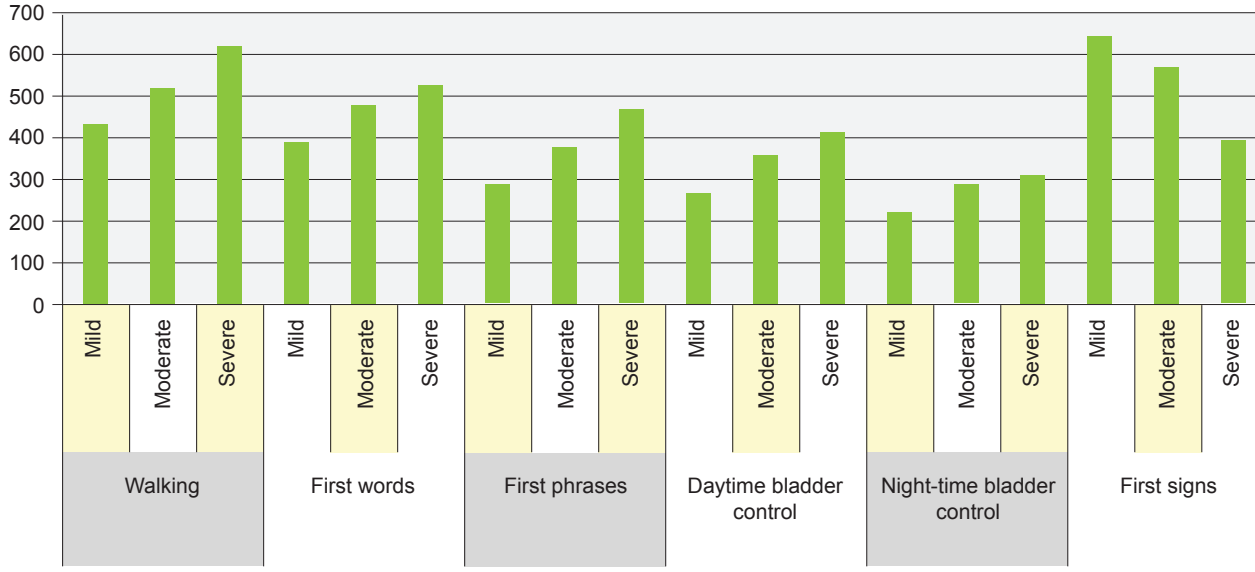

Figure 3 - Mean ranks of ages for onset of each milestone within each subgroup (based on global clinical severity of autism, assessed by CARS).

its early presentation is associated to best intellectual skills and adaptive functioning in school age and to lower specific clinical severity of autism.

One of the major limitations of our study was the fact that the information regarding the presentation of early neurodevelopmental milestones was obtained by caregivers based on their memory and therefore eventually inaccurate. However, the large number of patients in the study and data systematically obtained by experienced physicians will reduce this inaccuracy.

Clinical accuracy of diagnosis and assessment, the dimension of our group of patients and the significant results with relevant clinical association between language skills, clinical severity of autism and intelligence in school age may be considered as strengths of the study.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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