Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT)

Application Reference: M0007

Leber Hereditary Optic Neuropathy (LHON), OMIM #535000

caused by m.3460 G>A in *MT-ND1* gene

Thursday, 24 May 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe	
Members of the Executive	Dee Knoyle Bernice Ash Paula Robinson Catherine Burwood Mhairi West	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer) Inspector (Observer - Induction)
External adviser	Professor Shamima Rahman	
Legal Adviser	Sarah Ellson	Fieldfisher LLP
Observers		

Declarations of interest

- Members of the committee declared that they had no conflicts of interest in relation to this item.

The committee had before it:

- 8th edition of the HFEA Code of Practice
- Standard licensing and approvals pack for committee members
- Mitochondrial Donation Explanatory Note
- Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015

The following papers were considered by the committee:

- Executive Update with response from centre to Expert Advice from Prof. Shamima Rahman
- Expert Advice from Prof. Shamima Rahman
- Licence Committee Minutes of 28 January 1999 – PGD approved for Leber's Hereditary Optic Neuropathy
- Executive Summary
- Mitochondrial Donation: new case application form
- Patient Letter
- Clinical Expert Review Form

1. Consideration of application

1.1. The committee noted the description in the application for Leber Hereditary Optic Neuropathy (LHON), OMIM #535000 caused by m.3460 G>A in the *MT-ND1* gene.

1.2. The committee welcomed the advice of its Specialist Adviser, Professor Shamima Rahman, who confirmed that the condition was as described in the papers. Professor Rahman also confirmed that the evidence submitted by the clinic supported the view that PGD was inappropriate or likely to be unsuccessful.

1.3. Professor Rahman noted the Peer Review which supported the application. However, Professor Rahman expressed some reservations about whether the condition meets the committee's seriousness test and explained that there was a greater than 50% chance of the patient producing asymptomatic offspring without performing mitochondrial donation using PNT.

1.4. The committee had regard to its decision tree.

Administrative requirements

Application

1.5. The committee noted that the application has been submitted as required by General Direction 0008. The centre has submitted an application to perform mitochondrial donation using Pronuclear Transfer (PNT) for Leber Hereditary Optic Neuropathy (LHON), OMIM #535000 caused by m.3460 G>A in the *MT-ND1* gene for a named patient, on the relevant application form.

Licence - Express provision and variation

1.6. The committee noted that the centre's licence has an 'express provision', granted by the HFEA, to permit mitochondrial donation treatments using PNT and the centre's licence has been varied accordingly.

Embryologist

1.7. The committee noted that the procedure would be carried out by the embryologist named on the centre's licence, who is the only embryologist licensed at the centre to perform mitochondrial donation using PNT.

Patient selection criteria

Pre-implantation Genetic Diagnosis (PGD) considered

1.8. The committee had regard to its Mitochondrial Donation Explanatory Note 2.5 and 7.1 (levels of heteroplasmy/homoplasmy for a particular Mitochondrial DNA (mtDNA) mutation in the germ line) and reminded itself that PNT should only be offered where a patient has undergone an assessment that deems PGD inappropriate or likely to be unsuccessful.

1.9. The committee noted that the application includes a documented rationale as to why PGD may be deemed inappropriate and likely to be unsuccessful in this case. The application describes that LHON mutations are typically homoplasmic (as in this case).

Peer Review

1.10. The Peer Reviewer supported the application and agreed that the use of pre-implantation genetic diagnosis (PGD) in this case, would be inappropriate as the patient is homoplasmic for the m.3460G>A mutation.

Expert Advice

1.11. The Expert Adviser, Professor Shamima Rahman stated that there is 100% chance that this patient's children would inherit the mutation in the mitochondrial DNA as LHON mutations are homoplasmic and agreed that PGD was inappropriate or likely to be unsuccessful.

1.12. The committee noted that whilst Professor Rahman agreed that without mitochondrial donation therapy, it is inevitable that this patient will transmit the m.3460G>A mutation to her children, she also stated that the risk of this patient's children developing the disease (LHON) is relatively low.

1.13. The risk of this patient's children developing the disease (LHON) varies according to the sex of the child. Professor Rahman stated that a review of the literature suggests the lifetime risks for developing visual failure with the m.3460G>A mutation to be 32-49% for males and 15-28% for females. Professor Rahman and the committee noted that the HFEA had licensed PGD for LHON in 1999 but the minutes simply referred to testing the embryo and it considered that this may have been for sex selection, although this was not clear from the available information.

1.14. Professor Rahman advised that there is a greater than 50% chance that this patient's children would be completely asymptomatic without mitochondrial donation using PNT and advised that LHON disease affects a single organ and frequently does not cause any symptoms in individuals carrying the responsible mtDNA mutations.

1.15. References: Nikoskelainen 1994 Clinical picture of LHON. Clin Neurosci. 1994;2:115–20; Man et al 2003 The epidemiology of Leber hereditary optic neuropathy in the North East of England. Am J Hum Genet. 2003;72:333–9; Yu-Wai-Man P, Chinnery PF 2016 Leber Hereditary Optic Neuropathy. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. 2000 Oct 26 [updated 2016 Jun 23]).

Legal Advice

1.16. The Legal Adviser referred the committee to relevant parts of the Mitochondrial Donation Explanatory Note and reminded the committee of its obligations to consider the patient's family history of affected individuals, their mutation load (if it may be relevant), age of onset and clinical manifestations of the disease. The committee was advised that this application was to be considered on a case by case basis taking these particulars into account and considering the worst case scenario for this particular patient and her offspring.

Particular risk

1.17. The committee had regard to its Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, 8(a)(i) and considered whether there was a particular risk that any embryo which is created by the fertilisation of an egg extracted from the ovaries of the named woman may have mitochondrial abnormalities caused by mtDNA.

1.18. The committee noted the evidence that the patient has a clearly identified pathogenic mutation which gives rise to a considerable risk of any children having serious mitochondrial disease.

1.19. The committee noted that the application sets out relevant information about Leber Hereditary Optic Neuropathy (LHON), OMIM #535000, including the patient's family history of affected individuals, their mutation load and clinical manifestations of disease.

Significant Risk

1.20. The committee had regard to its decision tree, Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 8(a)(ii).

1.21. The committee considered whether there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease.

1.22. The committee noted that the patient is an asymptomatic woman carrying the m.3460G>A mutation in the mitochondrial *MT-ND1* gene (OMIM 516000). The pathogenic m.3460G>A mutation has been detected at homoplasmic levels in urine, buccal and blood derived DNA, in this patient's samples.

1.23. The committee noted that LHON is the most common form of mitochondrial diseases in adults and results in inherited visual loss. In the UK, three mutations have been linked to 40% of all adult-onset mitochondrial diseases. These include the m.11778G>A mutation (most common), or the m.14484T>C or m.3460G>A mutations. Men are four to five times more likely to be affected than women. The mutations demonstrate incomplete penetrance.

1.24. The committee considered the advice of its Expert Adviser, Professor Rahman and Legal Adviser. The committee discussed the risk and was satisfied, on the evidence before it, that the patient's offspring would be at risk of developing symptoms of the disease over their life spans.

Seriousness of the disease

1.25. The patient has no preceding pregnancy history, as she opted not to conceive until now, due to the potential risk of passing on a serious mitochondrial disease to her children.

1.26. The committee noted that Leber Hereditary Optic Neuropathy (LHON), OMIM #535000, can be, in the worst case scenario, a devastating disorder, impacting considerably on the affected individual's quality of life from early adulthood, with rapidly progressive visual impairment or sudden blindness, leaving the individual no time to adapt to the condition. The severity of negative impact on quality of life has been shown to be worse than in any other form of ophthalmologic disorders previously assessed. The committee considered the psychological impact on individuals who inherit this mutation, living with the threat of developing the disease and losing their vision, limiting their independence and future career. The committee also considered the emotional impact on women carrying this mutation, knowing that they would pass it on to their children.

1.27. The committee noted that most affected individuals present with monocular visual blurring, followed by insidious onset of similar symptoms in the other eye on average two to three months later. In more than a quarter of cases, visual loss occurs in both eyes simultaneously. LHON is caused by the death of cells at the back of the eye that are responsible for passing visual information from the eyes to the brain. Vision is mostly severely restricted to counting fingers or worse, with visual recovery extremely rare. Most affected individuals are registered legally blind.

1.28. The severity of the disease may vary from family to family and person to person.

Treatment

1.29. The committee noted that currently there is no curative treatment for LHON and whilst therapeutic strategies are emerging, management of affected individuals is largely supportive.

1.30. The committee noted that Idebenone, an antioxidant treatment, has been used for LHON, however this is not licensed for prophylactic treatment to prevent the onset of the condition and although there is a hope it may partially alleviate, it will usually not completely reverse the symptoms. Other therapeutic strategies including allotopic gene therapy are still in the early stages of development.

Reversion

1.31. Mitochondrial DNA (mtDNA) mutations are collectively a relatively common cause of genetic disease. Mitochondrial donation treatment can be used for patients with a severe mitochondrial disease to reduce the risk of passing the condition onto children born to a mother carrying a mtDNA mutation. The PNT technique requires egg donation from a donor with mtDNA without defects that may cause disease. Gametes are provided by three people involved in this treatment: the mother, father and egg donor. There may be some carryover of the mutant mtDNA and a theoretical risk remains of reoccurrence of significant mutant mtDNA levels in the child and subsequent generations that may lead to mitochondrial disease.

Recommendation

1.32. The committee noted the inspectorate's recommendation to consider this application to perform mitochondrial donation using PNT for the patient named in the application.

2. Decision

2.1. The committee noted that authorisation for Mitochondrial Donation using Pronuclear Transfer (PNT) for Leber Hereditary Optic Neuropathy (LHON), OMIM #535000 caused by m.3460 G>A in the *MT-ND1* gene, is conditional on the embryo subsequently being created by the fertilisation of an egg extracted from the ovaries of the woman so named: regulation 8(b).

2.2. The committee had regard to its Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, 8(a)(i), 8(a)(ii) and 8(b).

2.3. On the basis of the information presented, including the patient's family history and manifestation of the disease, along with the patient's medical history, and advice given by the committee's Legal Adviser and Expert Adviser, the committee was satisfied that there was a particular risk that any embryo which is created by the fertilisation of an egg extracted from the ovaries of the named woman, may have mitochondrial abnormalities caused by a pathogenic mtDNA mutation. The committee was also satisfied that there was a significant risk that individuals who inherit this mutation, particularly males, will develop serious mitochondrial disease leading to blindness.

2.4. The committee recognised the right of the patient not to be identified. The committee agreed to authorise this application, to allow the Mitochondrial Donation Practitioner named on the centre's licence to perform mitochondrial donation using PNT, for Leber Hereditary Optic Neuropathy (LHON), OMIM #535000 caused by m.3460 G>A in the *MT-ND1* gene, for the patient named in the application.

HFEA Code of Practice

2.5. The committee agreed that the centre should follow procedures in accordance with the HFEA Code of Practice and pay particular attention to the areas highlighted below in relation to mitochondrial donation:

Counselling and support

2.6. The committee emphasised that the centre needs to fulfil the HFEA's counselling requirements for all involved in mitochondrial donation and provide the necessary patient information. The committee noted that this would include consideration of the risks involved to enable patients to make fully informed choices.

2.7. The committee agreed that counselling should continue to be offered after treatment.

Welfare of a child

2.8. The committee noted that all centres are required to have in place documented procedures to ensure that proper account is taken of the welfare of any child who may be born as a result of treatment services.

Follow up to mitochondrial donation

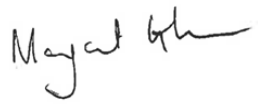
2.9. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical follow-up of children born as a result. The centre has close links with mitochondrial disease centres and NHS England to facilitate follow-up.

2.10. The committee encouraged the centre to ask for the patient's consent to contact them following mitochondrial donation treatment and should a child be born, to check up on the child's health and development in the future. As this is a new technique, the medical and scientific community needs to understand as much as possible about how it affects children and future generations. This will ensure they get the best possible care in the future as well as contributing to the continued understanding of mitochondrial disease. The committee understands that patients do not have to agree to the follow up but should be presented with this opportunity to help others affected by mitochondrial disease, now and in the future; this includes patients who live abroad.

3. Chair's signature

3.1. I confirm this is a true and accurate record of the meeting,

Signature



Name

Margaret Gilmore

Date

26 June 2018