Psychosocial Aspects of Predictive Genetic Testing for Acute Intermittent Porphyrria in Norwegian Minors

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Abstract Objective: The Norwegian Porphyrria Centre routinely offers genetic counselling and predictive genetic testing in families diagnosed with porphyria. The aim of this study was to investigate the subjective experiences of adolescents and young adults who were genetically tested for acute intermittent porphyria (AIP) as minors. What were the psychosocial consequences and how were these handled?

Methods: Qualitative interviews of ten Norwegians aged 16–21 years were performed and analysed based on interpretive description. All participants were initially predictively tested for AIP as minors, but three had subsequently developed manifest disease.

Results: The participants considered early diagnosis and lifestyle moderation advantageous, but finding motivation for precaution was difficult. AIP inflicted few psychosocial challenges and was a small part of the participants' identity, but risk of manifest disease was, nevertheless, a cause for concern for two participants with latent AIP. The participants were content with their present level of knowledge and they felt capable of obtaining relevant information when needed. AIP was experienced as a vague condition, and participants and their relatives attributed a variety of symptoms to the disease.

Conclusion and implications: Being genetically tested as a minor was experienced as useful and entailed relatively few adverse psychosocial consequences, although there was a potential for concern. Appropriate and individually tailored genetic counselling and written consent is subsequently advised. What constitutes a suitable age for testing will differ from individual to individual, but these results suggest that parents in collaboration with their children may be suited to decide what age is appropriate.

Keywords Acute intermittent porphyria · Genetic counselling · Minors · Predictive genetic testing · Psychosocial · Qualitative methods

Introduction

Acute Intermittent Porphyrria

Porphyrias are rare and mainly inherited diseases caused by reduced activity of different enzymes in the heme synthetic pathway. Each enzyme defect causes a specific disease. These enzyme defects may result in elevated levels of porphyrins or porphyrin precursors leading to a wide range of symptoms. Acute intermittent porphyria (AIP) is one of the most common forms of porphyria. Prevalence of the symptomatic disease is estimated to 1–2 per 100,000 (Herrick and McColl 2004). Attacks are characterised by abdominal pain, vomiting, headache, muscle aches, muscle weakness, pareses, hypertension, tachycardia, mental symptoms and respiratory paralysis (Sassa 2006). AIP has been referred to as “the little imitator” because sometimes non-specific symptoms are easily mistaken for other subjective health complaints (Crimlisk 1997). A range of medications can trigger symptoms, in addition to hormones, alcohol, physical and psychological stress, hunger and fasting (Normann and Puy 2002). Inheritance is autosomal dominant, with reduced

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penetrance (Badminton and Elder 2005). Disease severity varies from minor symptoms of abdominal pain to serious or frequent attacks requiring hospitalisation. Paralysis and respiratory failure are rare but potentially lethal complications, highlighting the need for early diagnosis (Herrick and McColl 2004). Symptoms very rarely develop before puberty, but there exists a few documented cases of AIP in children (Sandberg et al. 2001; Elder 1997; Hultin et al. 2003).

Genetic Counselling and Testing

The Norwegian Porphyria Centre (NAPOS) offers both diagnostic and predictive genetic testing for AIP. Norwegian legislation states that predictive genetic testing requires extensive genetic counselling, and written informed consent is mandatory (Norwegian Biotechnology Act of 5th December 2003, No. 100 relating to the application of biotechnology in human medicine, etc.). As a rule, predictive genetic testing of minors is not permitted unless such testing can facilitate treatment or prevention of the disease. In the case of AIP, one considers that early detection of mutation carriers will improve prognosis through lifestyle changes and avoidance of symptom-triggering medications. Based on this, NAPOS offers genetic counselling and predictive testing for minors. Mutation carriers without symptoms are referred to as latent AIP, and persons who have experienced one or more AIP attacks are diagnosed as manifest AIP. If a person is diagnosed with latent or manifest AIP, NAPOS will issue a personal ID card that can be used when the person is in contact with health services, and thus contribute to both avoidance of porphyrinogenic medication and the implementation of correct medical treatment.

Previous Research

There are few papers on psychosocial aspects of AIP and hardly any focus on young persons with the diagnosis. A qualitative study from Sweden, in which five women were interviewed on their experiences with serious AIP attacks, concluded that when these women had their attacks they lived in the “deepest darkness”, with indescribable pain, both physically and mentally (Wikberg et al. 2000). A British questionnaire study of 116 patients (Millward et al. 2001) found lower quality of life in patients with AIP, compared to patients with other types of porphyria. This resulted in lifestyle consequences for a significant number of the participants and especially for persons with manifest AIP. A follow-up study confirmed that depression and especially

anxiety were more common in persons with AIP than in the normal population (Millward et al. 2005). These reports indicate that AIP might have serious consequences for those involved and that there is a need for further investigations of the psychosocial aspects of this disease. Borry et al. (2006) analysed 27 papers from 1991 to 2005 that addressed the issue of guidelines for predictive testing of minors. The main reason for recommending such testing was the direct benefit the patient could achieve through medical treatment or prevention of disease. Unless there were pressing medical reasons for testing, all 27 papers proposed that one should postpone testing until the child could consent. There are few reports concerning predictive testing in minors for adult-onset conditions (Borry et al. 2008; Wade et al. 2010), and it is important to investigate whether young persons benefit from the information such testing yields, and whether risk information causes psychosocial harm to young persons genetically tested for AIP.

Objective

The aim of this study was to investigate the subjective experiences of young persons diagnosed with active or latent AIP as minors. What were the psychosocial consequences, and how were these handled?

Methods

Interpretive descriptive method was chosen as it is a qualitative approach suitable for smaller scale studies seeking clinical insight into subjective experiences (Thorne et al. 1997, 2004). Both the Norwegian Regional Ethics Committee and the Norwegian Social Science Data Services approved this study.

Recruitment and Sample

NAPOS recruited persons eligible for participation. They were contacted through mail, and asked to return written consent to participation, in October 2008 and February 2009. If the participant was younger than 18 years, written parental consent was also required. To meet the inclusion criteria, participants had to be registered at NAPOS, have been genetically tested as minors (< 18 years) and identified as AIP-mutation carriers. It was deemed purposeful that participants were old enough to reflect on the subject in question, but at the same time there should be closeness in time to the genetic testing. Based on this, a theoretical sample consisting of persons not younger than 16 years and

Table 1 Presentation of participants

Participant	Age at PGT ^a	Age at interview	Manifest or latent AIP	Disease manifestation in patients and relatives
1. Alex	10–12	21	IAIP	First-degree relative with unspecific symptoms
2. Morgan	11	17	IAIP	First-degree relative with one AIP attack. Second-degree relative with chronic and unspecific complaints
3. Billie	14	19	mAIP	Unspecific symptoms, more or less chronic complaints. Admitted to hospital twice. First-degree relative with unspecific and frequent complaints in earlier years
4. Drew	5–7	17	mAIP	Three AIP attacks requiring hospitalisation
5. Taylor	17	21	IAIP	No symptomatic relatives in immediate family
6. Chris	12	17	IAIP	First-degree relative with unspecific and frequent complaints
7. Morgan	15	16	IAIP	First-degree relative with several AIP attacks requiring hospitalisation
8. Bobbie	11	19	mAIP	One serious AIP attack. First-degree relative with a few attacks treated at home
9. Cameron	17	21	IAIP	First-degree relative with one attack
10. Francis	15	17	IAIP	First-degree relative with both unspecific and frequent symptoms and attacks requiring medical treatment

Unspecific symptoms – Symptoms perceived by the *participants*: fatigue, muscle aches, headaches, dizziness, etc that were not in combination with otherwise unexplained episodes of stomach/back pain with a duration of >12 h

^aPGT predictive genetic test

not older than 21 years was chosen. Persons with other serious medical conditions were excluded. Twenty-eight persons met the criteria and all were asked to participate. Twelve persons were positive to participation, but as one was difficult to get in touch with, and another was abroad, only ten persons were able to attend. All participants were initially diagnosed with latent AIP, but at the time of the interviews three had experienced one or more attacks and were diagnosed with manifest AIP. A short introduction of the participants is provided in Table 1 to contextualise statements. Analysis did not reveal gender-specific reactions, and participants are given gender-neutral pseudonyms. Relatives are invariably presented as males.

Data Collection

Individual qualitative interviews of six Norwegian females and four males were performed in the period of December 2008 to April 2009 in participants' homes or at a hospital in their proximity. The first author, a registered nurse and genetic counsellor with previous experience from qualitative interviews conducted all interviews. One participant had received genetic counselling from the interviewer in connection to prior genetic testing, without this seeming to influence given answers. Each interview lasted between 40 and 65 minutes and was based on a semi-structured interview guide containing eight topics with a series of open-ended sub-questions. Topics are listed in Table 2. All participants were asked the same questions, but not necessarily in the same order and depth. There was room for the participants to define new topics of interest. Interviews were audiotaped and transcribed verbatim consecutively.

Table 2 Main topics off interview guide

1. Disease presentation in the family
2. Participants own disease
3. Prevention of disease
4. Psychosocial consequences
5. Knowledge of porphyria
6. Being diagnosed as a minor
7. Inheritable disease
8. Genetic counselling

Data Analysis and Interpretative Descriptive Method

Data analysis was performed by the first author, and started as initial readings of the text to get a sense of the whole. For practical purposes, formal analysis commenced after completion of eight interviews, although guidelines for interpretive descriptive approach suggest simultaneous data collection and analysis (Thorne et al. 1997, 2004). There were, nonetheless, certain amounts of informal analysis in the form of reflections in the wake of each interview. A second reading identified nine categories that were used as basis for further coding (Morse 2008). For this coding, the data material was transferred into QSR N6 software (QSR. NUD*IST. Qualitative Research & Solutions Pty Ltd., 1997) for easier data management. Each category was then analysed internally, and summaries were written to more clearly present the participants' meanings and experiences. Based on critical reflection and discussions between the first and the last author, four main themes emerged. In addition, the research questions and what might be clinically relevant and interesting knowledge were of crucial importance. To validate and ensure that participant's initial meaning was not

lost, the total text was re-read and interviews were listened to again.

Results

Results are presented as four main themes. Quotes are used to illustrate and validate the participant's meanings.

Living with a Small Intruder

When participants spoke of their genetic status they all perceived knowledge of this as beneficial and useful. In their view, early genetic testing contributed to them stay healthy, and was not experienced as a cause for unnecessary worry. Although risk information was considered advantageous, nine participants were quite clear on the fact that their genetic status did not entail any change of plans in regards to education, occupation and social or physical activities. One participant with frequent and unspecific complaints of AIP contrasted this. The disease made Billie unable to take part in social activities and attend school the way peers did. Because of this, some friends and teachers gave the impression they believed Billie to be lazy.

Participants seemed ambivalent towards lifestyle modifications for prevention of manifest disease, but they would check medication before use. Some claimed to take it easy and to avoid stress, or stated that they exercised and were careful to eat regularly and sleep sufficiently. Nevertheless, they admitted they probably would lead the same life regardless of their genetic status. Cameron had latent AIP. When asked about strategies to avoid manifest AIP, the answer was:

I used to smoke but I recently cut down on that because I've been thinking smoking is not a smart thing to do when one has porphyria. That really is the only thing I've... But then again, I don't want cancer either, you know? So there are several reasons for me to cut down.

One participant stated that AIP was not a disease, but only a "small intruder" in life. Alex had chosen a career that might be unsuitable for a person with AIP. Several members of the family had asked about the amount of physical or psychological stress the chosen career entailed. Had the risk of triggering an acute attack been considered? The answer to this was:

It may come as it may, the dreams are bigger than the worries.

Participants did not change their lifestyles *because* of manifest disease or *in fear* of developing manifest disease. Because AIP was something several had never experienced, it was not a big motivator for precaution. Some said they probably ought to do more, but that this was not easy, Taylor said:

I am just not able to take precautions against something I've never really felt on my body. I might regret not doing it, but up until now I've lived more against the advice I have got, and it has worked out well so far.

Worrying About and Planning for the Future

It was evident that for two participants risk of disease was not unproblematic. They both had latent AIP, and expressed concerns for the future, and worried about the possibility of manifest AIP. They had relatives with chronic complaints attributed to AIP, in addition to other medical conditions. Morgan said:

I do go around thinking about it all the time, and then I watch my relative and listen to what he has experienced, and I look at my other relative and I'm not supposed to stress (...). I think about it just about every single day

These two participants were quite certain that manifest AIP would invariably lead to disability but this did not affect their choices for the future. Morgans' latent porphyria had not affected choice of education, but when asked about the potential for manifest disease the answer was:

It is a scary thought, in regards to it being permanent, and what I will actually be able to do afterwards. Some say I will not be allowed to stress as much if I have the disease. Will I be able to work with children like I want to, or? I'm very sceptical of that happening... I believe that at the very least I will not be able to work as much as I would like. And it would be a great shame if I were not able to work with children.

Also, one participant with more frequent AIP complaints had never heard of anybody with manifest disease who was able to work full time. This did not affect the choice of future career, but led to an education where student life was flexible and involved Internet-based lectures.

There were a few reports of discrimination based on genetic status. One participant had been refused acceptance to an education because of latent AIP. Two participants were declared medically unfit for military service because of latent AIP. One had freely provided this information, the other had not. To be declared unfit for service was not experienced as negative, on the contrary one of them said: "In this regard I owe the porphyria a big thank you".

Seeking Information as Needed

Participants believed that information about porphyria was important to their health, but at their current state in life they did not have a pressing need for more information. Cameron said:

I probably don't know enough, but what I know is sufficient. That is, I know as much as I need to know for now. But if I were to experience an attack I would probably want to know more about it. But right now I don't really feel I need to know any more

Participants generally knew where to get additional information. Most felt that both NAPOS and the two Norwegian patient organisations could be contacted, and also the Internet was frequently used. In addition, the ID card provided by NAPOS was deemed useful. Seven participants claimed to always carry the ID card with them, and some participants reported the card to be their main source of information.

Most participants reported their own age for genetic testing as appropriate, but some believed they had been too young. They had been tested at different ages, but reflected on the fact that they had not been able to understand or care about the implications. Drew said:

I was very young at the time. But I don't think there was anything wrong with that, really. It was OK. I just didn't understand very much, and it would have been different if I had been told now. I would probably be more curious about it now

AIP a Vague Condition

Most participants perceived AIP as a rather vague disease that they did not have first-hand knowledge of. Contributing to this opinion was individual and ambiguous symptoms and the fact that an attack could be triggered, and manifests itself in varying degrees. Participants also commented that medical authorities could not always offer precise answers regarding AIP. These factors combined implied that there would always be a degree of uncertainty with regard to AIP. When asked whether it was difficult to know what was a symptom of porphyria, Chris answered:

Yes, I do feel that, you might say. That it can be mixed up in so many things, that you can not clearly separate what is what, especially when I do not have it myself so to speak. If I suddenly get it one day, it is not certain I will recognise it right away. I might just think it is something else

When the participants were asked to describe porphyria in their family, it became evident that a variety of symptoms were attributed to AIP. If a family member said his or her health complaints were caused by porphyria then the participants accepted this as the cause. Participants knew that medications could trigger an acute attack but the mechanisms involved seemed to be vaguely understood. Some explained present health problems in relatives were caused by medication taken years back. Even though participants defined themselves as having *latent* AIP or not having porphyria *yet*, they would attribute symptoms such as feeling tired and "out of it" to AIP. Most participants did

not reflect upon this seeming contradiction, Taylor discussed this as follows:

Because I think, or, I have spent a lot of time becoming certain of what I can attribute to it. And there have been things that would be natural to assume was caused by porphyria but which I think, no. I cannot blame everything on that. I am often tired and so on, but I think a lot of people are, and if I start blaming porphyria for being tired or exhausted then that will just provide me with an excuse, instead of doing something about it.

Discussion

In general, the participant's lives were not very influenced by porphyria, and AIP was only a small part of their identity. One participant, with more chronic complaints of manifest AIP, contrasted this and two young participants with latent AIP worried about their genetic predisposition and were certain that active disease would entail serious consequences. Apart from the participant with chronic complaints, few lifestyle modifications were reported, and although participants believed they would benefit from taking precautions, these were not enough to motivate them into taking active steps to prevent AIP attacks. This ambivalence towards taking precautions is perhaps not surprising, and poses a general problem in health promotion (Shiloh and Ilan 2005; Pronk et al. 2004). That adolescents engage in more risk-taking than adults have previously led to the hypothesis that adolescents are poor decision-makers, lacking in cognitive skills and understanding of consequences. More recent studies indicate that adolescents do not lack in perception or appraisal of risk, but that risk-taking is largely influenced by emotions and psychosocial factors, and cannot be completely understood in terms of cognitive processes during low emotions or arousal (Steinberg and Morris 2001; Steinberg 2004, 2005). This fits with the present findings, where participants believed they would benefit from taking precautions, yet finding motivation was difficult.

Two participants worried about developing active AIP, and it is worth noting that both had relatives with more chronic complaints. Perception of risk is subjective and dependent of context and the expected nature of potential outcome (Austin 2010). That disease presentation in the immediate family might influence perception of the condition has been suggested in previous research (Michie et al. 2002; Tønder et al. 2003). Family members attributing a variety of symptoms to AIP, and participants' vague understanding of latent and manifest forms emphasise the need for relevant and unambiguous information. For patients to benefit from predictive testing and early diagnosis, knowledge of genetic status is not enough. The ability to use risk information in a productive and constructive way is essential.

This implies that genetic counselling should be tailored to individual needs, providing sufficient information on symptoms, treatment, medical follow-ups and information on judicial rights (Paus 2009). Participants also indicated that need for information varied according to their situation in life and this favours the opportunity to access repeated information through, for example, patient education seminars, news-letters, web pages or individual counselling, and might be especially important when genetic testing is performed on minors.

That latent AIP triggered few lifestyle moderations could be viewed as positive in minimising the potential ethical dilemma of stigmatising healthy individuals. On the other hand, the goals of genetic service should ultimately be to improve long-term health status (Wang et al. 2004). Few consequences might question the direct benefit patients achieve through predictive testing as minors, as proposed by ethical guidelines (Borry et al. 2006).

In this study, it was positive to note that participants claimed to check medications for adverse porphyrinogenic reactions, and this is likely to prevent future AIP attacks (Badminton and Elder 2005). In addition, participants experienced early genetic testing as beneficial, and although there were reports of discrimination, this was not perceived as negative or dramatic. Minimal adverse response to testing has also been reported in previous research (Wang et al. 2005). Participants were also satisfied with their current knowledge and felt capable of obtaining further information when needed.

Strengths and Limitations

This study did not include persons who were not genetically tested or were tested as consenting adults. Reasons for, and consequences of, choosing to wait or not testing are therefore not examined. Qualitative findings can provide useful understanding and descriptions of the challenges minors tested for AIP experience, but the results cannot lend themselves to statistical analysis and transferability should be considered in relation to context and sociocultural setting (Kuper et al. 2008). Further investigations into psychosocial aspects and quality of life in persons with both latent and manifest AIP are subsequently desired.

Conclusion and Clinical Implications

AIP entailed relatively few psychosocial consequences for the participants, but results point to a potential for increased anxiety, without necessarily generating lifestyle changes.

Discrimination based on genetic status was reported, and while the participant's experience of this was not negative, ethical implications need to be considered when predictive genetic testing is performed. Appropriate counselling and informed consent is advisable. What constitutes a suitable age for testing will differ from individual to individual, but these results suggest that parents in cooperation with their children may, after genetic counselling, be able to decide what age is appropriate.

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