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Recontacting in light of new genetic diagnostic techniques for patients with intellectual disability: Feasibility and parental perspectives

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ABSTRACT

A higher diagnostic yield from new diagnostic techniques makes re-evaluation in patients with intellectual disability without a causal diagnosis valuable, and is currently only performed after new referral. Active re-contacting might serve a larger group of patients. We aimed to evaluate parental perspectives regarding re-contacting and its feasibility in clinical genetic practice. A recontacting pilot was performed in two cohorts of children with intellectual disability. In cohort A, parents were recontacted by phone and in cohort B by letter, to invite them for a re-evaluation due to the new technologies (array CGH and exome sequencing, respectively). Parental opinions, preferences and experiences with recontacting were assessed by a self-administered questionnaire, and the feasibility of this pilot was evaluated.

47 of 114 questionnaires were returned. In total, 87% of the parents believed that all parents should be recontacted in light of new insights, 17% experienced an (positive or negative) emotional reaction. In cohort A, approached by phone, 36% made a new appointment for re-evaluation, and in cohort B, approached by letter, 4% did.

Most parents have positive opinions on recontacting. Recontacting might evoke emotional responses that may need attention. Recontacting is feasible but time-consuming and a large additional responsibility for clinical geneticists.

1. Introduction

One of the goals of a clinical genetic evaluation is to make a causal diagnosis in patients with intellectual disability. This can be helpful for parental acceptation of having a child with a disorder and to fulfill their 'need to know', to oversee the prognosis for the child, to guide follow-up and management, and to assess the recurrence risk in future pregnancies.

Technological improvement in genetic tests makes it increasingly possible to make a causal diagnosis. Where ten years ago karyotyping and directed resequencing of single genes was common practice, now high-resolution SNP array and trio exome sequencing have made their entrance into the clinical genetic practice. This has increased the diagnostic yield from 10% to about 30% (Monroe et al., 2016).

As these new techniques tend to develop every few years, re-evaluation and additional genetic testing using these new techniques is valuable for children with intellectual disability without a diagnosis and their parents (Hastings et al., 2012). Currently, the initiative for a new appointment to re-evaluate a child with these new techniques often resides by the patients and their families. Active recontacting does take place ad hoc, but structural recontacting is rare (Carrieri et al., 2016). A number of ethical, legal and (psycho)social issues have been raised considering active recontacting patients. A recent review on 'the duty to recontact' addresses these topics (Otten et al., 2015). Ethical and legal issues were often proposed as arguments in favor of the duty to re-contact, whereas (psycho)social issues and practical barriers were proposed as counterarguments (O'Connor, 2014; Otten et al., 2015).

Very little is known about the opinions of patients or their parents about recontacting, and about the experiences in practice (Otten et al., 2015). Empirical studies that explored how to perform recontacting and patient or parental opinions on the recontacting that had taken place were performed in only a few different patient cohorts: Fragile X families (Bernard et al., 1999), cancer genetics patients (Griffin et al., 2007; Hampel, 2009; Kausmeyer et al., 2006), and families that lost a child with a mitochondrial disorder (Sexton et al., 2008). These studies, including one study on patients (or parents of patients) with different conditions (Dheensa et al., 2017; Carrieri et al., 2017a), revealed a generally positive attitude towards recontacting in genetics among

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patients or their parents.

Since our aim was to get a better understanding of parental perspectives on recontacting, we informed parents of patients that had visited our clinic because of their intellectual disability about the availability of new technical diagnostic tools, and offered re-evaluation and additional genetic testing. We evaluated parents' general opinions about recontacting, and were especially interested in their experiences with and preferences concerning the way of recontacting, and whether recontacting was experienced as burdensome. Additionally, we wanted to study the feasibility of recontacting and the effect of recontacting by looking at the percentage of parents that could be reached and the percentage of patients that indeed made a new appointment.

2. Materials and methods

A pilot study in recontacting patients was performed and parents' experiences, opinions and preferences were evaluated using a self-administered questionnaire. For this study, we recontacted two cohorts: cohort A was contacted in 2010 by phone and cohort B in 2015 by a letter to inform them about new techniques (array CGH and exome sequencing, respectively). Both techniques result in a higher diagnostic yield when compared to other techniques already in use. We invited the parents in cohorts A and B for re-evaluation of their child at the Clinical Genetics Department of VU University Medical Center (VUMC) (Fig. 1). Ethical approval for this study was granted by the Medical Ethical Committee of the VUMC Amsterdam.

2.1. Cohort A

We selected a patient cohort, A, by using a Fragile X diagnostic DNA laboratory registry at our hospital DNA diagnostic laboratory. Fragile X testing was routinely performed in all boys and most girls with intellectual disability. All children that tested negative for Fragile X and in which clinical genetic counseling was performed between 1998 and 2008 were selected. A total of 297 children were selected and the medical records were reviewed to see if they indeed had intellectual disability, if another causal diagnosis was identified and if an array Comparative Genomic Hybridization (CGH) had been performed already. Inclusion criteria were: age of the patient between 4 and 18 years, intellectually disability or developmental delay, negative Fragile X testing result, and normal karyotyping result. Exclusion criteria were: a causal diagnosis and a previously performed array.

The parents of eligible patients (n = 151) were approached by telephone by a clinical geneticist in training (G.B.) to inform them about the availability of a new technique with a higher diagnostic yield (array CGH) and were invited for re-evaluation at our outpatient clinic. The information about the higher diagnostic yield, the chance of finding variants of unknown significance, and the small chance of unsolicited findings were mentioned. Furthermore, practical information about the appointment and test was given.

If during the telephone call informed consent for the questionnaire study was given, a questionnaire was sent to the parents, irrespective of their wish for a genetic re-evaluation of their child.

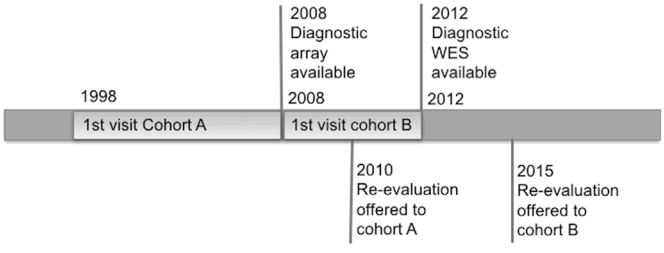

Fig. 1. The timeline gives an overview of the timing of the first visit, the introduction of new techniques and moment of recontacting during this study for the cohorts A and B.

2.2. Cohort B

Worldwide, clinics have started to use next generation sequencing (NGS) on a more routine basis. The Department of Clinical Genetics of the VUMC added whole exome sequencing (WES) to their range of genetic testing resources for diagnostics at the beginning of 2012 (Rigter et al., 2014). We again performed a recontacting pilot study in 2015. We now contacted parents by sending them an information letter about the possibility of re-evaluation of their child with unexplained intellectual disability and the possibility of additional genetic testing using WES. The written information on WES was comparable to the information about array CGH given in cohort A: it informed parents about the higher diagnostic yield, the chance of finding variants of unknown significance, and the small chance of unsolicited findings. The questionnaire to evaluate recontacting and a consent form for the questionnaire study were also included. Parents were asked to send back the filled-out questionnaire or an answer card if they did not want to participate in the questionnaire study.

The selection of cohort B was made based on the array requests from 2008 up to and including 2012 because of intellectual disability (n = 139). Medical records were analyzed to see if patients met the inclusion criteria: mild syndromic intellectual disability or moderate to severe syndromic or non-syndromic intellectual disability, normal array result, normal Fragile X testing result. They were excluded when a causal diagnosis was known, WES had already been performed, or when they had been included in cohort A of this study. In total 52 patients were selected to be recontacted by letter, presenting the number of patients included in cohort B after application of exclusion criteria. We chose not to maintain the age-related inclusion criteria in 2015, as the sample size was already very small. All addresses were checked to ensure that the letter was sent to their current address.

2.3. Evaluation of recontacting (feasibility)

Notes were made to evaluate feasibility of the study on, among others, the attainableness of parents, time effort to select suitable cases, and the number of tries before parents could be reached by phone. Moreover, records were made in Excel of parents who responded to the invitation for re-evaluation, allowing us to calculate the proportion of parents that made a re-evaluation appointment.

2.4. Survey instrument

The questionnaire was specifically developed for this study. Topics addressed were based on literature data on recontacting. The questionnaire consisted of 21 questions and it took approximately 15 min to complete. Respondents were questioned about demographic characteristics including the age of the patient and the respondent, information on siblings, and the severity of the child's developmental delay as perceived by the respondent. Questions on parents' opinions and experiences regarding recontacting in genetics in light of new insights and technological advances were included. These were two general statements "All (parents of) patients should be recontacted in light of new insights" and "I would like to be recontacted when new insights emerge", and three statements about the recent approach (by phone or letter) to inform them on the possibility of additional genetic testing: "I was pleased to be recontacted for follow-up genetic testing"; "I was pleased with the method of recontact (by letter/by phone)"; and "the recontact letter/phone call regarding additional genetic testing evoked emotional feelings". All these items were answered on a five-point Likert scale (strongly disagree (1) to strongly agree (5)). To get a better view of the impact of recontacting, parents were asked what emotions they felt when being recontacted and what would be reasons to appreciate or not to appreciate being recontacted. To learn about the effect of recontacting, parents were asked whether they were planning to make a new appointment, and for what reason they would accept or