The onset of hand stereotypies in fragile X syndrome

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doi: 10.1111/dmcn.13924

EDITOR—While researchers and clinicians have gained significant insights into the post-diagnostic development of fragile X syndrome (FXS), they are still searching for signs that might enable earlier identification. There remains a dearth of empirical knowledge of the prodromal development of FXS in general and the emergence of stereotypic behaviour in particular. This led us to extend our previous work on early parental concerns1 by retrospective video analyses aimed to characterize developmental traits of FXS in the first 2 years of life. Specifically, hand stereotypies (e.g. hand flapping, hand biting) have been reported as the prevalent form of motor stereotypies in FXS, observed in 70% to 88% of individuals.2 So we investigated the onset and characteristics of hand stereotypies in 13 infants later diagnosed with FXS (Table I). Parents were asked whether and when they had first recognized hand stereotypies (age bands: 1–6mo, 7–12mo, 13–18mo, or 19–24mo). They were asked to review medical reports or diaries for a better recall of events. In parallel, we analysed a total of approximately 25 hours of home videos taken of the 13 infants during family routines, mostly before diagnosis (Table I).

Our video analyses revealed hand stereotypies in 11 out of 13 children by 24 months. The earliest presentations were observed in four male infants aged 6 months or under and four infants (two male) aged 7 to 12 months. This seems to be in line with the well-documented phenotypical differences between males and females in FXS,3 but calls for greater samples with more female individuals for verification. The most frequent forms of hand stereotypies observed were hand flapping (8/11), followed by repetitive hand pronation/supination (5/11; Table I). All 11 children showed recurring hand stereotypies, which indicates a persistent stereotypic behaviour and has been similarly reported for older individuals.4

Table I: The onset of hand stereotypies (HS) reported by parents and observed on home videos of 13 children with fragile X syndrome

| Child no. | Sex | Age of diagnosis (y:mo) | Total length of recording (h:mm:ss) | Recording available between (mo) | HS observable on video | HS perceived by parents | Onset of HS observed on video (mo) | Onset of HS reported by parents* (mo) | Observed form(s) of HS on video |
|-----------|-----|------------------------|------------------------------------|-------------------------------|------------------------|------------------------|-----------------------------------|-----------------------------------|---------------------------------|
| 1b        | M   | 3:5                    | 4:05:15                            | 1–24                          | N                      | Y                     | n/a                               | X                                 | n/a Hand supination and pronation |
| 2b        | M   | 3:5                    | 4:05:15                            | 1–24                          | Y                      | Y                     | 3                                 | X                                 | Flapping                        |
| 3b        | M   | 4:11                   | 2:38:32                            | 19–24                         | Y                      | Y                     | 21                                | X                                 | Flapping                        |
| 4         | M   | 15:0                   | 0:03:27                            | 19–24                         | N                      | 19                    | n/a                               | 1–6                               | Flapping                        |
| 5         | M   | 1:6                    | 0:02:56                            | 1–12                          | Y                      | Y                     | 6                                 | 5 after 24                        | Flapping, hand opening and closing, hand supination and pronation |
| 6         | M   | 10:0                   | 3:26:40                            | 1–18                          | Y                      | Y                     | 5                                 | n/a                               | n/a Hand supination and pronation |
| 7         | M   | 7:1                    | 0:04:39                            | 13–24                         | N                      | N                     | n/a                               | n/a                               | n/a Hand supination and pronation |
| 8         | M   | 1:10                   | 0:43:18                            | 1–18                          | Y                      | Y                     | 4                                 | 7–12                              | Flapping                        |
| 9b        | F   | 10:0                   | 1:33:58                            | 1–24                          | Y                      | N                     | 9                                 | n/a                               | n/a Hand supination and pronation |
| 10a       | F   | 8:6                    | 0:42:17                            | 1–18                          | Y                      | N                     | 11                                | n/a                               | Flapping                        |
| 11        | M   | 1:1                    | 2:57:57                            | 1–24                          | Y                      | --                    | 7                                 | --                                | Flapping                        |
| 12        | F   | 3:2                    | 3:34:27                            | 7–24                          | Y                      | Y                     | 17                                | X                                 | Hand supination and pronation     |
| 13        | M   | 3:9                    | 0:34:04                            | 1–12                          | N                      | Y                     | 8                                 | n/a                               | Flapping                        |

*Age ranges correspond to the options provided on the parental questionnaire (1–6mo, 7–12mo, 13–18mo, 19–24mo). bChildren 9 and 10, as well as children 1, 2, and 3 are siblings (with children 1 and 2 being twins). --, missing data; X, parents confirmed the appearance of HS but did not remember their onset; F, female; M, male; N, no; n/a, not applicable; Y, yes.
Notably, there was little correspondence between the video analyses and parental reports. Of the five children whose parents had negated the presence of hand stereotypies, four clearly demonstrated them on video. It was particularly difficult for parents to recall the age of onset of stereotypic behaviours (Table I). This puts a question mark over the reliability of the assessment of developmental data based on parental recall. But then again, nor is retrospective video analysis infallible: for example, we cannot conclude with certainty from the apparent absence of hand stereotypies on a video (Child 7, with limited footage) that these stereotypies were absent. And yet, despite the inherent limitations of this method (which have been discussed extensively), retrospective video analysis enables a detailed assessment of aberrant neurofunctions which cannot be captured by caregiver recall.

Our data revealed a very early onset and the intraindividual persistency of specific forms of hand stereotypies in the early development of FXS. Future studies with greater samples and, ideally, prospective designs are required to identify early signs of FXS such as hand stereotypies and their developmental trajectory. A comparative study on early hand stereotypies across syndromes may provide further insights into disorder-specific profiles before diagnosis, adding to our knowledge of the prevalence and forms of hand stereotypies in different syndromes. Along with other early neurofunctional biomarkers, the assessment of hand stereotypies might contribute to an early identification of developmental disorders that are typically diagnosed at a later stage, such as FXS, to name but one.

ACKNOWLEDGEMENTS
The study was supported by the FWF P25241 and TCS24, and the OeNB Jubiläumsfond (16430).

REFERENCES
1. Zhang D, Kaufmann WE, Sigafoos J, et al. Parents’ initial concerns about the development of their children later diagnosed with fragile X syndrome. J Intellect Dev Disabil 2017; 42: 114–22.
2. Moss J, Oliver C, Arron K, Burbidge C, Berg K. The prevalence and phenomenology of repetitive behavior in genetic syndromes. J Autism Dev Disord 2009; 39: 572–88.
3. Oakes A, Thurman AJ, McDuffie A, Bullard LM, Hagerman RJ, Abbeduto L. Characterising repetitive behaviours in young boys with fragile X syndrome. J Intellect Dev Disabil Res 2016; 60: 54–67.
4. Singer HS. Motor stereotypies. Semin Pediatr Neurol 2009; 16: 77–81.
5. Marschik PB, Pokorny FB, Peharz R, et al. A novel way to measure and predict development: a heuristic approach to facilitate the early detection of neurodevelopmental disorders. Curr Neurol Neurosci Rep 2017; 17: 43.