Title: A qualitative study to explore the views and attitudes towards prenatal testing in adults who have Muenke syndrome and their partners

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Abstract

Muenke syndrome constitutes the most common syndromic form of craniosynostosis, occurring in 1 in 30,000 live births. The phenotype is variable, ranging from no clinical findings to complex presentation. Facilitating reproductive decision making for couples at genetic risk of having a child with Muenke syndrome is an important aspect of genetic counselling. Prenatal genetic testing for Muenke syndrome is accurate; however the value of testing is uncertain with a variable phenotype. The purpose of this study was to explore attitudes towards prenatal testing in couples where one partner had tested positive for the Muenke mutation. We used a qualitative approach based on thematic analysis and collected data using individual semi-structured interviews with eight parents. Five key themes were: The Muenke journey; Impact and knowledge of diagnosis; Knowledge and attitude to prenatal testing; Stigma and sharing of information; and Information retention. Knowledge of Muenke syndrome and prenatal testing was poor. Genetic information was provided when treatment of their affected child was their paramount concern. Couples reported not sharing genetic information with family due to fear of stigmatisation. Couples cannot make reproductive decisions if lacking appropriate understanding of the choices: timely genetic counselling regarding prenatal testing is needed when relevant to them.

Keywords. Genetic counselling. Prenatal testing. Muenke syndrome.

Craniosynostosis. NIPD.

Introduction

Muenke syndrome constitutes the most common syndromic form of craniosynostosis and occurs in approximately 1 in 30,000 live births (Moloney et al. 1997). Craniosynostosis is characterized by the premature fusion of one or more cranial sutures resulting in malformation of the skull. Potential consequences of interrupted skull growth include increased intracranial pressure, which in turn can cause associated visual problems and developmental delay (Wilkie et al. 2010). Muenke syndrome is molecularly defined by the presence of a single nucleotide transversion in the fibroblast growth factor receptor 3 (FGFR3) (Muenke et al. 1997). Importantly Muenke et al. (1997) showed that Muenke syndrome patients have in the past been misdiagnosed with other craniosynostosis syndromes such as Saethre Chotzen, Pfeiffer, Crouzon and Jackson-Weiss syndrome, because of overlapping phenotypes. In current practice (due to extreme phenotypic variability) it is unreliable to diagnose Muenke syndrome on clinical findings alone, and research has shown that molecular testing is the only accurate basis for providing genetic counselling (Graham et al. 1998; Kruszka et al. 2016; Moloney et al. 1997). Prenatal testing for Muenke syndrome is technically possible and whilst the test itself is accurate (Johnson & Wilkie 2011), the value of such a test is uncertain when the phenotype is so variable.

There is little literature on prenatal testing for Muenke syndrome, but evidence exists in relation to other conditions with variable phenotypes. In a qualitative study that focussed on Treacher Collins syndrome,77% of respondents reported that their desire to know would factor high in their decision to go ahead with testing (Wu, Lawson, Jabs, & Sanderson 2012). Participants included 31 affected adults and their

relatives cared for in 40 different clinical genetic centres in the mid-Atlantic region of the United States of America; this included centers in cities, rural and suburban areas. The authors included spouses/partners and other extended family members with the intention of potentially gaining a better understanding of how families who were at risk of craniofacial birth defects would utilize prenatal genetic testing in the future. Wu et al. (2012) found that parents who already had a child with Treacher Collins syndrome were significantly more interested in having prenatal testing with the view to termination of an affected fetus. The authors suggested that for some families the experience left them feeling unwilling to have another affected child. The risk of having a child with Treacher Collins syndrome was of greater concern to 65% of the respondents than the risk of miscarriage from the test. As most of the participants had health insurance, were Caucasian and married, the findings may not be transferable to other families affected by Treacher Collins Syndrome. Looking at families affected by neurofibromatosis Type 1 (NF1), Benjamin et al. (1993) found that of 29 participants who were considering a family 41% would want testing and that only three would terminate an affected pregnancy, demonstrating that for some families knowledge of the diagnosis during pregnancy is important.

However, Cesaretti et al. (2013) observed that there was a different attitude towards prenatal testing in women with a family history than in women who represented as sporadic cases. This qualitative study included 43 women (with a total of 79 pregnancies) referred to one Obstetrics Center. In those with family history of NF1, 90% (9/10) of women were not interested in testing, whereas of those women without any first-degree relatives affected by NF1, 83% (5/6) were interested in chorionic villus sampling (CVS). It appeared that familiarity with the disease played

a part in women's decisions regarding prenatal diagnosis. Those with little experience were more likely to request testing. However, Ponder et al. (1998) found that affected parents with NF1 of more severely affected children reported guilt at having known the risk of passing on the disease without having understood the variability of the disease. The ability to understand that something that is merely inconvenient to oneself could be much more severe in your child was challenging to parents.

There appears to be conflicting evidence about the basis for prenatal decision making in conditions with variable phenotype, and we were not able to identify any studies specifically related to Muenke syndrome. The aim of this qualitative research therefore was to explore attitudes towards prenatal testing in parents whose offspring were at risk of Muenke syndrome.

Methods

Study design

This study was conducted using the qualitative paradigm: this method is particularly useful when the researcher wishes to explore the experiences of the participants in an area not yet thoroughly researched (Ritchie & Lewis 2003). For this study, we used the Thematic Analysis approach developed by Braun and Clarke (2006) to plan the study, collect data and analyse the data.

Ethical approval for this study was granted by the National Research Ethics Service Committee London - Riverside as a substantial amendment to an existing study and by the University of Plymouth Ethics Committee.

Participants and recruitment

Participants were eligible for the study if they were: (1) part of a couple (2) of reproductive age (18 – 42 years for women, 18 and above for men) and (3) one partner had a prior molecular diagnosis of Muenke syndrome. Participants were excluded if: (1) they or their partner was pregnant (2) they or their partner had a miscarriage of termination of pregnancy within the last year or (3) they were unable to give informed consent. We made a deliberate decision to include only participants who were of reproductive age as it was strongly felt by the authors that the questions addressed would be more directly relevant to them. We felt this was a more rigorous approach than asking couples outside that age group to consider a fictitious scenario.

Participants recruited had preciously attended the craniofacial clinic and consented to a craniofacial malformations study. The Chief Investigator of that study agreed to introduce the researcher to potential participants by means of a letter of introduction. This was sent to potential participants with a Participant Information Sheet and reply slip. If they were willing to be interviewed, a suitable time and place was arranged and informed consent was obtained prior to the interview commencing.

Procedures (data collection)

Semi-structured interviews were used to collect data because they allow flexibility to explore the emerging issues (Smith 1995). An interview guide was developed covered the following broad topics: personal experience and understanding of Muenke syndrome, knowledge of prenatal options available to them if they were planning a pregnancy and whether knowing in advance through testing of a

pregnancy that their fetus was affected would be beneficial or not. By using open ended questions, the participants were invited to fully describe their own experiences and feelings. Partners were interviewed separately as it was felt that this would result in richer data due to the possibility that unaffected and affected adults may have viewpoints and/or a participant may be inhibited by the presence of their partner (Hertz 1995; Taylor & de Vocht 2011). In addition, it has been found that males talk may speak more freely and give more complex answers if interviewed alone Kenen, Smith, Watkins, and Zuber-Pittore (2000). Six interviews were conducted face-to face, four in the participants' homes and two in the craniofacial unit at the participants' request. Two were conducted by Skype (participants were in their home) due to distance from the study centre. Interviews ranged in length from twenty to sixty minutes, with an average time of 35 minutes. Field notes were made immediately following the interview (Gillham 2005).

Data analysis

The interviews were digitally recorded and transcribed verbatim by the researcher. Personal identifiers were removed. Field notes taken directly after each interview aided analysis and interpretation of the context of the interview and were also transcribed. The data was analysed using the six stages advocated by Braun and Clarke (2006). Initial codes were generated and applied to transcripts. Potential themes were identified and then organised into broader themes and sub-themes. Relevant data were assigned to each theme. Themes were reviewed again against coded extracts of the data and then the whole data set to ensure accuracy. Relevant themes emerged and were named and reported. To ensure rigour transcripts were

independently coded by the second author and compared to the first author's coding. Differences were discussed until consensus was reached.

Ethical issues

All potential participants were assured that their clinical care would not be affected if they declined and they could withdraw at any time following consent. Because of the sensitive nature of the topic it was anticipated that some participants could find that the interview triggered emotions that may require additional genetic counselling. Provision for this was secured with the geneticists and psychologists with whom the participants were familiar. If it had been considered that the participant was unduly distressed, then the interview would have been terminated and issues addressed and the participant would have been referred on if appropriate. The researcher ensured to check that the participant was not pregnant or had suffered miscarriage or termination in the interim period prior to interview.

Results

Demographic characteristics of the sample

The number of potential participants was limited due to the rarity of the condition. Seven couples that met with the inclusion criteria were identified and approached. A sample of four couples was subsequently recruited (Table 1). Of the three couples who were not recruited, one subsequently became ineligible due to pregnancy, while two couples did not respond to the invitation.

All participants were of white European origin and aged from 30-39 years. Of the affected participants, there were three men and one woman. One couple had two affected children with varying spectrums of the phenotype. Two couples had one

affected child and other unaffected children. One couple had one affected child only. All affected children had been tested molecularly and Muenke syndrome had been confirmed. Affected children with craniosynostosis had all had cranial surgery at approximately one year of ageThe findings are reported under key themes: 1. The Muenke journey, 2. Impact and knowledge of diagnosis, 3. Knowledge of, and attitude to prenatal testing, 4. Stigma and sharing of information and 5. Retention of information

Theme 1. The Muenke journey

During the course of the interviews it became apparent that the couples had a story to tell; and were describing the long and arduous journey that they had been through. This often began with a difficult birth, compounded by confusion surrounding a delayed diagnosis:

"but everyone was saying "oh because he had this difficult delivery "like going up and down …" (Jess, Interview 7, line 41-42)

"*the doctors and consultants in the hospital said its part of the quite intense labour and the head will after a few weeks go back in to its normal shape"* (John, line 11-13)

This difficult beginning was followed by the shock of their child requiring major surgery:

"*the fact that he started talking about surgery straight away the first time we met him it then became more of a shock as to how serious it might be*" (John, Interview 2, line 58-60)

and

"*I hadn't explained to ourselves to how major perhaps … or maybe I hadn't taken it in how major this would have been, the fact that part of his skull was gonna be lifted off his head and reshaped*" (John, line 58-60)

The subsequent genetic diagnosis compounded these feelings and some participants displayed anger and distress at being told:

*"the craniosynostosis is big enough … we do not want more" (*Jess, line,233-238*)*

Most of the affected adults were diagnosed following their child's diagnosis but had often had challenges growing up. Some participants described feeling a sense of control because of the diagnosis. For the affected but previously undiagnosed participants, their own diagnosis resulted in feelings that their past suddenly made sense. One participant had a particularly hard adolescence, so for him, the diagnosis had been a relief.

*"At school, when I first started school I was held back a little bit and I was always going for those, like remedial classes" (*Ian, Interview 8, line 104-105*)*

When asked whether it was helpful to have a diagnosis, he responded:

"*Uh, yes in a way, it was interesting to find out that, oh ok there is actually some substance to what happened before, and some sort of reasoning and it would maybe be nice to go back on time; and all like whisper in my ear that I've got this and there is some sort of I don't know limitations" (*Ian, Interview 8, line 217-277*)*

For some participants, the genetic diagnosis was accompanied with feelings of remorse and self-blame.

"Um so and we couldn't get where all this has come from you know, and a little bit of blame starts coming in you know, was it that operation I had whilst I was pregnant? with her? was it the water infection? you know, maybe that one beer I had early on in my pregnancy? was it that? you know" (Samantha, line 110-115)

In summary, reactions and emotions varied, ranged from and included anger, disbelief, shock and sometimes a sense of relief. The participants then, sometimes only minutes after hearing the initial diagnosis, would learn that their child needed life threatening surgery to correct the synostosis. At the same time they were approached for genetic testing, and shortly afterwards were faced with a second diagnosis, this time a genetic one. These experiences had an impact on the findings described in the remaining themes

Theme 2. Impact and knowledge of diagnosis

Participants were asked what they knew about Muenke syndrome and how they referred to it. Interestingly the participants (with the exception of one couple), whilst being familiar with the name 'Muenke', referred to it by other terms. All of the participants had a good basic understanding of Muenke syndrome and expressed this through their knowledge of Muenke syndrome as a rare genetic disease inherited in an autosomal dominant pattern. They were aware that they had a 50% chance of passing the disease on to their children , although some participants had a more detailed knowledge and discussed in detail the variability of the disease.

"*and because um there was a 50% chance um that if I went on to have another child and then that child would have the same condition*" (Debbie, Interview 1, line 138-141)

The participants were pragmatic when discussing other affected family members. Interestingly most of the participants were confident, before parent mutation testing was performed, where the mutation had originated.

"*Yeah, I think my mums probably passed it to me, because she's very much like me, well she's a lot shorter than me umm her feet aren't so big like wide but her hands are very very chubby fingers"* (Alex, line 270-275)

It is relevant to mention how some of the participants felt when mutation testing was performed. All of the participants were happy to have genetic testing themselves and had a good understanding of why they were having it. There were mixed reactions to the wider family being tested however. Some participants were willing to ask grandparents to be tested, whilst in contrast others felt that the phenotype in the family was obvious and so further testing would be an unnecessary procedure to put their parents through. One participant describes how he was unprepared to put his mother, who had an obvious phenotype to him, through testing:

"but I said there's no point in putting people through that if we know where it's come from" (Alex, line 278-279)

One participant relayed how he had hoped that the mutation was *de novo* in his son so that any future children he had were not at risk. Another participant described that she felt relieved that the mutation was detected in her partner and not herself.

"So it's a whole lot of, I've never, never blamed … because obviously, he didn't know … but when we found that it was a condition, and it was passed through (him) … I was relieved" (Samantha, line 117-119)

Muenke syndrome has a variable phenotype and the participants, when probed further on their understanding of Muenke syndrome, had very limited detailed knowledge of the possible manifestations. They were familiar with the associated craniosynostosis and deafness and some participants were aware of the possible developmental delay. For participants who had more than one child affected, the variability was obvious and the understanding better.

Theme 3. Knowledge of and attitude to prenatal testing

Participants were asked about their knowledge of prenatal testing and options for future pregnancies. Few participants were aware that they could have extra fetal ultrasound scans in subsequent pregnancies. In contrast, participants with one affected child who subsequently became pregnant had more detailed knowledge. When asked, none of the participants had heard of CVS. Whilst some of the participants had heard of amniocentesis, none of them were familiar with the finer details or the timing of the test.

Two of the participants mentioned pre-implantation genetic diagnosis (PIGD), but were unsure of the specific details of the procedure. None of the participants had

heard of non-invasive prenatal diagnosis (NIPD). Participants were asked to recall if they had been offered prenatal testing for subsequent pregnancies or received genetic counselling to discuss future pregnancies. Whilst most of the participants could recall having some form of genetic counselling, few could recall details of prenatal testing that had been discussed.

"There was at the time um discussion about tests at certain stages in early pregnancy" (John, Interview 2, line 238)

"that's it, we were offered those tests last time and talked through the details of them" (Debbie, line 212-213)

Participants who could not recall genetic testing being offered were adamant in their responses.

"No, it wasn't, it wasn't offered, it wasn't you know" (Samantha, Interview 6, line 207)

Having ascertained the participants' knowledge of prenatal testing, the next question was whether they had already had or would be prepared to have a prenatal test. Because the participants' knowledge was very limited they were given more detailed verbal information regarding the timing of the tests and what the tests involved. None of the participants were aware of NIPD and with one exception (a father who was unsure, since he would do nothing with the information gained from having the test); there was overwhelming support for having a test that posed no risk to the pregnancy.

"so I think if there was another if there had been another test if we were offered another test, that there was definitely no risk to the baby then definitely it would have been something I would get done" (Debbie, Interview 1, line 257-261)

Table (2) demonstrates actual pregnancies since the familial mutation was known, testing offered and performed during pregnancy, the outcome of the pregnancy and finally the participant's desire for more children and family planning post diagnosis. One participant had strong views on termination and was not prepared to risk her fetus by having a prenatal invasive test, but was happy to have a cord blood sample taken following the birth of her second child to detect the familial mutation. Similarly, the following participant considered the associated risk with amniocentesis too high.

"*And when I was pregnant um but I just didn't want to take that, 'cos I didn't want to risk the miscarriage"* (Susan, Interview 3, line 20-21)

Some participants considered the associated risks of amniocentesis to be a small one and were prepared to have the test. All couples described their decision-making process as a joint one. When probed, one participant felt that it should be his partner who would have the final say because he felt being pregnant gave her more rights over the final decision.

"but if I thought for one minute that she really wanted it done you know, then I would've let her go, obviously, she's the one that's pregnant as well and I'd respect her wishes and I'd let her go for it. Because she's the one that was pregnant and was actually having it done to her body" (Alex, Interview 5, line 447-451)

In contrast another participant admitted that he felt so strongly about having an affected child that he would try and change his partner's mind if her view did not reflect his own views. When given information on NIPD, most participants were clear that they would consider having the test in future pregnancies.

It is of note to add that all the affected participants were adamant that they would not want to pass on the mutation to subsequent children. This manifested in one participant having a vasectomy following an early termination some years previously. The couple had not been offered prenatal testing and regretted the decision in the light of the new information they received during the course of the interview. For another couple who were against termination, the solution to not passing on the gene was to limit the size of their family and similarly, another couple decided against further children but stressed the decision was made for financial reasons, as well as not wanting to risk another affected pregnancy.

Due to the lack of knowledge about the variability of Muenke syndrome, the participants were given more verbal information during the interview, and then asked again whether they still felt it was worthwhile to have a prenatal test, when any results could only tell them that a fetus was affected and not what the exact phenotype would be. One participant felt that the knowing in itself would be worthwhile.

"I think … prepare yourself …….(if) the test came back … the child didn't have the FGFR3 gene then you'd be totally pretty much at ease and if you were told then the opposite then I think you'd just pre- prepare yourself ***for knowing that they had it***

and then you'd then deal with the rest once the baby was born. So I think it would put your mind at ease a wee bit … not totally because if they have it and they can be fine or are they going to have you know a more severe case' (Debbie, Interview 1, line 572-581)

One participant felt that knowing something would help parents make decisions.
*"… it's knowing what you could be dealing with, even the **mildest** can be quite hard to deal with, so it's giving a parents a choice to know what they're dealing with rather than guessing, that it could, it couldn't be" (Samantha, Interview 5, line 399-407)*

All of the participants felt that knowing 'in itself' would be useful. However, most agreed that the lack of information would add to the uncertainty and for some participants this would result in them terminating a theoretical pregnancy.

"*I don't think we would carry on with the pregnancy, just because of knowing the possible variability of the facts of this syndrome … we would not want to put that on our child." (Jess, Interview 7, line 1109-1114)*

Theme 4: Stigma and sharing of information

Throughout the course of the interviews an unexpected theme emerged as the participants relayed their story. There was an overwhelming desire not to share genetic information surrounding the diagnosis because of the fear of associated stigma. More strikingly this included close family members with whom the participant would normally share important information.
All of the participants were happy to share their child's craniosynostosis diagnosis with family and friends but remarkably all of the participants, bar one, had only

shared their child's genetic diagnosis with immediate family and some participants had not told anyone including their own mothers. One participant was relieved that her parent's carrier testing was negative and that the mutation was *de novo* in herself, alleviating the need to tell her sisters, with whom she was normally very close:

"I think it's a bit of both, um, I didn't want them to worry but also I think that I preferred, there's only a few. I kept, there's not too many, my parents maybe know, and a close friend knows, it's just something I think it's quite personal as to … how much detail you want people to find out because sometimes there's quite a lot of … like stigma around genetic conditions and that you don't want some people to know sometime that kind of detail about yourself and really I think it was probably mostly it was from my sisters point of view it, ***I could tell them anything****, but I think there's just that kind of worry um that I just didn't really want to have to kind of burden to put on them*" (Debbie, Interview 1, line 342-354)

Some participants were protective of their affected partners. For example, one participant said:

"*so her mum and dad were told and my mum and dad were told, and then close friends of ours, um maybe 3 or 4 people because we didn't feel that anyone err, it wasn't information that anyone really needed particularly um because it's not only the kids but you know …, and it's a private we see it as a private matter*" (John, Interview 2, line 318-325)

When asked whether he had shared the information with his siblings, he responded:

"not that I recall, um I may be wrong, perhaps … shared, as she would be fairly close with my sister, so perhaps she felt that she could um confide with her, but people nobody really um thought of it as a genetic thing, they just thought of it as something that happened a one off to …, and we didn't feel the need to share information they didn't need to know you know" (John, line 337-346)

Other participants were equally uncomfortable discussing the genetic diagnosis.

"I did not know how to handle it so much that none of my relatives know! That he has syndrome! …Nobody knows about it (said quietly)" (Jess, line 1221-1231)

When asked why this was, she continued:

"*Well, first of all, the more people you share it with, the more chances of him finding out from someone else rather than from me … I do not want him to be told that he has got* ***that*** *from someone else. Second of all you do not know other people's reaction. If you tell them you've got some syndrome, even though they know you for ages, even though we were all friends and everything is fine but you tell them like oh we have got a syndrome, what they might think about you, they will ask you first like what are the impacts." (*Jess, Interview 7, line 1236-1258*)*

One participant was asked whether his mother-in-law who was living with the family, knew her grandson's diagnosis.

"yeah yeah the craniosynostosis, (drops his voice and says quietly) not the Muenke" (Ian, line 914)

However, one participant wanted to prepare her family for an affected child as they were integral to her support system.

"my family um they knew there could have been a chance of … having the gene and so they were sort of psyched up too, I had them sort of well-prepared so they were very supportive throughout my pregnancy as well" (Susan, line 102-105)

Theme 5. Retention of Information

During the course of the interviews the participants demonstrated limited detailed knowledge of Muenke syndrome and in particular the associated variability. For the majority of the participants it had only been a couple of years since they had been told of the familial mutation and usual practice is to send parents a detailed clinic letter from the geneticist and to provide genetic counselling from a geneticist either in craniofacial clinic or locally. Some of the participants either could not recall receiving such a letter or had no idea where to find it. Most of the participants could not remember the geneticist's or other significant doctor's names involved with their child's treatment.

Some participants could recall being given information to read but most felt that the time that had elapsed had affected their memory of this.

"there were different papers and records that were given on Muenke syndrome and craniosynostosis, there was quite a lot on them, we also joined the support group and looking up things on that" (Debbie, line 368-371)

"it was maybe 2 years ago or a year ago that I read the leaflets and I can't remember all the symptoms" (John, line 211-212)

"and it's that long ago too, you're talking over 2 years ago as well, it's a long time ago" (Susan, line 353)

The overriding theme with all the participants was that the surgery required to correct the craniosynostosis took precedence and that the additional genetic information that they were given was less important as they focused on their child's recovery. This is demonstrated by one participant's description of meeting the geneticist in clinic.

"*He was in the early meetings I'm sure I remember him being in there from the start, but I suppose I chose not to think of that, I was thinking of major things, like the plastic surgeon and the surgical works that was gonna have to be done soon, so the genetics was almost as if we went around the room and ... it just went in there and out there (referring to genetic information)"* (John, Interview 1, line 102-110)

Discussion

The findings of this research indicate that following the birth of a child with a congenital malformation, the reactions of parents followed a course that began with an initial shock, and included, for many, disbelief, denial, sadness, anger and/or anxiety. The shocked response of parents following the diagnosis of a child with a disability has been well documented in the literature (Droter, Basiewicz, Irvin, Kennel, & Klaus 1975; Fajardo 1987; Gotz & Gotz 2006; Myring et al. 2011; Quine & Pahl 1987; Solnit & Stark 1961). Wong-Gibbons et al. (2009) found that mothers of

children with craniosynostosis reported greater stress if they perceived their child's condition to be noticeable to others, which is confirmed in the present study, where one mother stayed in to avoid repeated questioning of her child's diagnosis. In concordance with this finding, Rumsey and Harcourt (2007) and Nelson, Kirk, Caress, and Glenny (2012) found that parents whose children look 'different' may be susceptible to questions about their child's appearance and or perceive that people may see their child in a less favourable manner, causing them distress. Burokas (2013) and Rumsey and Harcourt (2007) reported that the strong emotional responses specifically arising from congenital defects involving the infant's skull and face were further compounded by the life threatening surgery the infant required and suggested that this could affect the relationship and bond that the parents' developed with the child. Participants in this study did encounter stress regarding their child's surgery but did not appear to have difficulties in forming a bond with the child; however, the small cohort may not have been representative of parents who have a child with craniosynostosis.

The molecular diagnosis of Muenke syndrome to adults or children with a subtle or no clinical phenotype is often bought to the attention of a clinician when a child with a more severe phenotype is born into the family (Yarnell et al. 2015). Kruszka et al. (2016) performed a natural history study of people with confirmed molecular diagnosis of Muenke syndrome and found that 15% of their participants did not have craniosynostosis and were previously undiagnosed. The participants in this present study, who were previously undiagnosed, were found to be relieved by their molecular diagnosis and in addition had an overwhelming feeling of their past making sense, and the challenges in their childhood being accounted for. There

have been many case studies reported in the literature, but these studies have not commented on this psychological aspect of the molecular diagnosis (Agochukwu, Solomon, Benson, & Muenke 2013; Escobar, Hiett, & Marnocha 2009), and as such it would be interesting to see if further qualitative studies with a larger cohort had similar findings to the present study

The additional genetic diagnosis following the craniosynostosis diagnosis caused further distress to the participants in this study. There is limited evidence in the literature as to the impact of a secondary genetic diagnosis following major surgery. Rumsey and Harcourt (2007) allude to the difficulties parents face following cleft palate surgery and subsequent reproductive decisions as to whether to have further children. Agochukwu, Solomon, and Muenke (2012) state that the genetic diagnosis of craniosynostosis does not define or change a families' identity, and should be viewed positively by patients in helping them prepare for the future. In specific reference to Muenke syndrome, diagnosis should help ensure that screening for hearing and developmental evaluations are in place and that families should be counselled accordingly (Agochukwu et al. 2012).

While participants had a good understanding that Muenke syndrome was a rare genetic disease and were familiar with the dominant inheritance pattern, when probing to determine the participants understanding of the variability of Muenke syndrome the findings show that participants had limited detailed knowledge regarding variability. Similarly, in a larger qualitative study, Ponder et al. (1998) found that all 30 respondents knew that neurofibromatosis Type 1 was heritable but had a lack of information about a more severe phenotype and as such were unaware

of the risk of disability in future children. For participants in the present study who had more than one child affected, the variability was more obvious and the understanding better. Similar to the authors of the present study, Ponder et al. (1998) chose to focus their data analysis on information received from participants who were aged 21 to 35 years, stating that they felt reproductive choices would be more relevant to this age group.

The participants in this study had very limited knowledge of prenatal testing, which makes it difficult to compare results with the existing literature looking at the views of adults toward prenatal testing, as many of those studies appear to report on participants who have sound background knowledge (Anderson 2007; Beeson, Golbus, Opitz, & Reynolds 1985; Klitzman, Thorne, Williamson, Chung, & Marder 2007). Looking at the attitudes towards prenatal testing in the existing scenario, the participants fell into two categories, where they either considered the risk of an invasive test too high or that it was an acceptable risk. After using qualitative questionnaires to collect data from 71 pregnant respondents (16 weeks gestation or less), Marteau et al. (1991) reported that uptake of amniocentesis was influenced by attitudes of an affected pregnancy as well as the perceived risk of having an abnormal child. Similarly, the participants in the present study (who in contrast, were not pregnant) felt they would terminate an affected pregnancy based on their desire to have an unaffected child. There was an overwhelming support for NIPD and most participants would have considered that type of non-invasive testing, including participants that had previously been adamant that testing was not of interest to them. The findings of the perceived advantages in this current cohort towards NIPD are consistent with the existing literature (Allyse, Sayres, Goodspeed, & Cho 2014;

Hill, Compton, Karunaratna, Lewis, & Chitty 2014; Hill, Compton, Lewis, Skirton, & Chitty 2012; Skirton, Goldsmith, & Chitty 2015). Concurring with the findings of Skirton et al. (2015), whose qualitative thematic analysis study involved 27 individuals, some participants in this study were concerned over accuracy of the test and would want an invasive test to confirm results.

When further challenged as to the value of prenatal testing when only limited information was being given and the actual phenotype of their unborn child would remain unknown, all the participants demonstrated that some information would be valuable to them regardless. These findings are consistent with other larger qualitative studies in the literature discussing attitudes towards testing disease with variable phenotypes (Benjamin et al. 1993; Wu et al. 2012). They differ from the findings of Ponder et al. (1998) and Terzi et al. (2009), who reported that the biggest deterrent towards prenatal testing was the variability of the phenotype, although arguably, they did not discuss NIPD as an option in these studies.

There was an unexpected finding of reporting concerns about genetic stigma in the present study. The participants appeared to be using the initial diagnosis of craniosynostosis and corrective surgery to hide the genetic diagnosis. This finding adds to existing literature as there appear to be no studies in the literature where a previous diagnosis was used to conceal the secondary genetic diagnosis.

Jones et al. (1984) identified six dimensions of stigma, to include concealability. Described as a dimension of stigma, where certain characteristics can remain undetected; genetic carrier status is such an example. Genetic disease has been linked to guilt and shame in previous studies (Chapple, May, & Campion 1995;

Kessler, Kessler, & Ward 1984; McDaniel 2005; Piazza & Bering 2010; Ponder et al. 1998). Most affected participants in this study were undiagnosed prior to the birth of their child and did not share these emotions, unlike those studied by Ponder et al. (1998) who did display guilt at unwittingly passing on a genetic condition. However, some participants in this present study acted in similar ways to the nine parents interviewed by Donoghue et al. (2014), who were searching for reasons as to why this had happened to them in pregnancy, highlighting the need for clear information to be given at the time of diagnosis.

Authors of previous studies have discussed the dissemination of genetic information in the family where family members are 'at risk' of the condition (Claes et al. 2003; D'Agincourt-Canning 2001; Forrest, Curnow, Delatycki, Skene, & Aitken 2008; Lehmann, Weeks, Klar, Biener, & Garber 2001). This present study reports concealment of a child's genetic diagnosis where other family members are not at risk and where genetic information is regarded as private even amongst close family members in whom the participants would normally confide.

One hypothesis for not sharing information could be the traumatic journey that the participants in the present study have been on. Snowdon and Green (1997) state that when knowledge of carrier risk comes after the birth of an affected child, then the emotional struggle to accept the child's diagnosis may provide a barrier to effective communication. Wilson et al. (2004) describe communication as a process and not a single act and that progression towards disclosure is affected by sociocultural beliefs and tensions in the family. Furthermore, Wilson et al. (2004)

hypothesise that people may be motivated to withhold information to protect from harm and exert control, this could be true of the participants in the present study who could be trying to take back control after a turbulent period in their lives. The present study reported that the participants felt there was no need to share as the information may not be relevant to others and was viewed as personal and private and to avoid perceived negative consequences; this finding was consistent with those of other authors (Higa, McDonald, Himes, & Rothwell 2016; Shaw & Hurst 2009; Wilson et al. 2004). Whilst the findings were consistent with the present study, it is of note that Higa et al (2016) conducted a larger qualitative study interviewing 19 participants, Shaw & Hurst (2009) interviewed only British Pakistani families and Wilson et al (2004) reviewed 30 studies. Whilst in contrast, Modi, Quittner, and Boyle (2010), Berlin, Sass, Davies, Jandrisevits, and Hains (2005) reported that disclosure of their genetic disease was associated with a 'perceived' neutral or positive affect on most relationships. Dyson et al. (2010) reported that there was often ambivalence towards disclosure, where people vacillated between disclosing and concealing; an exception being with adults in authority, such as teachers, where parents felt that it was important for them to know.

The participants in the present study rationalized one of the reasons for not sharing the genetic diagnosis with others was that if they did share, then there would be a greater possibility of others telling their child their genetic diagnosis before they had a chance tell their child themselves. They felt strongly that the best person to tell a child was the parent. This is consistent with findings of a larger qualitative study involving interviews with 33 families (79 individuals) by Metcalfe, Plumridge, Coad, Shanks, and Gill (2011); who reported that when parents who told their child their

diagnosis themselves, and treated communication about the disease and its risks as an ongoing process, the children coped better and had a greater knowledge of the disease and associated risks and implications.

One of the main aims of genetic counselling is to provide information to patients that they can understand and utilise to make decisions (Michie, French, Allanson, Bobrow, & Marteau 1997). The findings of this present study are consistent with the existing literature suggesting that families have difficulty recalling and understanding the information they receive at the time of genetic diagnosis (Aspinwall, Taber, Kohlmann, Leaf, & Leachman 2014; Jacobs, Dancyger, Smith, & Michie 2015; Vos et al. 2011; Watson et al. 1998). The qualitative retrospective studies (Aspinwall, Taber, Kohlmann, Leaf, & Leachman 2014; Vos et al. 2011; Watson et al. 1998) included much larger numbers of cancer participants and the observational study by Jacobs et al (2015) again involved larger numbers (ranging from 32 to 77 participants, affected and unaffected) and was cancer focused. These studies were conducted with varying time periods for recall and clearly exhibited the difficulty associated with relying on recall of participants. The participants retained very little information pertaining to the variability of Muenke syndrome and, more strikingly about the prenatal testing options that would be available to them in future pregnancies. One explanation for the poor retention of information could be the timing of the information. Referring back to the journey the participants in this study have been on it could be argued that the participants were in a state of shock and heard nothing following the craniosynostosis diagnosis and the impending surgery. The findings of this study report that the priority of all the participants was to focus on the surgery and the recovery of their child, some using this as a conscious decision

to deflect from the genetic testing and impending diagnosis but for most the genetic diagnosis was given some time after surgery and was described as an additional shock that they struggled to cope with and as such retain the information. There were no specific studies identified in the literature looking at retention of genetic information following a prior diagnosis involving surgery. For the affected participants, who found the genetic information a relief, making sense of their past, then the recall of the information pertaining to the variability of the phenotype was more accurate. One possible explanation for this would be the relevance of the information and clarity of the inheritance throughout the extended family following the genetic diagnosis, suggesting that patients are more likely to remember information if they can apply it to their everyday lives.

Study limitations and strengths

This study has a number of limitations, particularly the small sample size. The sample size was small partially due to the rarity of Muenke syndrome and partially due to the inclusion criteria requiring the participants to be of reproductive age. The adults that present to craniofacial clinic are referred when their child is first diagnosed with craniosynostosis and it is at this point that they are tested molecularly if Muenke syndrome is suspected clinically. As such there is limited access to adults who are requesting prenatal genetic counselling for Muenke syndrome, while their offspring at the time of the study were not of reproductive age. Another limitation to drawing conclusions about reproductive intensions was the poor knowledge across the participants pertaining to prenatal tests. Arguably the participants were given new information during the course of the interview, without time to digest and reflect this new information which may not be representative of

their true views if they had had more time to consider the implications of the tests fully.

However, the researchers aimed to include a diverse sample of couples with different numbers and ages of children and from different ethnic backgrounds. This was achieved, even across the small sample. The affected adults were mostly male with one affected female, which potentially could have influenced the findings. Use of a second coder strengthened the rigour of the study. The thorough literature conducted prior to the research resulted in the decision to interview partners separately, arguably eliciting richer data.

Practice Implications

Findings from this study demonstrate a need for prenatal information to be given at a time that is more relevant to the recipient and as such more likely to be retained. Written information can be given in craniofacial clinic and during genetic counselling when molecular results are given to the family. However, this research has shown that this information is not usually retained and that written information may be misplaced or destroyed over time.

Strategies that might improve retention of information could include (1) asking parents of children with Muenke syndrome about their reproductive plans in follow-up craniofacial clinics, (2) offering an appointment to young affected adults for pre-conceptual/prenatal counselling. The latter could be initiated by including an alert to the family doctor on the discharge letter to refer the individual either back to the craniofacial clinic or the genetic department when they are considering planning a family. Genetic counsellors are well equipped to provide this service, and there are

small numbers of molecularly confirmed adults, so an addition burden on geneticists in craniofacial clinic is not anticipated. Finally, (3) developing written advice leaflets on Muenke syndrome and prenatal testing that could be sent to the family doctor and the young adult and their families would seem an opportunistic way to both educate health professionals who are not familiar with Muenke syndrome and the young adult themselves. This information could also be available on the craniofacial and genetic department websites but would need to be updated in line with the advancing techniques in preconception and prenatal testing. The prenatal information could be transferable to the other mutation positive craniofacial syndromes alongside a disease specific information leaflet.

Research recommendations

Due to the inherent nature of this small qualitative study, the findings cannot be generalised to all individuals and families with Muenke syndrome. Instead, however, the aim has been to describe the experiences of the participants involved in this research in depth and as such the findings have some important implications for all health professionals involved in the care of families affected by Muenke syndrome. All health professionals, not only geneticists and genetic counsellors, caring for these affected children should be aware of the Muenke journey and the additional stress and impact that two consecutive diagnoses have on these families.

Further research with a larger cohort to explore the views of adults whose offspring are at risk of Muenke syndrome would be useful to substantiate or not the findings in this small study. Any future studies could include a review of patient and medical records and correspondence, to determine whether the topic of prenatal diagnosis had been covered in previous consultations.

Conflict of Interest

The authors declare no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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Table 1: Key demographic characteristics of participants

Pseudonym	Gender	Age range	Affected Confirmed by Molecular Diagnosis	Phenotype	Children	Affected Child's Phenotype	Other suspected affected family members
Debbie	F	30-39	Muenke	Mild	2 Mutation positive	Craniosynostosis (1 x surgery required) Hearing loss Mild – No craniosynostosis	NO
John	M	30-39	NO	N/A	2	A/A	N/A
Edward	M	30-39	Muenke (diagnosed as child)	Craniosynostosis (surgery x 2 required) Hearing loss	1 Mutation positive	Craniosynostosis (1 x surgery required) Hearing loss	YES
Susan	F	30-39	NO	N/A	1	A/A	N/A
Alex	M	30-39	Muenke	No Craniosynostosis Bilateral Hearing loss short fingers and toes	1 Mutation positive	Craniosynostosis (1 x surgery required) Bilateral hearing loss	YES
Samantha	F	30-39	NO	N/A	2	A/A	N/A
Ian	M	30-39	Muenke	No craniosynostosis Hearing loss Early speech delay	(2) 1 Unaffected Mutation Negative 1 Mutation positive	Craniosynostosis (1 x surgery required) Hearing loss Early speech delay	YES
Jess	F	30-39	NO	N/A	2	A/A	N/A

Table 2: Testing and outcome of subsequent pregnancies (after initial diagnosis in family)

	Mutation positive	Subsequent pregnancies since mutation known	Testing offered	Testing in pregnancy	Outcome of Pregnancy	Family planning/contraception post diagnosis	Desire to have further children
Debbie	Muenke	Yes	Amnio	Scans Cord bloods at delivery	Affected	Not specified, but decision to have no more children clear	No
John	No	Yes	Amnio	Scans Cord bloods at delivery	Affected	Not specified	Yes
Susan	No	Yes	Amnio	Scans	Affected	Not specified, but decision to have no more children clear	No
Edward	Muenke	Yes	Amnio	Scans	Affected	Not specified, but decision to have no more children clear	No
Alex	Muenke	Yes	None	N/A	Termination	Vasectomy	No
Samantha	No	Yes	None	N/A	Termination	N/A	No
Jess	No	No	N/A	N/A	N/A	Oral Contraception	Yes
Ian	Muenke	No	N/A	N/A	N/A	No	Yes

Legend

Amnio = amniocentesis

N/A = not applicable