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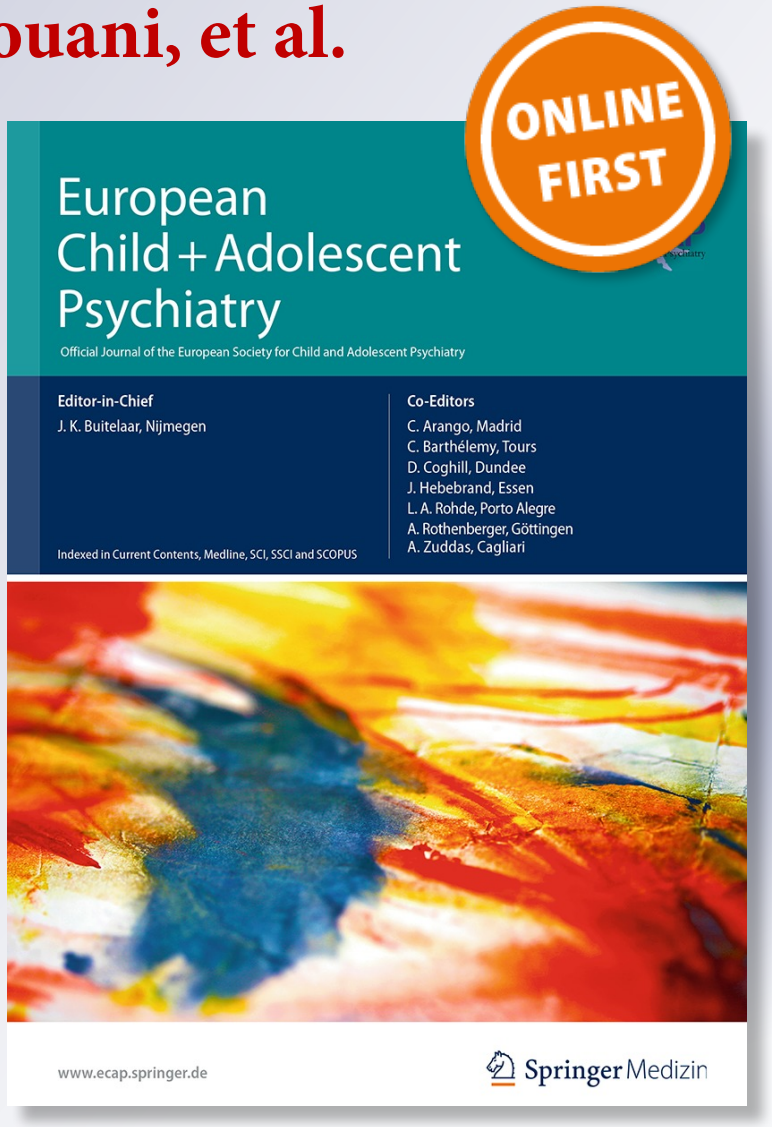

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ORIGINAL CONTRIBUTION

Infant's engagement and emotion as predictors of autism or intellectual disability in West syndrome

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Abstract West syndrome (WS) is a rare epileptic encephalopathy with early onset and a high risk of autistic outcome. The *PréAut* grid assesses this risk following WS onset by taking into account synchrony and emotion in interactions and by evaluating the baby's active desire to engage in pleasant interactions (especially the infant's early active behaviors that encourage being gazed at or kissed by the mother or to share joy with her). We followed a sample of 25 WS patients prospectively from disease onset and assessed whether the *PréAut* grid before 9 months, and the checklist for autism in toddlers (CHAT) at 18 and 24 months predicted autism or intellectual disability (ID) outcomes at 4 years. We found that the *PréAut* grid at 9 months (sensitivity = 0.83; specificity = 1) had similar prediction parameters as the CHAT at 18 months (sensitivity = 0.90; specificity = 0.83) and 24 months (sensitivity = 0.92; specificity = 1). WS patients with a positive *PréAut* screening at 9 months had a risk of having autism or ID at 4 years, which is 38 times that of children with a negative *PréAut* grid [OR = 38.6 (95 % CI 2.2–2961); $p = 0.006$]. We conclude that the *PréAut* grid could be a useful tool for the early detection of autism or ID risk in the context of WS. Further research is needed to assess the *PréAut* grid in other contexts (e.g. infants at high-risk for non-syndromic autism).

Keywords Autism · Intellectual disability · West syndrome · Outcome · Risk assessment

Introduction

Autism is a developmental syndrome that involves impaired social interaction, impaired communication, and stereotypies or restricted interests. Despite evidence that

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some symptoms of autism spectrum disorder (ASD) are present early in life [1], autism diagnosis is generally made between 3 and 5 years of age [2]. Delays in diagnosis are not only constrained by a shortage of specialist services, but also by clinical and developmental limitations regarding infant/toddler assessment. Research based on retrospective parental reports, family home movies, and prospective studies using high-risk samples, has identified specific early signs that predict the early diagnosis of autism [3–5]. These domains included atypical social interaction (atypical eye gaze, absent orientation to name, poor imitation, absent social smiling, reactivity, atypical social interest and affect, reduced expression of positive emotion), impaired language, motor problems, reduced play, and impaired cognitive development [6]. However, Rogers [7] noted a lack of predictive symptoms at 6 months of age. This circumstance is unfortunate, as recent studies have indicated early diagnosis and intensive developmental and behavioral treatments may improve outcome [8]. Considering the subtlety of the early symptoms, interest is currently growing in the conception of elementary tools that can be used by doctors and general health personal within the framework of systematic exams of infants and young children.

Various studies have attempted to develop such screening tools. Such studies face several challenges. First, when such studies deal with general population samples, they often cannot assess the sensitivity and specificity of the tool because they generally only assess children who have screened positive and do not capture false negatives. These studies estimate the accuracy through a positive predictive value (calculated from the observed false-positive rate) and try to approach sensitivity through the lag between observed and theoretical prevalence rates [9]. Second, studying high-risk samples allows for easier tracking of false negatives. However, properties of screening instruments to differentiate ASD with other developmental diagnosis are not assessed. In addition to the accuracy of the tool, very early screening involves another issue: the uncertain stability of ASD before the age of 2 years [10]. The initial diagnosis may change in various directions: suspected autism may evolve toward recovery or delayed development without autistic traits; conversely, late-onset autism may begin after an early screening. Currently, it is difficult to truly discriminate between a lack of accuracy in our current evaluations or a true scalability issue in ASD. Nevertheless, several instruments have been developed (for a review see [9]): the check list for autism in toddlers (CHAT); the communication and symbolic behavior scales developmental profile: infant-toddler checklist (ITC); the checklist for early signs of developmental disorders (CESDD); the baby and infant screen for children with autism traits (BISCUIT); the autism observation scale for infants (AOSI); the early screening of autistic traits questionnaire (ESAT); the social communication questionnaire (SCQ); and the first year inventory. To our knowledge, no published study has validated a screening tool for infants below 1 year of age. These facts highlight (1) that developmental milestones and early communication and social behaviors are not sufficient to determine first year infant developmental trajectories that will later be diagnosed as autism; (2) other proposals should be implemented within a clinical approach to improve very early screening.

From birth, infants experience many mental states during the day, including sound sleep, strong screaming, crying, and mindful and calm arousal periods in reaction to their social environment; these mental states are called "awareness". Maternal stimulation contributes to the modulation of awareness states and has cognitive implications, allowing the child to explore his family environment [11]. Early interactions are characterized by synchronies between infant and caregiver. The two partners reciprocally adapt using gaze, head, and hand position, and language [12]; typically, very young babies can take an active and leading role in these interactions [13]. A study of home movies of infants who will later develop autism showed that (1) studying synchronic and reciprocal behaviors between infant and caregiver was able to differentiate infants with a pathological development from typical developing infants as early as the first 6 months of life [14]; (2) parents tried to engage with more emotional interactions with their children [15]. Recently, the British Autism Study of Infants' Siblings reported that early dyadic interaction and reciprocity between at-risk infants and their parents were associated with later diagnosis of autism [16]. Therefore, the early detection of autism should benefit from the concepts of synchrony and early reciprocity, as well as from emotional engagement during interaction [12]. The *PréAut* grid was based on the hypothesis that babies who are at risk for autism could be lacking an innate need to interact and to be a source of pleasure for the person with whom they are interacting. Thus, to better determine behavioral dysfunction in infants who will later develop autism, the *PréAut* grid evaluates the baby's active desire to engage in synchronous joyful interactions [17].

The current study assesses *PréAut's* ability to predict ASD in at-risk infants with West Syndrome (WS, or infantile spasm). WS is a rare epileptic encephalopathy occurring early in life [18] and is caused by a brain abnormality or damage in 60–90 % of cases (e.g. Tuberous Sclerosis; lack of oxygen at birth) [19]. Fifty percent of children develop intellectual disability (ID) and/or ASD [20, 21]. Prognosis is influenced by the etiology; the "treatment lag" between the appearance of spasms and the treatment onset; previous developmental or neurological

impairments; the age of spasm onset; the persistence of EEG hypsarhythmia; the presence of other types of epilepsy, and the response to treatment [22]. Given the risk of ASD, WS defines a high-risk group. We prospectively followed 25 infants with WS from disease onset until 4 years of age. We assessed whether the *PréAut* grid at 9 months and the CHAT at 18 and 24 months predicted ASD or ID outcomes at 4 years of age.

Methods

Design and participants

We recruited all cases from the Neuro-pediatrics Department Center for Rare Epilepsia of Necker Enfants-Malades Hospital, Paris, from November 2004 to March 2010. Inclusion criterion was as follows: child presented with WS. Exclusion criteria were as follows: early severe encephalopathy with extremely severe developmental delay; parents' refusal to consent to follow-up assessment and/or to the research protocol, or families who lived too far from the hospital. The Institutional Review Board (Comité de Protection des Personnes from the Groupe-Hospitalier Necker Enfants Malades) approved the study, and both parents gave written informed consent after they received verbal and written information on the study.

Of the 34 children screened in the unit during the study period, 32 were potentially eligible for participation, as they met the inclusion criteria and consented to be enrolled in the study. Seven patients dropped out before the age of three. Figure S1 (supplement online) summarizes the timing of inclusion (according to disease age of onset) of all children that were maintained until 4-year follow-up. Despite the severity of the condition and the distance from the hospital of several families, a small percentage of patients (21 %) was lost during the 4-year follow-up thanks to the close relationship between the neuro-pediatrics staff and the families.

Outcome measurements

Risk of ASD was assessed at 4 and/or 9 months with the PREAUT grid and at 18 and 24 months with the CHAT. Development of the *PreAut* grid was derived from the observation of babies who will later be diagnosed with autism through family home movies: they do not spontaneously search to engage in pleasant interactions with others. Items were formulated to highlight this lack of social initiative (infant's early active desire to be gazed at by his/her mother or to share happy moments with her). The first part of the grid includes four items, and the second part includes six complementary items that are completed only if the baby shows at-risk behaviors after the first four questions. The following two principles are important: (1) the more the infant is emotionally engaged during an interaction, the more the score increases; (2) a judgment of whether the baby is able to lead and engage in a reciprocal interaction is included in all questions, as this factor is considered to be essential for defining normal interactions. Babies are scored as "positive" if they do not spontaneously look at the observer, do not spontaneously elicit the gaze of their mother (or their other significant caregiver), and do not provoke positive reactions from their mother (or their other significant caregiver). Afterwards, a classification of responses based on a binary decision tree was used to determine the scores of each item to put the total score of infants without any social initiative below a cut-off of three. The *PréAut* grid and tables summarizing the principle of notation are presented in Annex S1 (supplement online). Depending upon WS age of onset, the *PréAut* grid was assessed either at 4 months ($N = 4$) and/or at 9 months ($N = 18$). Twenty infants had at least one assessment. An inter rater reliability study was conducted using 14 videos and 3 raters. Kappa coefficients for each of criteria were between 0.74 and 1.

The CHAT assesses the risk of autism by screening nine behaviors reported by parents (e.g. social interest, motor play, pretend play, pointing, showing) and five behaviors observed by the examiner (gaze exchange, pretend play, protodeclarative pointing, pointing comprehension, realizing a tower). Babies are considered to be "positive" if they fail to point (protodeclarative pointing), both as reported and observed [23].

Intellectual disability was assessed through the Brunet-Lézine developmental examination, performed for all children at the age of 2 years. The Brunet-Lézine developmental examination estimates a developmental quotient (DQ) based upon normative data available for 2-year-old French toddlers. For the Wechsler intelligence scales, the mean DQ for the typically developing sample is 100 [24].

Diagnosis of autism was based upon several measurements and an expert assessment that was blind to other variables. At age three, all parents completed the Autism diagnostic interview-revised (ADI-R) to assess autism signs by dimensions and developmental delay. ADI-R produces scores [25] to confirm the presence of criteria for ASD in any domain: reciprocal social interaction (threshold = 10), communication (threshold = 8), repetitive and stereotyped behaviors (threshold = 3), and development (threshold = 1). At age two and three years, all patients were assessed with the Children's Autism Rating Scale (CARS) [26]. The CARS includes a clinical threshold for autism and also rates levels of increasing severity. An expert clinician (LR) who was blind to child history assessed autism and ID from 20-min videotapes of child/

mother play at 2 years of age. Finally, a diagnosis of autism, ASD and ID at age four was based upon a consensus approach using direct assessment of the child by a clinician with expertise in autism (LO) as well as by clinical information from the CARS at 3 years of age, ADI-R parental interview, DQ and, when available, the diagnosis from the child's psychiatrist. Diagnosis agreement was high (23/25). The two divergent diagnoses were between PDD-nos and AD, meaning that ASD status was not changed.

Statistical analysis

All statistical analyses have been performed using the statistical package R version 2.12.2. The significance level α was set to 0.05, and all statistical tests were two-tailed. For each potential predictive variable, sensitivity and specificity were calculated for ASD alone or ASD + ID without ASD, separately. We chose to group ASD and ID in the context of WS, as both of these conditions are highly comorbid. To confirm this phenomenon in our sample, we performed an admixture analysis to determine the best fitting model for DQ in WS. Given the literature, we hypothesized a model with two subgroups, including one in the range of severe ID and another in the range of subnormal intelligence. Qualitative variables were compared using Fisher's exact test, and group comparisons were conducted using either Mann–Whitney's test (in the case of two groups) or the Kruskal–Wallis test (in the case of more than two groups). When possible, odds ratios and 95 % confidence intervals were calculated.

Results

Characteristics of the participants

The study included 25 participants with West syndrome (17 girls and 8 boys). Characteristics of the participants are summarized in Table 1. At age 4 years, 7 (28 %) children had AD, 2 (8 %) had PDD-nos, 3 (12 %) had severe ID with no autistic signs, and 13 (52 %) had no diagnosis of either ASD or ID. Response to treatment was adequate/good for half of the patients, intermediate for a quarter and poor in another quarter. DQ ranged from 16 to 106. We conducted an admixture analysis to test whether the observed distribution for DQ in patients with WS was a mixture of Gaussian distributions. The quality of the model was assessed with the Bayes Information Criterion (BIC), a statistical quantity that assesses jointly (1) how well the model fits the data and (2) how parsimonious it is. Given the sample size, we tested only one, two, and three Gaussian models. The best model (lowest BIC = 242.27) was the model with two components with equal variance. The mean DQ estimated in this model was 32 (SD = 11.6) and 81.3 (SD = 11.6) (Fig. S2, supplement online). Most children with ASD were in the low range DQ group.

Table 1 Characteristics of the children with West syndrome prospectively followed until age 4 years ($N = 25$)

Sex *N* (%)	Female 17 (68), Male 8 (32)	
Mother's level of education status *N* (%)	Good: 7 (28), medium: 12 (48), low: 6 (24Y)	
Father's level of education status *N* (%)	Good: 8 (32), medium: 8 (32), low: 8 (32)	
Age of onset: mean (SD) (range)	139.5 (74.5) (6–285) days	
Antiepileptic treatment	Vigabatrin ($N = 25$), topiramate ($N = 11$), levetiracetam ($N = 7$), lamotrigine ($N = 5$), valproate ($N = 5$), benzodiazepines ($N = 6$), carbamazepine ($N = 3$), oxcarbazepine ($N = 3$), felbamate ($N = 3$), ketogen diet ($N = 5$), neurosurgery ($N = 3$), other ($N = 4$)	
Steroids	Hydrocortison ($N = 15$), ACTH ($N = 8$)	
Response to treatment *N* (%)	Good: 13 (52), intermediate: 6 (24), resistant: 6 (24)	
Psychiatric diagnosis at follow-up *N* (%)	Autism: 7 (28), PDD-NOS: 2 (8), ID without autism: 3 (12)	
	All subjects	Subjects with ASD only
DQ at age 2: mean (SD) (range)	59.5 (27.6) (16–106)	39.4 (11.5) (24–62)
CARS at age 2: mean (SD) (range)	27.8 (10.4) (15.5–45)	35.8 (7.45) (23–42.5)
CARS at age 3: mean (SD) (range)	27 (10.2) (15–45.5)	32.6 (8.4) (23–45.5)
ADI-R social score: mean (SD) (range)	9.19 (8.98) (0–24)	18.1 (4.8) (13–24)
ADI-R communication score: mean (SD) (range)	6.95 (5.74) (0–14)	12.75 (1.4) (11–14)
ADI-R stereotypies score: mean (SD) (range)	2.15 (2.38) (0–8)	5.0 (2.2) (2–8)

PDD-NOS pervasive developmental disorder-not otherwise specified, *ID* intellectual disability, *DQ* development quotient, *CARS* children autism rating scale, *ADI-R* autism diagnostic interview-revised

Table 2 Sensitivity and specificity of early diagnostic tools according to psychiatric diagnosis at age four in children with West syndrome

	Sensitivity	Specificity
According to ASD		
PréAut—grid 9 months	75	86
PréAut—grid 4 or 9 months	60	80
CHAT—18 months	88	71
CHAT—24 months	89	81
According to ASD or ID		
PréAut—grid 9 months	83	100
PréAut—grid 4 or 9 months	75	100
CHAT—18 months	90	83
CHAT—24 months	92	100

PDD-NOS pervasive developmental disorder-not otherwise specified, *ID* intellectual disability, *CHAT* checklist for autism in toddlers

Predictive value of early assessment

Table 2 summarizes the sensitivity and specificity of early diagnostic tools according to psychiatric diagnosis at age four in children with West syndrome. Given the low number of infants with WS onset during the first 4 months of age, sensitivity and specificity for the *PréAut* grid at 4 months were not calculated. Sensitivity was good for all of the diagnostic tools, including the *PréAut* grid at 9 months. When ASD (AD or PDD-Nos) were assessed independently of ID, specificity ranged from 71 to 86 %. When all of the developmental disorders (ASD and ID) were considered, specificity improved, with values ranging from 83 to 100 %.

Table 3 shows the variables associated with an increased risk of developmental diagnosis at age four in children with WS. Prediction was better for all developmental disorders combined and gender was not associated with outcome. Positive *PréAut* screening at 9 months tended to be associated with ASD alone, and was significantly associated with ASD or ID at follow-up. A younger age of WS onset and lower DQ at age two were also predictors. However, a better response to anti-seizure medication was associated with a better developmental outcome. Regarding the predictive value of the measured early diagnostic tools, all of the tools were significantly associated with developmental outcome. In particular, WS patients with positive *PréAut* screening at 9 months had 38 times higher risk of autism or ID at 4 years of age compared with those with a negative *PréAut* grid [OR = 38.6 (95 % CI 2.2–2,961); $p = 0.006$].

Table 3 Variables associated with an increased risk of psychiatric diagnosis at age four in children with West syndrome

	Estimate	*P* value
According to ASD		
Sex	OR = 2.1 (95 % CI 0.3–17.4)	0.6574
PréAut—grid 9 months	OR = 14.1 (95 % CI 0.8–1,010.5)	0.088
PréAut—grid 4 or 9 months	OR = 5.4 (95 % CI: 0.4–94.16)	0.263
CHAT—18 months	OR = 15 (95 % CI 1.3–859.6)	0.024
CHAT—24 months	OR = 28.2 (95 % CI 2.5–1,629.8)	0.002
DQ—24 months	70.8 (±27.9) vs 39.4 (±11.5); $W = 117$	0.0117
Age of onset (days)	153.1 (±82.1) vs 117 (±57.3); $W = 87.5$	0.185
Response to treatment	Fisher exact test	0.075
According to ASD or ID		
Sex	OR = 1 (95 % CI 0.1–7.6)	1
PréAut—grid 9 months	OR = 38.6 (95 % CI 2.2–2,961.1)	0.006
PréAut—grid 4 or 9 months	OR = 27 (95 % CI 2–1,758.8)	0.006
CHAT—18 months	OR = 34 (95 % CI 2.7–2,119.9)	0.002
CHAT—24 months	OR = 89.4 (95 % CI 6.1–6,154.9)	0
DQ—24 months	82.8 (±11.5) vs 34.2 (±13.7); $W = 156$	2.4e-05
Age of onset (days)	172.2 (±79.5) vs 106.9 (±54.6); $W = 109.5$	<0.001
Response to treatment	Fisher exact test (response higher in the group without diagnosis)	0.001

OR (95 % *CI*) odd ratio (95 % confidence interval), *PDD-NoS* pervasive developmental disorder-not otherwise specified, *ID* intellectual disability, *CHAT* checklist for autism in toddlers

p significant level with Bonferroni correction $p < 0.0083$

Discussion

We found that the *PréAut* grid had similar predictive parameters as the CHAT at 18 months and 24 months. More interestingly, the risk could be assessed near disease onset: WS patients with positive *PréAut* screening before 9 months of age had 40 times the risk of having autism or ID at 4 years of age compared with those with negative *PréAut* grids. Figure 1 summarizes the variables associated with a diagnosis of either ASD or ID at 4-year follow-up. As expected, age of onset and DQ at age two [20, 22] were also risk factors for either ASD or ID at FU, whereas response to treatment was a protective factor [19]. We conclude that, in the context of WS syndrome, the *PréAut* grid could be an interesting screening tool for neuropediatricians to refer children with WS to early specific assessment of ASD and early behavioral treatment.

Also, the current results support our hypothesis that taking into account the active participation of the infant in

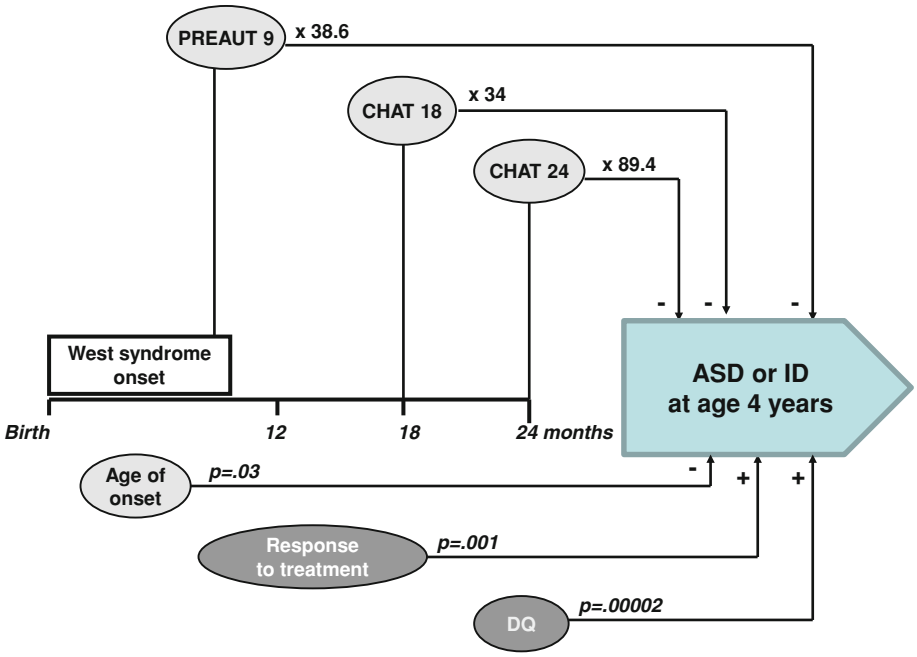

Fig. 1 Variables associated with autism spectrum disorder or intellectual disability in children with West syndrome at age 4 years. *ASD* autism spectrum disorder, *ID* intellectual disability, *PREAUT* programme de Recherche et d'Etudes sur l'Autisme, *CHAT* checklist for autism in toddlers

reciprocal synchronous affective exchanges may be helpful in assessing his/her early risk of ASD. This hypothesis was supported by (1) recent developmental studies that have emphasized the importance of emotion, reciprocity, and synchrony during early development both at biological and behavioral levels [27, 28], (2) comments from parents of children with ASD [5], (3) studies on the early risk of ASD in siblings [6, 16], (4) studies of home movies [14, 15], and (5) finally, testimonies of individuals with autism [29].

However, further research should be conducted to assess the *PréAut* grid in other contexts (e.g. infants at high risk for non-syndromic autism). A large epidemiological study is ongoing using the *PréAut* grid for autism early detection involving ten districts in France and over 10,000 families [30]. As explained in the introduction section, it is likely that the *PréAut* grid would not achieve the same sensitivity and specificity in the general population. Also, its use in a high-risk sibling sample could be of interest. Also, signal social processing applied to ASD is a powerful method to explore the dynamic and reciprocal adaptation of the temporal structure of behaviors between interactive partners [31]. Coordination of behaviors and social interaction are multimodal and will require automatic analysis of movements [32] and vocalizations [33]. Given that interaction between infant with WS and caregiver was prospectively recorded at 9, 18, and 24 months in standardized situations (3 min of free play), our aim is to apply these computational analyses to achieve it.

The current study has several limitations: (1) the limited sample size; (2) parents and clinicians were aware of the high rate of ASD or ID; (3) the absence of a control group; (4) seven patients were lost at follow-up leading to possible biases; (5) ASD and ID were comorbid in most cases. Therefore, separating the two conditions was too challenging and generalization to non-syndromic ASD may be limited. Our study also has several notable strengths: (1) the sample was followed prospectively from disease onset; (2) all patients were observed in a neurological center that specializes in Epileptology and in a context of free access to care, allowing all facilities to utilize best treatment.

We conclude that the *PREAUT* grid could be a useful tool to define the early risk of autism or ID in the context of WS. Our results emphasize that taking into account synchrony and emotion may be helpful in assessing the early risk of ASD. However, further research is needed to assess the PréAut grid in other contexts (e.g. infants at high-risk for non-syndromic autism), as the current results obtained in the context of WS may not be generalizable.

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Conflict of interest The authors have no conflicts of interest.

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