Identifying Early Developmental Profiles in Children with FXS: A Retrospective Home Videos Analysis

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Abstract: One of the major difficulties concerning Fragile X Syndrome has been early diagnosis enabling early intervention. The obstacle stems from the dismissal of signs that might raise suspicion that the syndrome is present and therefore subsequent diagnosis.

The present research aims to validate a methodology employing retrospective home video analysis to explore possible early signs in children with Fragile X Syndrome. As part of this trial the videos of 6 children aged less than 30 months were analysed. We utilized a set formed by three behavioural analysis grids, mainly to analyse social attention, joint attention and sensory-motor development of said children.

The retrospective home video analysis demonstrated its effectiveness in early sign identification. We verified that children with FXS had a non-social stimuli preference (e.g., prolonged visual fixation on objects), had difficulties directing attention to social stimuli (e.g., attention and response to name calling), demonstrating impairments in joint attention, and displayed prolong and repetitive interaction with objects as well as positive affective expressions. Our findings indicated that children with FXS seem to be able to discriminate between social and non-social stimuli (e.g., vocalization to people) and presented stereotypes behavior from 0 up till 30 months. Use of home videos is a potentially important methodology in identification of early sign. Identified signs from this study may serve as markers for medical referral to genetic diagnosis.

Keywords: Home videos, attention, Fragile X Syndrome, sensory-motor developments, early risk.

INTRODUCTION

Fragile X Syndrome (FXS) is the most common known of inherited intellectual disability and is linked to a broad spectrum of developmental disorders [1]. It affects both sexes, although the phenotypical presentation in men is more severe, given that men only have one X chromosome and this disability has an X linked heredity pattern [2]. FXS is also the best known inherited cause of autism spectrum disorder (ASD) [1], and it is believed that nearly 60% of subjects with FXS have ASD co-morbidity [3].

The syndrome is the result of X-linked genetic mutations, specifically in the FMR1 gene (Fragile X Mental Retardation 1) responsible for the production of Fragile Mental Retardation Protein, a key protein for brain development. Within the FXS spectrum, FMRP production might only be reduced or the gene might be silenced, stopping the production of the protein, which then results in full mutation [4]. FXS prevalence is estimated to be around 1:4000-6000 men and 1:4000-8000 women with full mutation [5, 6]. Pre-mutation prevalence is around 1:250-813 men and 1:130-250 women [1].

Some of the syndrome's key characteristics include wide phenotypical variability: physically (e.g., elongated face) [7], cognitive (e.g., intellectual disability, executive functions, and early attentional deficits) [8], emotional and behavioural (e.g., anxiety, ASD or ADHD-like behaviours) [9] and sensory-motor skills (e.g., early risk signs such as hypotonia, motricity and sensorial integration impairments [8]. ASD finds in FXS its principal known genetic cause, responsible for 5% of all cases [10]. Both syndromes have overlapping features, although they have different underlying explanations [11]. When comorbidity exists, the developmental prognosis and functionality is worse [12]. The disorders are diagnosed differently: FXS is diagnosed via genetic testing, specifically using *Southern Blot* or PCR (polymerase chain reaction) diagnosis [13]; ASD can be identified with behaviourally-defined methodologies. Acknowledging the difference between FXS and ASD is relevant because it enables adequate clinical decision-making, whether genetic counselling, access to early educational interventions and/or appropriate pharmacological support [14].

One of the main problems prompting the present line of research is the often late and slow diagnosis of FXS. Researchers and health professionals from several backgrounds, as well parents and children, face a diagnostic odyssey [15] from identification of the first signs until the effective diagnosis - usually arriving later [16]. However, there is evidence that markers of developmental problems may arise early on, in the first

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months of life, with several studies stating the occurrence of those signs from as early as 6-months old [17]. The discontinuity/lapse between first concerns and conclusive diagnosis is the result of a symptom or signal-based diagnosis referral [18]. This is exacerbated when there is no conclusive presence or absence of phenotypical traits [19] given that physical features are themselves not particularly useful markers in the first years of life [18].

The present study proposes as a suggested methodology, during the period prior to diagnosis, the study the retrospective analysis of home videos. This methodology calls on the videos that families often collect throughout children's development, allowing for the early developmental profile analysis of children with FXS and ASD [17]. This methodology enables the early signalling/detection of developmental difficulty indicators [20].

The retrospective video analysis methodology is an ecologically validated procedure, to objectively observe children's behaviour in a naturalistic setting, namely, observing the children interacting with "real life" [21]. This methodology also has its limitations: difficulties controlling the sample's variables, videos quality [21], the wide variability of scenes filmed by the caregivers [22, 23], the reduced dimension of the sample, or even potential difficulties as to the accurate identification of the children's age [24]. Other limitations stem from some unobserved behaviours, and which do not necessarily mean are absent from the children's behavioural repertoire [25]. Beside the aforementioned limitations, this method demands significant training in the observation of specific behaviours and requires a lot of practice applying the codification protocols [25].

To carry out research intended to retrospectively observe children's development, codification grids were employed. These grids have a crucial role, whether from a research perspective or in support of a diagnosis [26]. For example, results from studies resorting to retrospective analysis of children with FXS and ASD, using codification grids, early developmental behavioural signs were discovered starting from 0-6 months [23], 6-9 and 9-12 months [17]. Baranek, Danko *et al*. [17] were the first researchers to utilize retrospective analysis with children with FXS. Delays were found in playing, motor control skills, and the presence of repetitive movements, when compared to children on the other sample groups. The authors suggested that, future research, should study joint attention and its relationship with early development of autism features in FXS. Joint attention can be defined as the ability to coordinate attention between a social partner and an object/situation of mutual interest. It is a developmental milestone usually attained between 9 and 14 months of age. It involves, for example, a child being capable of switching its gaze between an object/situation and the face of the carer, with intent of sharing interest [24].

As has been mentioned, children with FXS may exhibit early signs; therefore, improving the symptom-based approach is a good option for a earlier diagnosis. The present research hinged on two questions: Will awareness of early behaviours of FXS children benefit from the methodology of retrospective video analysis? Which early indicators of risk, in children with FXS, might be possible to identify through family videos during the developmental period prior to 30 months? Research goals were: a) verify the utility of family videos to the retrospective detection of signs, previous to the genetical diagnosis, who tend not to be considered and b) identify early risk signs that might be identified before 30 months in children with FXS full mutation.

METHODS

Participants

A convenience sample was utilized given the difficulties concerning collecting samples in this type of population [27]. Six children who diagnosed FXS molecularly: five subjects were male (83%) and one subject was a female (17%). The inclusion criteria were: 1) confirmed molecular diagnosis, 2) being up to 30 months old in the videos, and 3) parents approved to share the family videos for research purposes.

Materials & Design

A qualitative methodology of an exploratory and descriptive character was chosen, with the intent of comprehensively exploring the issue, obtaining descriptive data about the children, resorting to video analysis assisted by grids to register observed behaviours [28]. Based on the review of bibliography, these observational grids proved to be useful for behavioural analysis of children with FXS [28]. While planning the observation, it was decided that grids have a closed form, meaning that behaviours are defined a priori and are registered systematically and objectively [27]. These instruments allowed the measurement of the frequency or the

presence/absence of behaviours, whilst also enabling a qualitative analysis of some of the scale items. The descriptive analysis allowed us, even in a small sample, to acknowledge other features of the population being studied [29]. Finally, the observed data was organized in a deductive way (based on existing theory), and interpretations and hypothesis were put forth for the results emerging from the investigation [29]. Three grids were used to collect data based on behaviours observed in the videos: *Coding Scale* [17]; *Behavioural Categories* [24] and *Grid for the Assessment of Attention in Infants through Home Videos* [23]. These were grouped in order to compound a new single instrument.

Scoring and Coding

The behavioural codification scale [21] had 14 variables divided in seven behavioural categories: Gaze aversion and visual contact, Affect, Social Touch, Postural Attunement, Response to Name, Motor and Object Stereotypies, and Sensorial Modulation (Tactile, Auditory, Visual and Vestibular). Most of the coding variables presented results as frequency during time intervals. Subsequently, frequencies were converted into ratios (i.e., proportion of time that the behaviour was observed throughout the video). Some other variables (e.g., intensity of affective expressions, level of play with objects, and response/aversion to sensorial modulation) were quantified in a Likert scale with four possible answers. After validating the behavioural observation through video analysis, Baranek proposed utilizing the same methodology in order to study sensory-motor features in the first year of life in children with FXS [17].

Behavioural Categories

Clifford and Dissanayke [24] developed a codification protocol of social behaviour in children with ASD through family video analysis. It encompassed 10 items: 1) *Visual Contact*, 2) *Response to Name*, 3) *Social smile,* 4) Shared *Positive affect,* 5) *Joint attention gaze switching,* 6) *Initiating joint attention,* 7) *Responding to joint attention,* 8) *Social referencing,* 9) *Initiate requests,* 10) *Responds to requests*.

Grid for the Assessment of Attention in Infants through Home Videos

This grid was an adaptation of the *Grid for the Study of Normal Behaviours in Infants and Toddlers* [30] for children under six months. The grid describes daily-life behaviours that might be observable in videos. Originally, the grid was comprised of 17 items divided into three developmental areas: social behaviour, intersubjectivity and symbolic activity [30]. In 2002 a review was conducted in order to select the more representative behaviours for developing children [23], reducing it to 13 items: 1 – *Looking at people*, 2- *Looking at objects*, 3 - *Orienting toward people*, 4 - *Orienting toward objects*, 5 – *Postural attunement*, 6 – *Seeking contact*, 7– *Smiling at people*, 8 – *Smiling at object*, 9 – *Attuning behaviours*, 10 - *Vocalizing to people*, 11– *Vocalizing to objects*, 12 – *Anticipating the other's aim*, 13 – *Explorative activity with an object*. These items were grouped into three developmental areas: social attention, non-social attention, and social behaviour. The behaviours present in the grid were recorded based in their presence or absence.

Procedures

The present study was ethically approved by the Scientific Committee from CIEP (Center for Research in Education and Psychology) of University of Évora. Families of children with FXS were contacted and registered into the database of one of the authors of the study, and then other caregivers of children with FXS were invited to participate, having been contacted through social network-specific groups. Participants' consent was obtained.

The videos were analyzed by two psychologists from the research team. One psychologist was a specialist in the observation of children with Fragile X Syndrome and the other was a master's student. The research group also had support from an external member who specialized in psychomotor development assessment.

A total of 90 families were contacted. Subsequently, 38 videos were received, including scenes with family routines and activities such as meals and children playing. In terms of criteria for inclusion of videos, the visibility/presence of the child throughout all the scenes was considered a prerequisite. All the videos met the inclusive criteria. At the time the videos were shot, the children had no FXS diagnosis. The videos provided by the sample families allowed the observation of children from the 24 to 30 months. Every time the age of the children was not explicit or evident, the parents were contacted in order to provide the information. To facilitate the analysis, the videos were divided in 20 second intervals [31] similarly to the studies by Maestro *et al*. [30] and Baranek [21]. In order to create a single grid, the items of the three instruments were numbered according to their presentation order in the scales.

RESULTS

In order to proceed to the results analysis, an individual analysis to the results of each child was first conducted, and afterwards a group analysis, where the average of the behaviours of children for each one of the age groups (0-6 months up till 24-30 months) was calculated. In group analysis, relative frequencies of behaviours were computed, in accordance to children's age. In Table **1**, children were organized by age group from 0-6 months (1 child), 6-12 months (3 children), 12-18 months (2 children), 18-24 months (2 children) and 24-30 months (4 children).

0-6 months

In the age group of 0-6 months, the results presented refer to only one child. Regarding child 1 registers, 341 seconds were observed and coded in six videos from 0-6 months. As main results, the child looked towards the camera 16.4% of time. While directing attention towards new non-social stimuli, child 1 was always capable of focusing on it (3/3) and had no averse response to it. While interacting with objects, child 1 was visually fixated during 30.2% of time.

Particularly important, the child did not attend the three name prompts given to her. Three times the child was given name prompts, the child had no response to three name prompts (0/3) (item 8/16). It is important to mention that the item "number of name prompts" was the same for item 8 and 16, therefore, produced the same result. No "affective expressions" (item 9) were registered, consequently, the item was not applied. The 3 times the child was touched by the caregiver (item 10), the child exhibited no social aversion/withdrawal. Concerning stereotypies, the infant exhibited "arm stereotypy" (item 11) for 37 seconds (10.8%). Even more frequent were the head, mouth, and tongue stereotypes (item 12), exhibited for 121 seconds (35.4%). "Leg stereotype" (item 13) was observed for 23 seconds (6.7%), and "posturing" (item 14) seemed to be observable in the infant for 7 seconds (2.05%). In item 15, the average result for quality of visual contact throughout all the intervals corresponds to 2 (visual contact with moderate deficiency, rarely looks to the other, empty gaze). The social smile (item 17) appeared in 5 out of 21 intervals (23.8% of total intervals), followed by positive affect (item 18) also present in 5 out of 21 intervals (23.8% of total interval). The behaviours described by item 19 through 24 were absent from the total interval, in all of cases the result was 0 out of 21 intervals (0%).

In 21 intervals, the infant looked 5 times to other subjects (item 25) (behaviour present in 23.8%) and looked 16 times to objects (item 26) (behaviour present in 76%). The child directed attention spontaneously to other persons/human voice (item 27) in 4 out of 21 intervals (19%). The behaviour of directing attention to objects/ non-human sounds (item 28) occurred more frequently, in 11 out of 21 intervals (52%). The postural attunement skill (item 29) towards another person/other people was present in 9 out of 21 intervals (behaviour present 42.8% of the time). While the child attuned the body posture towards the caregiver, the infant also made spontaneous movements (item 30) in order to reach her, producing this behaviour in 9 out of 21 intervals (behaviour present 42.8% of the time). The infant smiling to other people (item 31) was present in 5 out of 21 intervals (24%) and the smile directed to objects (item 32) was exhibited only once in 21 intervals (4.7%). The frequency with which the infant and the caregiver provided attuned behaviours (item 33) was 4.7%, meaning that the behaviour was displayed in 1 out of 21 intervals. Child 1 vocalized 8 times to a person (item 34) (behaviour with 38% frequency through 21 intervals), and no vocalization towards objects (item 35) was registered in the total interval (0%). The behaviour of anticipating (an)other's intention (item 36) was absent in all 21 intervals (0%). Finally, in 3 intervals, the infant, explored toys (item 37), exhibiting the behaviour in 14% of 21 intervals.

6-12 months

In the age group of 6-12 months, three children were included. On average, the children looked to the camera 22% of the total video time (item 1). When called, they were able to answer 89% of the times (item 2). They didn't mouth any objects (item 3) and exhibited spinning behaviour (item 4) during 1% of total video time. It should be noted that in this specific case, only one infant manifested this behaviour. Visual fixation (item 5) was manifested in 21% of total video time and playing with objects (item 6) was observable during 18% of the time. After being stimulated by a non-social tactile object (item 7), the children only exhibited aversion/withdrawal behaviours 16% of the time, although this criterion was not applicable to child 4. The item "name calling and response" (item 8/16) exhibited 63% of responses. Level 3 affective expressions were recorded (item 9), meaning that it was a positive affective expression, no children manifested avoidance/withdrawal concerning social touch (item 10). Arm stereotypies (item 11) were present during 3% of the video time; head, mouth and

Table 1: Group Analysis of Relative Frequencies of Behaviours for Children (0-30 Months)

Group Analysis		0-6 months (Child 1)	6-12 months (Children) 1+ 4+6)	12-18 months (Children 5+6)	18-24 months (Children 5+6)	24-30 months (Children 1+2+3+5)
		Average	Average	Average	Average	Average
	1-Looking at camera	16.4%	22%	32%	14%	10%
	2- Visual orientation directed to new non-social stimuli based on opportunities	100%	89%	100%	100%	50%
	3- Mouthing objects	1.1%	0%	0%	4%	2%
	4- Spinning objects	0%	1%	0%	0%	0%
	5- Visual fixation on objects	30.2%	21%	56%	65%	55%
	6- Object play rating	2%	18%	14%	20%	25%
	7- Aversion/withdrawal response from non-social tactile stimuli based on number of opportunities	0%	16%	NA	NA	0%
	8- Nº Name Prompts and respective response	0%	63%	NA	100%	75%
	9- Affective expressions	NA	3	3	3	3
	10- Aversion/withdrawal to social touch	0%	0%	NA	NA	NA
	11- Arm stereotypy	10.8%	3%	21%	0%	0%
	12- Head/mouth stereotypy	35.4%	6%	0%	0%	0%
	13- Leg stereotypy	6.7%	1.5%	0%	0%	0%
	14- Posturing	2.05%	13%	0%	0%	0%
	15- The infant looks directly into the person's face/eyes	2	2	NA	1	1
	16- Infant looks directly at person calling them in a 3s period	0%	63%	NA	100%	75%
	17- The infant initiates or returns a smile to the caregiver	23.8%	36%	32%	27%	18%
	18- The infant demonstrates positive affect with social smile (e.g., smiles, shows joy, excitement, visual contact)	23.8%	7%	5%	0%	7%
	19- Joint attention gaze switching	0%	0%	0%	0%	5%
	20- Initiating joint attention	0%	6%	0%	0%	21%
	21- Responding joint attention	0%	0%	0%	0%	2%
	22- Infant looks at another person's face in the presence of something ambiguous/threatening for information	0%	2%	0%	0%	6%
	23- Initiates requests	0%	0%	0%	0%	0%
	24- Responds to requests	0%	2%	0%	25%	21%
	25- Looking at people	23.8%	23%	0%	0%	15%
	26- Looking at objects	76%	94%	91%	85%	94%
	27- Orienting toward people	19%	26%	50%	35%	16%
	28- Orienting toward objects	52%	58%	86%	100%	81%
	29- Postural attunement	42.8%	30%	50%	50%	19%
	30- Seeking contact	42.8%	20%	0%	12%	18%
	31- Smiling at people	23.8%	36%	23%	19%	20%
	32- Smiling at object	4.7%	17%	13%	12%	5%
	33- Attuning behaviours	4.7%	10%	0%	0%	7%
	34- Vocalizing to people	38%	23%	50%	12%	23%
	35- Vocalizing to objects	0%	8%	25%	25%	22%
	36- Anticipating the other's aim	0%	0%	0%	0%	0%
	37- Explorative activity with an object	14%	34%	64%	81%	60%

tongue stereotypies (item 12) occurred 6% of the total time; leg stereotypies during 1.5% (item 13). Posturing was exhibited 13% of the time (item 14). While analysing quality of visual contact, item 15, the average was 2. This means that the infants had a moderate deficit in visual contact with other people, rarely interacting through the eyes, gazing during short periods of time, a period comprised of "empty" and "lifeless" looks. In 36% of intervals, the infants smiled socially (item 17) to the carer and in 7%, the social smile was followed by positive affect (item 18). With regard with gaze switching (item 19), no infant looked with the goal of confirming if the carer was looking. On average, behaviours with the intent of drawing the caregiver's attention (item 20) were present in 6% of intervals, but none of the children shared joint attention with the caregiver (item 21). In 2% of intervals the children searched for cues on the caregivers' face while facing an ambiguous situation (item 22) - even though only one infant presented this behaviour. Concerning the request of objects (item 23) to the caregiver, none of the children made one, although they replied to objects requests coming from their caregivers (2%) (item 24). In 23% of intervals the infants looked to other subjects (item 25), and in 94% they looked to objects (item 26). The children, exhibited spontaneous gaze direction to other people (item 27) in 26% of intervals, and spontaneous gaze direction to objects in 58% (item 28). The infants were observed attuning their body (item 29), spontaneously, to another person in 30% of intervals and they moved in a spontaneous way, looking to reach another person in 20% (item 30). In 36% of the intervals, the infants smiled to people (item 31) and in 17% one could notice the presence of smiles directed at objects (item 32). With regard to behaviours attuned with the other (item 33), the average was around a 10% frequency during the intervals, however - only one child presented such behaviour though. The vocalization to people (item 34) was present in 23% of intervals, while vocalization to objects occurred 8% of the intervals (item 35). None of the three infants presented any behaviour of anticipating (an)other's aim (0%) (item 36). The exploring objects behaviour was present in 34% of intervals (item 37).

12-18 months

Among this group, comprised by 2 children, Child 5 and 6 looked to the camera (item 1), on average, 32% of the total observation time. When non-social stimuli were present (item 2), the frequency of attention direction to the new stimuli was 100%. None of the children mouthed objects (item 3), nor did they spin any objects (item 4), however, the visual fixation on objects (item 5) was noticeable in 56% of total video time and playing with objects took up 14% of that time (item 6). It was only possible to identify affective expressions in one of the infants (item 7), who evidenced level 3, corresponding to positive affective expressions (item 9). There was no opportunity of verifying social stimuli, so it was described as "Not Applicable" (item 10). Concerning stereotypies, only the presence of arms stereotypies (item 11) were registered during 21% of total video time. In 32% of the intervals, the child smiled for the caregiver (item 17) and in 5% was evident that the smile was followed by positive affect (item 18). None of the children looked to other people (item 25), but the behaviour of looking to objects was recorded in 91% of intervals (item 26). In 50% of intervals, the capability of directing attention to people/human voice was evident (item 27), the percentage increasing to 86% at the moment of directing attention to objects and non-human sounds (item 28). In 50% of intervals, the infants exhibited postural attunement regarding the body of another person (item 29), however, they did not try to actually move to reach the other person (item 30). In 23% of intervals the infants smiled to people (item 31) and in 13% they smiled at objects (item 32). Finally, vocalizing to people (item 34) was a behaviour present in 50% of intervals and vocalization to objects (item 35) was present in 25%. It is worth noting that the ability to anticipate another's aim was seemingly absent (item 36). The frequency of exploration of an object was registered in 64% of intervals (item 37).

18-24 months

In this group, two children were analysed. The children 5 and 6 looked to the camera in 14% of the total time (item 1), directed attention to new non-social stimuli every time they were presented (item 2), mouthed objects 4% of the time (item 3), spun no objects (item 4) and presented visual fixation to objects in 65% of total time (item 5). It was possible to observe the children playing with toys in 20% of the total time (item 6). Item 7 was not applicable, given that in item 8/16 the response to stimuli was 100%. On average, the affective expressions were positive (item 9). Item 10 was not applied and children did not present any type of stereotypies nor posturing (item 11, 12, 13, 14). The average of visual contact quality (item 15) was 1, meaning a slight deficiency in visual contact, in interaction with other people, eye contact constituted of

short duration and "lifeless" stares. Social smiles (item 17) were observed in 27% of intervals. When another person requested an object (item 24), the infants responded to the request 25% of intervals. Children looked to objects (item 26) in 85% of intervals. In 35% there seems to be evidence pointing to the capability to direct attention to people or to a human voice. The ability to direct attention to objects or non-human sounds (item 28) was present in every interval (100%). In 50% of intervals, the infants were apparently capable of attuning their body in another person's direction (item 29) and in 12% the presence of spontaneous movements was verified (item 30). In 19% of intervals, the infants smiled to people (item 31) and in 12% the intervals they appeared to smile towards objects (item 32). None of the infants presented the ability to attune their movements/facial expressions with another person's behaviour (item 33). Regarding vocalization, in 12% intervals, it was directed at people (item 34), however, 25% of intervals, it was directed towards objects (item 35). No infant anticipated another person's intention (item 36). In 81% of intervals it was possible to observe infants exploring objects (item 37).

24-30 months

Finally, the results' from the 4 children within the 24-30 months age group were presented in Table **1**. Referring to the first item, children looked 10% of their intervals at the cameras, directing their attention to non-social stimuli in 50% of opportunities presented (item 2). While interacting with objects, infants mouthed said objects 2% of total time (item 3), they did not spin objects (item 4), and visually fixated on objects during 55% of the intervals (item 5). Playing with toys took up 25% of total time (item 6). Item 7 was only applied to one infant, and no aversion to non-social stimuli was observed, as the result is 0%. The ability to respond to name calling was 75% (item 8/16). Affect shown was considered positive (3) (item 9). Item 10 was not applied; stereotypies and posturing were also not observed (0%) (item 11, 12, 13, and 14). Visual contact was considered adequate to age and social, attributing 0 to the item 15. Reference, however, should be made to the slight visual contact deficit in one of the infants (1). In 18% of intervals, the infants smiled to their caregivers (item 17), and in 7% of intervals both smiled and showed positive affect (item 18). In 5% of intervals the presence of gaze switching between infant and caregiver with the intention of directing the caregiver's attention was verified (item 19). In 21% of intervals, the infants exhibited behaviours intended to request the attention of the caregiver (item 20) and in 2% of intervals they shared joint attention with the caregiver (item 21). Ambiguous situations were also observed, in which an infant looked for references or cues from the caregiver, in 6% intervals (item 22). The children requested no objects (0%) (item 23) but responded to object requests in 21% of intervals (item 24). In 15% of intervals the behaviour of looking to people was present (item 25) and in 94% intervals children looked to objects (item 26). Directing spontaneous gaze towards people was observed in 16% of intervals (item 27), while looking to objects was observed 81% of the time (item 28). The spontaneous postural attunement towards another person's body was present in 19% intervals (item 29). Spontaneous movements to contact the other person were identified in 18% intervals (item 30). Smiling to people was present in 20% of intervals (item 31) and smiling to objects was present 5% of intervals (item 32). In 7% of intervals, attuned behaviours between the infant and caregiver were registered (item 33). In 23% of intervals, the capability to vocalize towards people was presented (item 34) and in 22% of intervals the capability to vocalize to objects was present (item 35). Item 36 was absent. In 60% of intervals the infants explored an object (item 37).

DISCUSSION

The results should be carefully considered because the time of recorded video collected varies from child to child and the absence of a specific behaviour on the video might not mean that it was absent from the infant behavioural repertoire [25]. Acknowledging that the sample was small, there is no intent to generalize any conclusions solely based on the present study is of key importance. That said, the results obtained may be discussed within four categories, based on the review of literature: a) social attention vs. non-social attention; b) social interaction vs. interaction with objects; c) emotional expression; and d) stereotypies and posturing. Measuring the social attention vs. non-social attention dimensions in items: 1,2,5, 8, 15, 16, 19, 20, 21, 22, 23, 24, 25, 26, 27 and 28. Focusing on the social interaction vs. interaction with objects dimension i items 3, 4, 6, 7, 10, 29, 30, 33, 34, 35, 36 and 37. The emotional expression was encompassed by items 9, 17, 18, 31, and 32. The discussion about stereotypies and posturing dimension revolved in items 11, 12, 13, and 14.

Social Attention vs. Non-Social Attention

Looking to the camera was always present. In individual analysis, this behaviour is present a

considerable portion of time. Bailey *et al*. [8] stated that children with FXS had impairments in executive functions and attention, specifically in switching the focus of attention, staring during prolonged periods at the same place/point. One might suggest that interest in the camera, evidenced by most children in our sample, serves as marker for their preference for non-social stimuli, as is the case of ASD [32]. The visual orientation directed to non-social stimuli capability seems to be a competence preserved in infants with FXS: the infants were capable of directing attention to almost every situation in which the stimuli was presented. Visual focus on objects is one of the behaviours with a high frequency. Baranek, Danko *et al*. [27] found higher values among children with FXS (9-12 months) than in children with ASD or with typical development. Even though it isn't possible to compare, in the context of the present research, this results with the results of other groups, it seems to suggest that the presence of this behaviour, at such high frequency, being exhibited from 0 up to 30 months, suggests an apparent increasing trend to bolster its intensity.

In response to being called after stimuli, children appear to manifest some difficulties. In FXS, delayed response or absence thereof to stimuli (e.g., response to the name calling stimuli) might be explained by sensorial hypo or hyper-responsivity [19, 33].In the initial developmental phase (0--6 months), infants might exhibit a profile of hypo-responsivity to stimuli, and therefore, they might need to be stimulated more often [33]. If we consider Child 1, one observes that from 0-6 months, there was no response to stimuli after being called three times. From 6-12 months, the infant was stimulated four times until she responded. Only this child manifested difficulties while answering to her name being called, all the other infants were able to respond when stimulated. Item 15 is of key importance, given that it reveals, in most cases, that children with FXS have a deficit while establishing visual contact. These difficulties were already referred by Cohen [34] and, recently, were reinforced by Hall *et al*., [35] through studies using *eye tracking*. Short duration visual contact might be the result of the infant's desire to engage other people. In order to reduce the visual stimulation, the infant rapidly looks away [34, 36].

Concerning items 19, 20, 21 and 22, as regards joint attention abilities, that is, the capability to alternate the gaze between people and objects and, for instance, to attempt to reach an object. We verified a low frequency at every age. In the case of children with ASD, these attentional skills seem to emerge from 17-30 months. In our sample, starting at 18-24 months, only response to object requests is present; but from 24-30 months, three out of four children evidenced joint attention skills. Based on this one might suggest that these behaviours start to emerge in the same 17-30 months period that Clifford and Dissanayke [24] identified for children with ASD. Another possibly significant issue that was detected was that frequency with which children "looked to object" is superior than the frequency with which they "looked to other people", similarly children spontaneously looked more to non-social stimuli than to social stimuli.

Interaction with Objects vs. Interaction with People

While analysing the interaction of children with objects, one should mention the low frequency or absence of "mouthing objects" behaviour. Baranek [21] noted that infants with ASD mouthed objects with high frequency. Hereby one might conclude that, even though there is an apparent preference for non-social stimuli in ASD as well as in FXS, the more frequent behaviours seem to diverge between each pathology. The spinning objects behaviour had a low frequency, but might serve as a marker for stereotypies. From the observation of videos, one might suggest that the ability to play with objects is underdeveloped. It was possible to observe that infants used toys mainly to repeatedly manipulate them, and some difficulties emerged while distinguishing between repetitive play and stereotypic use of objects [22].

Thus, one might hypothesize that children with FXS, despite spending more time interacting with objects, might be doing so in a stereotyped and rigid way, restraining the ability to explore the object and learning other functions the object might have [37]. The item response "aversion/withdrawal facing a non-social stimuli" was present, but this item is a key issue for children with FXS and their intervention. In most of the cases, these infants are capable of interaction without avoidance/withdrawal from social contact. Attuning behaviour such as directing the body towards another person's body (attuned posture) is present in all ages. The infants with FXS were able to attune their body towards the posture of another person with whom they were interacting, contrary to what children with ASD [23], who have difficulties attuning their posture. With regard to spontaneous movements to contact other people, only from 12-18 months was the absence of these behaviours detected, in contrast to infants with autism who do not actively look for interaction with other people [38]. Children with FXS exhibited the

desire to interact with other people, diminishing the anxiety levels while interacting with a family member, as demonstrated in the majority of the situations through the current research and as has been mentioned in other studies [8]. One must mark the difficulty in discriminating facial stereotypies and social smiles, and arms stereotypies might be interpreted as movements intended to draw the other person's attention.

Concerning attunement between the infant's behaviour and the caregiver's behaviour it was always low, being absent among the 12-18 month and 18-24 month groups. Comparatively, in children with ASD the ability to attune to behaviours while interacting with other person is almost inexistent [23]. A possible explanative hypothesis is that the difference between children with FXS and ASD might be found in "theory of mind" development. Children with FXS have a preserved capability to understand other people intentions and beliefs (i.e., theory of mind) which doesn't happen with children with ASD [39]. That might be why children with FXS are more capable of attuning their behaviour to other people's intentions, feelings, desires or thoughts. Vocalizing to people is present in all age groups. The infants exhibited more vocalization to people than to objects, opposing, in this case, the expected preference for non-social stimuli. In other research, children with ASD rarely vocalize to people and to objects, however, findings from Maestro *et al*. [23, 32], state that children with ASD vocalize more frequently to objects. This has not born out in the present study, given that children with FXS, in almost all ages, vocalized more to people than to objects, one might suggest that infants with FXS are more skilled in discriminating among social contact and non-social contact.

While analysing the videos, it was possible to ascertain the delays in language development noted in literature. The delays in language might be connected to difficulties in muscular tonus in turn producing difficulties in motor execution of the mouth, delaying pre-linguistic [40]. Given that babbling precedes syllable sounds, sometimes there is a delay in babbling that explains why the child remains at the pre-linguistic communication level much longer [40]. One might also consider the influence of difficulties controlling physiological activation (arousal), which in turn is associated to repetitive sounds production [40]. It's possible to suggest that in the videos, children seem to vocalize more because of repetition than because of interaction. However, while interacting with caregivers or with objects they seem to be more aroused and initiate more vocalizations. Concerning anticipating other people's intention and anticipating specific actions, such behaviours were not recorded at any point. This finding is also shared by children with ASD and might possibly be understood as an indicator for difficulties in understanding other people's reactions [23]. Finally, exploratory activities of objects had a somewhat high frequency in almost all age groups, because as has already been stated, the infants explore objects for a long time, even though in a restricted and stereotypical way [17, 22, 37].

Emotional Expression

Concerning affective expressions, these were always positive, an average rating of 3, across all ages. However, the recordings provided did not enable us to observe positive or negative affective expressions. Infants with FXS seem to exhibit, however, a positive affect, contradicting findings in the literature review which stated that such infants are irritable, have tantrums and unstable moods [5, 41]. This finding might be explained by the short duration of the videos or by families selecting/keeping more favourable video depictions of their children [17, 21, 42]. Emotionally, these children seem to predominantly manifest emotional neutrality, being focused on their inner world, while repeating motions or stereotypically using objects. With regard to smiling, every infant from the sample smiled more to people than to objects. Once more, this points to infants with FXS being able to discriminate social and non-social stimuli.

Stereotypies and Posturing

While observing the registered behaviours, from the age of 0-6 months, all forms of stereotypies were found. The most frequent ones were head, mouth, and tongue, followed by arms stereotypies. Less frequently leg stereotypies and posturing were also identified. From 6-12 months stereotypies are present, posturing was more frequent, followed by repetitive movements. These findings contrast with those stated by Baranek, Danko *et al*., [17], about having leg stereotypies as the main indicator of belonging to the FXS group. It is possible to attribute this difference in findings to the fact that the infants' legs were not always observable during the videos. The 12 -18 months group only registered the existence of repetitive arm movement. Kaytser el al. [43] argue that hand-flapping is the more common behaviour in FXS and it was, in this age group, the more frequent type. At other ages, no

stereotypes or posturing were registered. Other motions such as some vocalizations, mumblings and rocking were observed, even if these were rarer. It was possible to identify a low muscular tonus in some children, what might help explain posturing and slow leg movement. By referring to low muscular tonus, or hypotonia, Baranek, Danko *et al*. in 2005 [17], also resorting to video analysis, defined this as one of the more prominent features/indicators among infants with FXS. Hypotonia might also explain some anomalies while sitting and crawling. Similar to other studies [43] the infants exhibited stereotypies, mainly while playing and when they appear to be more aroused.

There are several limitations to the present study. The first concerns the sample dimension; although it is difficult to collect a bigger sample in a low incidence pathology like this one, it is very important to underscore this limitation while considering the interpretation of the results, because of the inherent limits and range in research using small samples. One could have included a comparison group and/or control group, so this is also a limitation, and one might suggest that in future studies comparison (e.g., ASD) or control groups should be included in order to allow the assessment or discrimination of developmental profiles in children with FXS. In that case, it would be important that the coders are naïve to the child's diagnosis and look to randomly code videos of children with FXS and the control group. It would be interesting to analyse the interaction between caregivers and children, observing their behaviours, while utilizing adequate instruments. Such studies would enable the exploration of the intersubjective process co-created between the FXS child and the caregiver. With this in mind, it would be relevant to describe differences in social interaction in children with FXS with people with whom they are familiar and with people with whom they are not familiar, in order to understand the influence of social anxiety.

Limitation of Study. Please add the limitation of study. Factors that may affect your conclusion such as the small number of sample, the difference length of video recording

CONCLUSION

This study's main goals were to validate the retrospective video analysis methodology and explore potential early risk indicators in infants with FXS. Concerning the value of the retrospective video analysis, one can conclude that it is an important and useful method to employ while studying developmental profiles in children with FXS. The method enabled the observation of several infants' behaviours while interacting with objects and people, It also enabled the identification early risk indicators in infants with FXS. Upon analysis it seems appropriate to suggest that children with FXS have a preference for non-social stimuli, which might in turn be considered as a developmental early risk marker in children within the autism spectrum (e.g., prolongued visual fixation on objects vs. social stimuli) The preference for non-social stimuli was present from 0-30 months, meaning that attentional orientation deficits emerge early and persist through time. Regarding our findings about infants' interaction with people and with objects, it was possible to observe that they spent more time interacting with objects, namely, exploring them, but always in a repetitive way or playing in a very restrictive and cyclical manner. The item "mouthing objects" had a low frequency, so one might suggest a distinctive pattern between children with autism, who mouth objects frequently, and children with FXS.

Regarding interaction with people, it is noteworthy the results for postural attunement, in all age groups, and spontaneous movement in order to interact with other people, enable us to suggest that these infants try/desire to interact with other people. Concerning the behavioural attunement between child and caregiver, however, this always registered as low frequency or absent. Children vocalized more to people than vocalized to objects, in all ages, however, this vocalization appears more repetitive than interactive.

In sum, these findings suggest that children with FXS are able to attune with other people's behaviours, even though they have some difficulties. These children seem to be more motivated for/prone to interaction than what has been described, for instance, in children with ASD. These infants did not appear able to anticipate other people's intention or specific actions. However, they were able to discriminate between social and non-social contact. The affective expressions were positive at all ages. However, at the emotional level, we observed that, in many situations, the infants appear to manifest emotional neutrality and seem to be focused in their own world, repeating motions or stereotypically using objects. Children smiled more at people than towards objects, at all ages. These results allow us to argue that children are able to distinguish between social and non-social stimuli.

With regard to stereotypies and posturing, one might state that from 0-6 months and 6-12 months all manifestations of stereotypies were present, most frequently head, mouth, tongue and arms stereotypies. From 12-18 months, only arms stereotypies were presented, and in other age groups no stereotypies or posturing were registered.

Even when taking into consideration these limitations, the usefulness of the retrospective video analysis to the study the development of children with FXS and identify early risk signs was validated. Concerning the interest of this research for professionals' practice, it is reasonable to highlight the many possibilities this methodology presents in order to study infants' development. In this regard, early intervention teams might be able to use this methodology to monitor children and mark early risk indicators, asking parents, routinely, to share their children's videos. Besides that, one might suggest that a preference for non-social stimuli in contrast to social stimuli exists, starting at 0-6 months, and it seems relevant that the evaluation grids or some of its items might be contribute to an early diagnosis on FXS and, that way, help reducing the "diagnostic odyssey".

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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