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Predictors in Outcome of Children with Autism Spectrum Disorder

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Abstract

Introduction: It has been studied that very early intervention may help improve neurodevelopmental disturbances arising from impoverished socio-emotional interactions in the first years of life, however, there is still a lack of knowledge regarding developmental prognostic indicators.

Objectives: With this study we aimed to investigate developmental trajectories of children with Autism Spectrum Disorders in order to identify predictive prognosis factors.

Methods: We examined clinical features of 55 children with Autism Spectrum Disorders, in two moments of evaluation, with an interval of three years. They were assessed with the Childhood Autism Rating Scale and with Autism Diagnostic Observation Schedule as a symptom of severity measure, at both moments, and with Ruth Griffiths Scale to evaluate developmental profile. We selected two groups, based on the results obtained at moment 2. We also selected questions from a questionnaire to parents in order to understand if early parents' concerns can predict prognosis.

Results: Over time, the number of worse cases decreased significantly. We found a strong correlation between Personal Relation ($r=0.798$, $p<0.001$), Imitation ($r=0.622$, $p<0.001$) and Verbal ($r=0.730$, $p<0.001$) and non-verbal communication ($r=0.699$, $p<0.001$) and the score obtained in the second evaluation. Also, Interactive gestures, Joint attention, Reciprocity and Pleasure in interaction obtained strong correlations with the final scores.

Discussion: Personal Relation, Imitation and both verbal and non-verbal communication, as well as Interactive gestures, Joint attention, Reciprocity and Pleasure in interaction may have a good predictive value in the development of children with Autism Spectrum Disorder.

Keywords: Autism Spectrum Disorder (ASD); Development; Predictors

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Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM 5), describes Autism as a Developmental disorder characterized by severe and pervasive impairment in several areas of development, including reciprocal social interactive skills, communication skills and stereotyped behaviour, interests and activities.

ASD (Autism Spectrum Disorders) includes Autistic disorder, Asperger Syndrome and Pervasive Developmental Disorders not

otherwise specified (PDD-NOS) that were considered different diagnosis subtypes, in DSM-4 but they are not individualised in DSM-5. It is difficult to predict the evolution in early childhood. A marked impairment in emotional competence and social interaction is extremely noted because emotions are essential to regulate social interactions which, in turn, influence emotional development. Social-affective engagement has far reaching developmental repercussions, and there is a substantial body of experimental research suggesting that not only do children with ASD express emotions differently, but also there are autism-

specific deficits in emotion perception and understanding [1]. There are no consistent indications of a relationship between emotional competences, social competences and ASD subtypes [2]. However, it would be interesting to study some of these features with reliable instruments in order to define prognosis, in early stages [3].

During the second and third years of life, symptoms of autism usually intensify and spread to multiple areas of functioning. While typical infants undergo a remarkably growth in social, communication and imaginative play competence, infants with autism show syndrome-specific difficulties in these areas [4,5]. Developmental theory links imitation and play and these two areas of difficulty may represent a core impairment in ASD and can help to discriminate children with ASD from other disabilities from a very early age [6].

A deficit in the development of joint attention is also one of the earliest symptoms of autism [7]. Charman [8] demonstrated that early joint attention and imitation, measured at 20 months were related to social and communication evaluated with Autism Diagnostic Interview Revised (ADI-R) at 42 months. It has also been found that initial IQ and language at age 6 were associated with the Adaptive Behaviour composite score of the Vineland Adaptive Behaviour Scale (VABS) [9] at age 14. Charman [8] demonstrated that there were many significant associations between Non-verbal IQ language and ADI-R, reciprocal social interaction and Non-verbal Communication scores, at age 3, and communication and socialization scores of VABS, at age 7.

Very early intervention may help not only to improve existing difficulties but also to prevent or attenuate subsequent neurodevelopmental disturbances arising from impoverished socio-emotional interactions in the first years of life [10]. Unfortunately, early diagnosis and specific strategies related to early intervention in ASD still constitute an enormous and complex puzzle. Can imitation and play be related with joint attention and emotional and social skills? Could those features be used as predictors to define subtypes and prognosis in ASD? Understanding the nature and timing of symptoms may be of critical importance to predict developmental trajectories within ASD and contributes to early diagnosis and intervention planning [11].

In order to understand some aspects that can predict different developmental trajectories in children with ASD, this study examined clinical features of 55 children with ASD who were reevaluated 3 years later, comparing the best outcome group and worse outcome group, with different instruments.

Objectives

The current study investigates developmental trajectories of two child groups with ASD with an interval of three years. We also tried to find out in what areas children that presented the best outcomes differed from children with worst outcome, in order to understand predictive factors so that we can adjust better intervention strategies.

Participants and Procedure

A total of 55 children with ASD (46 males and 9 females) were included in this study at 3 years old and reevaluated at 6 years. The children were recruited from a child Psychiatric consultation in a General Hospital in the city of Porto, Portugal.

The mean age of the girls at the time of the first evaluation was 3.4 years; mean age on the second evaluation was 6.5 years, and boys' mean age at the time of the first evaluation was 3.8 years and 7.3 years at the time of the second evaluation. Diagnosis of ASD was originally given by independent clinicians (psychiatrist, paediatrician and psychologist) with many years of experience. DSM-5 was used for diagnosis at the time sampling around 2 years of age.

All children were evaluated with Childhood Autism Rating Scale [12] and met criteria for autistic disorder. We included only children with CARS ≥ 30 because this is considered the distinctive value between ASD and normative development. All children were also evaluated with Autism Diagnosis Observation Schedule [13] as a symptom of severity measure and with Ruth Griffiths Scale as a measure of developmental profile. We also gave parents a questionnaire with some questions about their first concerns related to their children in order to understand if that may predict evolution in some way. All children were reevaluated 3 years later with CARS and ADOS and we selected two groups, with best and worse outcome, based on the global results of CARS and ADOS at moment 2. Worse outcome group had CARS above 36 and ADOS above 8. At moment 2, the worse outcome group had 6 girls and 20 boys and 3 girls and 26 girls in the best outcome group. All the children had some kind of intervention at least 4 hours per week and they had no associated co-morbidity (which was an exclusion criteria). It was not the purpose of this study to evaluate the type of intervention and the use of medication was not considered in this study. In order to identify potential prognosis predictors, we decided to investigate the correlation between some variables in ADOS and CARS at the first evaluation and the global results at second evaluation. We selected the variables that were more relevant according clinical features and literature [4-8] Social Relation, Communication, Imitation (in CARS) and Joint (or Shared) Attention, Reciprocity, Interactive Gestures and Pleasure in Interaction (in ADOS). We also investigated potential correlations with the parents.

Instruments

The Childhood Autism Rating Scale (CARS) [12] helps to identify children (2 years and older) with Autism, specifically, distinguishing them from developmentally impaired children who are not Autistic. In addition, it distinguishes between mildly-to-moderate and severe Autism. Its brevity makes it a very useful tool to help you recognize and classify Autistic children. The scale assesses behavior in 14 areas usually affected in autism, and a more general category of impression of autism.

These 15 items include: Relating to People, Imitation, Emotional response, Body Use, Object Use, Adaptation to Change, Visual Response, Listening Response, Taste, Smell, and Touch Response

and Use, Fear or Nervousness, Verbal Communication, Nonverbal Communication, Activity Level, Level and Consistency of Intellectual Response, General Impressions. The scores for each domain range from 1 (within normal limits) to 4 (severe autistic symptoms). The score ranges from 15 to 60, and the cut off point for autism is 30 (15-30-Non-autistic; 30-37- Mildly-Moderately autistic; 37-60-Severely autistic).

The Autism Diagnostic Observation Schedule (ADOS) [13] is an instrument for diagnosing and assessing Autism. The protocol consists of a number of structured and semi - structured tasks which involve social interaction with the examiner so that he can assign subject's behaviour and relate it with predetermined observational categories and quantitative scores related with ASD.

Both ADOS and CARS are not validated for the Portuguese population, however, due to the cultural transversality of the behaviours evaluated, its validations have not been found as imperative. All the evaluations were conducted by accredited psychologists with an ADOS specialization (from the University of Barcelona), strictly following the authors instructions.

Parents' questionnaire consisted in a semi-structured interview, based on clinical features, with 30 questions (open and closed) to understand parents' perspective, about the moment of concern, type of concern, supports involved and child's evolution. We only studied the answer to closed questions (yes or no) about specific symptoms like: Social Impairment, Communication (verbal and not verbal), Imitation and Playability, in order to identify some potential prognosis predictors.

Results

Statistical analyzes were performed using the SPSS program. The data were described in proportions in the case of categorical variables and in means and standard deviations in the continuous variables with normal distribution. The Fisher Exact test was used to test the significance of the associations, the Pearson and Spearman test for the correlations between the variables and Logistic and Log-Linear Regressions. All analyzes had the 0.05 level of significance.

Over time there's a tendency for a better prognosis, the total mean of the second evaluation are statistically lower than the ones on the first evaluations, as the total mean statistically decreases (**Table 1**) and the percentage of worst cases declines from 56.4% to 32.7% in the CARS evaluation and from 96.4% to 52.7% in the ADOS evaluation. This positive tendency justifies a more detailed study of the variables that are the main potential prognosis predictors.

CARS – QI Personal Relation (PR)

On the first evaluation, 83% of the cases with results higher than 2 on the Personal Relation question had a total score higher than 36 on CARS, which reveals a significant association between this item's score and the final result ($\chi^2=17.18$, $p<0.001$).

On the second moment, only 59% of the children with a result higher than 2 on this item had a total CARS score higher than

Table 1: Means and standard deviation of the totals obtained in CARS and ADOS on both evaluations (moments 1 and 2).

	Mean (SD)	
Total CARS 1	36.62 (3.541)	<0.001
Total CARS 2	33.78 (2.724)	
Total ADOS 1	11.29 (3.588)	<0.001
Total ADOS 2	8.58 (2.14)	

36 on the second evaluation. Even if the effect is lowered, the association maintains its statistical significance ($\chi^2=18.75$, $p<0.001$) with a correlation between the result of QI on the first evaluation and the total of the second evaluation ($r=0.798$, $p<0.001$).

CARS - QII Imitation

At the first moment of evaluation, only 19% of the cases with results greater than 2 in the QII item obtained a total score higher than 36, representing, therefore, a bad predictor of the total obtained in the same moment of evaluation, without statistical significance of the relation ($\chi^2=1.61$ $p>0.05$). However, the association between the results obtained in this item and the total score becomes stable over time, and a statistically significant association was observed between the results of the QII in the first moment and the total of the CARS in the second moment ($\chi^2=5.93$ $p<0.05$). It was verified that 29% of the total number of children with a CARS total score higher than 36 at the second evaluation had a result higher than 2 in the imitation item at the first moment of the evaluation. Also, the correlation verified between the results obtained in the Imitation item and the total score of CARS is higher in the total scores of the second evaluation ($r=0.622$, $p<0.001$), than in the total scores obtained in the first evaluation ($r=0.601$, $p<0.001$), although both with statistical significance.

CARS - QXI Verbal Communication

At the time of the first evaluation, 68% of the cases with scores greater than 2 in the Verbal Communication question, obtained a CARS total score higher than 36, revealing a significant association between the score of this item and the final score ($\chi^2=17.25$, $p<0.001$).

The effect of the result obtained in this item of the CARS on the total of worse cases is greater in the second moment of evaluation, with 82% of the results superior to 2 in the verbal communication item (QXI) in the cases with total CARS score >36 in the second moment of evaluation. As expected, the association remained significant ($\chi^2=15.36$, $p<0.001$), with a significant correlation between the result at QXI at the first assessment time and the total at the second assessment time ($r=0.730$, $p<0.001$).

CARS - QXII Non-verbal Communication

Regarding Non-verbal Communication, 64% of the cases with results greater than 2 in this item, obtained a total superior to 36 in the CARS total, on the first evaluation, with a significant

association between the result to this question and the final result ($\chi^2=10.72$, $p<0.001$). This association increases in intensity over time, with a total of 82% of the total results exceeding 36 in the second evaluation having had results higher than 2 in the Non-verbal Communication item at the time of the first evaluation.

The association is statistically significant ($\chi^2=13.75$, $p<0.001$), as well as the correlation between the responses to this item in the first moment and the total score in the second moment ($r=0.699$, $p<0.001$).

CARS - general analysis

All items of the scale have significant inter-item correlation values, with Pearson coefficients always higher than 0.842 and $p<0.001$. Each of the items explains a variance of more than 50% of the total result of the CARS in the second moment of evaluation, and there is also a significant interaction between the Personal Relations item and the Imitation item, as well as between the items Verbal Communication and Non-verbal Communication.

Thus, the formula that best explains the total result of CARS in the second moment of evaluation is: $CARS\ Total\ (moment\ 2) = \beta_0 + \beta_1\ Personal\ Relationships + \beta_2\ Imitation$, corresponding to the following: $CARS\ Total\ (moment\ 2) = (2.04)\ Personal\ Relations + (2.11)\ Imitation - 24.15$ (Table 2).

Since there is a significant increase in the R^2 of items XI and XII when calculated together, their importance is shown to be statistically significant and they are also significant predictors of the total result of CARS in the second moment, however their presence in the linear regression model does not improve it.

ADOS

In the ADOS evaluation, the relationship between the score in the first evaluation and the total score in the second evaluation was marked in the interview process carried out with the parents: Beginning of Shared Attention and Pleasure in Interaction.

Regarding the item of Shared Attention, it was verified that it does not have a significant impact on the total score of the first evaluation, with only 51% of the results above 0, and with a Fisher test with $p>0.05$.

However, this association becomes significant over time, presenting as an important indicator of good prognosis for the second evaluation. Only 19% of the children with a null score in

this item in the first evaluation, had a total of over 8 at the time of the second evaluation ($\chi^2=17.46$, $p<0.001$).

Regarding the Pleasure in Interaction item, we observed a similar phenomenon, with no statistically significant association between the result of the item in the total score of the first evaluation and 56% above 0 score, but with the association gaining robustness over time, with a $\chi^2=23.21$, $p<0.001$, in relation to the total of the second evaluation, where only 8% of the results equal to 0 in this item at the time of the first evaluation had a total score higher than 8 at the time of the second evaluation.

ADOS-General Analysis

Both items correlate significantly with the ADOS total in the second moment of evaluation, representing the item Pleasure in Interaction a more robust predictor.

Although we did not find a statistically significant association between the items Interactive Gestures and Reciprocity in the total of the second ADOS evaluation, we can speculate that this is due to limitations related to sample size, because also in these variables we can observe significant correlations both item- item as total item, as we can see in Tables 3 and 4.

Parents' questionnaire

A semi-structured interview with several questions in which you have open and closed questions of simple answer about socialization, imitation, language and play, was administered to parents and these were analyzed. It was found that the parents who identified earlier changes correspond to the cases with worse evolution (CARS above 38), before the child's one year of age. In the milder cases, parents cared more about the difficulty in speaking or socializing, from the age of 2 years. In all cases there was essential concern with language and socialization (the answer yes means there is an inadequate behavior). The results are in agreement with the data identified in the clinic and in the ADOS. It was verified that the milder cases did not show obvious limitations at 2 years, either in imitation ability or pleasure in playing with the adult.

In the questionnaire applied to the parents it is possible to verify two indicators with a significant association with the CARS and ADOS evaluation in the second moment: Imitation and Play, as can be seen in Table 5. Thus, parents' perceptions on the child's behaviour seem to be better with lower instrument scores.

Also, the correlations between these dimensions and the total of CARS and ADOS are shown to be statistically significant (Table 6).

In the logistic regression, the Omnibus test presents statistically significant results, thus confirming the predictive value of these variables in the total result of CARS and ADOS in the second moment of evaluation. The Hosmer and Lemeshow test presents the value of $X^2=0$ and $p=1$, confirming the importance of the Imitation and Playability variables as predictors.

Discussion

High stability has been found for clinical diagnosis made by expert professionals, supported by standard criteria for ASD, as reported

Table 2: Effects of individual items (first evaluation) in CARS total (second evaluation).

Variables	R ²	F	Standard error	p<0.001
Personal Relation (PR)	0.637	89.57	1.67	
Imitation (I)	0.658	100.24	1.61	
Verbal Communication (VC)	0.533	56.31	1.88	
Non-verbal Communication (NVC)	0.579	71.41	1.79	
RP × Imitation	0.701	60.49	1.51	
VC × NVC	0.611	40.11	1.73	

Table 3: Correlation values between the results of the first evaluation in the identified items and the total of the second evaluation.

Item	Total ADOS 2	Joint attention	Pleasure in interaction
Total ADOS 2	1	0.683**	0.770**
Joint Attention	--	1	0.739**
Pleasure in interaction	--	--	1

** p<0.001

Table 4: Pearson's correlation values between the results of the first evaluation and the total of the second evaluation.

Variables	Interactive gestures	Joint attention	Reciprocity	Pleasure in interaction	TOTAL ADOS 2
Intructive gestures	1	0.597**	0.728**	0.648**	0.688**
Iniciate Joint attention		1	0.707**	0.739**	0.683**
Reciprocity			1	0.732**	0.744**
Pleasure in interaction				1	0.770**
Total ADOS 2					1

** p<0.001

Table 5: Frequency of results in percentage, by total of CARS and ADOS in the second moment of evaluation.

Variables		CARS			ADOS		
		>36	<36	χ ²	>8	<8	χ ²
Imitation	Adequate	50.00%	89.20%	p<0.05	56.00%	93.10%	p<0.05
	Inadequate	50.00%	10.80%		44.00%	6.90%	
Play	Adequate	31.30%	75.70%	p<0.05	36.00%	82.80%	p<0.05
	Inadequate	68.80%	24.30%		64.00%	17.20%	

Table 6: Spearman correlation values between the results of the first evaluation and the total of the second evaluation.

Variables	ADOS	CARS	Imitation	Playability
ADOS	1	0.766**	0.555**	0.585**
CARS	--	1	0.428**	0.408**
Imitation	--	--	1	0.706**
Play	--	--	--	1

** p<0.001

in another studies [13,14]. The best outcome group had better scores on all items in first and second evaluation which may have a predictive value. In the worse outcome group we found always severe impairment in socialization and communication, but we also found impairment in Playability and Imitation, in moment 1, which was a different result from the best outcome group.

We found a correlation between Imitation, Communication and Personal Relations, on the first evaluation with CARS and the best outcome group. These findings are similar to other studies. Charman [8] demonstrated there were many significant associations between language and ADI-R Reciprocal Social Interaction and Non-verbal Communication scores, at age 3, and VABS Communication and Socialization domain scores at age 7.

In the present study we also found that CARS seems to have a good predictive value in the development of children with ASD. This predictive value is more evident on Imitation and Personal Relations. However, its predictive power is weaker for the earlier development, at the time of diagnosis and more pronounced in the later development of those areas. CARS seems to be a reliable instrument to predict ASD trajectories.

The results from our study suggest study that the level observed in Personal Relations, Imitation, Communication-Verbal and Non-Verbal Communication, in CARS, and Interactive Gestures, Beginning of Shared Attention, Reciprocity and Pleasure in Interaction in ADOS, in the initial contact with the children, might help to identify developmental trajectories, namely of a favourable prognosis, for children with lower scores in the identified items, independently of the total obtained in the scale.

In this study, parents' Imitation and Playability perceptions of the child are also robust possible predictors of favourable developments. Few studies have evaluated the relationship of early parental concerns with prognosis. A recent study [15] emphasizes the importance of early parental concerns with certain early behaviours that may have predictive value in the diagnosis of ASD. Sacrey [14] draws identical conclusions through a study in which a questionnaire was applied to parents of children at risk of ASD, all of whom were evaluated at 3 years to identify the highest and lowest risk. The study emphasizes that in high-risk cases parents identified early sensory and motor changes before 6 months. In cases of lower risk, the concern was more related to language or socialization and only after 1 year of age.

These data point to the need to evaluate such items considering the information given by the parents and the observation in consultation, which is often more valuable than conducting a lot of expensive tests. It also draws attention to the need and advantage of having screening tests at paediatric and family doctor visits, to detect early warning signs and to provide timely guidance to at-risk children and their parents.

Landa [10] enhanced that evidence suggests that young children with ASD benefit with early intervention and programs to teach parents to implement child-interaction strategies with a parent-coaching supervising.

According to Vivanti [16] response to early intervention in autism is variable and reflects the need of reporting data about the association between predictor and outcome variables because we know so little about this. We need reliable instruments to measure what is related to adaptive capacities and educational strategies and to evaluate previous family structure and resources in order to understand outcome.

Cohen [3] studied a retrospective analyse of the trajectories of adaptive skills and severity symptoms in ASD subgroups and confirmed prediction that each subgroup had different trajectories that varied with the type of adaptive behaviour assessed with ASD-DT (Decision Tree based on ASD Inventory) suggesting that this instrument may have a prognostic value useful for clinical application.

Based on these results, together with the data from the literature highlighting the importance of the early development of social competencies [1,4,5,7], we can conclude that early diagnosis and intervention is urgent and that integrating parents'

contribute throughout the process is essential. From our clinical experience, we observe that when the parents are involved from the beginning, with acceptance and adequate understanding of the diagnosis, the whole intervention runs better and more successfully. These findings may be useful to implement parent training interventions that help parents interact and communicate with their toddlers with ASD. This might be a good alternative to promote the development of their child's social and communicative skills [10,17].

Conclusion and Limitations

Further investigation is necessary in order to replicate results and to develop more reliable instruments to define subtypes and prognosis, in early stages. One limitation of this study is that sample is very small with a heterogeneous group of children, meeting different profiles, although they are all included in ASD, confirmed by clinical observation, on moment 1 and moment 2. Female patients are under-represented. It could be useful in further investigation, with a larger sample, to add another instrument in second evaluation to compare the results, in order to make a correlation with possible predictive elements. Also, this study did not evaluate the effect of intervention on the outcome of groups. It could be interesting in future studies to analyze controlled variables related to family resources and type of intervention. Evaluations represent a particular moment in time, and this needs to be taken into consideration when interpreting and generalizing results. Further investigation is necessary in order to replicate results and to develop more reliable instruments to define subtypes and prognosis in early stages.

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