Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)
Mitochondrial Donation using Pronuclear Transfer (PNT)
Application Reference: M0012
Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND1 gene (m.3460G>A)

Thursday, 25 October 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Anthony Rutherford Ruth Wilde Emma Cave (New Member Induction - Observer)	
Members of the Executive	Dee Knoyle Bernice Ash Catherine Burwood Paula Robinson	Committee Secretary Committee Secretary (Observer) Senior Governance Manager (Observer) Head of Planning and Governance (Observer)
Specialist Adviser	Professor Bert Smeets	
Legal Adviser	Gerard Hanratty	Browne Jacobson 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 summary
- Application form (including patient statement)
- Peer review form
- PR response to peer review
- Written advice from Statutory Approvals Committee Specialist Adviser
- Person Responsible response to written advice from Statutory Approvals Committee Specialist Adviser
- Statutory Approvals Committee minutes 24 May 2018 – M0007

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Professor Bert Smeets, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application for Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND1 gene (m.3460G>A) is consistent with the peer review.

1.3. The committee had regard to its decision tree.

Administrative requirements

Application

1.4. The committee noted that the application had 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), caused by a mutation in the MT-ND1 gene (m.3460G>A), for a named patient, on the relevant application form.

Licence - Express Provision and Variation

1.5. 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

1.6. The committee noted that the Mitochondrial Donation Practitioner named on the centre's licence is the only embryologist licensed at the centre to perform mitochondrial donation using PNT.

Patient selection criteria

Pre-implantation Genetic Diagnosis (PGD) considered

1.7. 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 took account of the fact that PNT should only be offered where a patient has undergone an assessment that deems PGD inappropriate or likely to be unsuccessful.

1.8. The committee noted that the Peer Reviewer supported the centre's view that PGD would be unsuitable for this patient.

1.9. The committee noted that the Specialist Adviser to the committee also supported the centre's view that PGD would be unsuitable for this patient as this patient is homoplasmic for this mutation.

Particular Risk

1.10. The committee had regard to its Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, Regulation 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 a named woman may have mitochondrial abnormalities caused by mtDNA.

1.11. The committee noted that the application sets out information about LHON, caused by a mutation in the MT-ND1 gene (m.3460G>A), including the patient's clinical history and family history of affected individuals, their mutation load and clinical manifestations of the disease.

1.12. The committee noted that this patient is asymptomatic and has no preceding pregnancy history as she opted not to conceive until now due to the potential risk of transmitting serious mitochondrial disease to her off-spring. The pathogenic m.3460G>A mutation has been detected at homoplasmic levels in urine-derived DNA, buccal-derived DNA and blood-derived DNA in this patient's samples. Patients with similar mutant mtDNA loads have had children affected by serious mitochondrial disease. The patient's mutant mitochondrial load would appear above the threshold level for clinical manifestations. She would be deemed still at increased lifetime risk of developing symptoms of mitochondrial disease due to the nature of these mutations (incomplete penetrance and variable expression).

1.13. The committee considered that the patient has a clearly identified pathogenic mutation. The details of the particular factors underlying this rationale have been omitted to protect the identity of the patient.

Significance and seriousness

1.14. The application describes that LHON mutations are typically homoplasmic, as in this case, and demonstrate incomplete penetrance and variable expression.

1.15. LHON is the most common form of mitochondrial disease and results in often devastating inherited visual loss during young adult life. The 3460G>A mutation, that this woman harbours, is the most severe and is associated with profound visual loss and a Multiple Sclerosis-like syndrome. Men are four to five times more likely to be affected than women, for reasons not fully understood. Affected individuals often present with monocular visual blurring, followed by insidious onset of similar symptoms in the other eye on average 2-3 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 often severely restricted to counting fingers or worse, with visual recovery extremely rare. Most affected individuals are often registered legally blind. The precise factors that determine phenotypic expression have not yet been identified, nor is the pattern of disease expression readily evident from examination of family pedigrees.

1.16. Although visual loss does not characteristically progress after the acute disease phase, the time of impairment (i.e. acute phase of the disease) could have a strong negative impact on the quality of life. The impact of the emerging evidence of more widespread multi-system involvement was also considered by the committee.

1.17. Those with more widespread multi-system involvement including cardiac and extra neurological manifestations such as progressive dystonia (muscle spasms and contractions) and a MS-like illness (that has a more aggressive course) have a considerably greater disease burden and impact on health-related quality of life.

Peer Reviewer & Specialist Advice

1.18. The Peer Reviewer did not consider sufficient information was available to make an assessment on the significance of the risk as the application did not mention the known links to cigarette smoking. The Peer Reviewer also stated that there is evidence that the recurrence risks are less in non-smokers.

1.19. The Specialist Adviser to the committee did however provide this information, stating the recurrence risk as being ~10% for female offspring and ~40% for male offspring, with evidence that these risks are less in non-smokers. Acquired blindness at a young age is a serious condition. This condition could have more widespread multi-system involvement, like MS in this case, although at varying frequency. Although treatment using Idebenone has beneficial effects in preventing further vision impairment and promoting vision recovery in patients with LHON, it does not lead to clinical recovery in all patients. The Specialist Adviser also commented that visual impairment could have a major impact on the mental, social and economic well-being of the patients.

1.20. The Peer Reviewer stated that the chance of a child being affected is less than 30% without mitochondrial replacement therapy and that low levels of heteroplasmy are associated with reduced risk of blindness. Once the vision is impaired, there is no progression. There is, however, a (~10%) chance of spontaneous visual recovery. This is less for the m.3460A>G mutation. The absolute life time risks of visual failure are low, particularly for women (~10%) and the risks may be even lower if the person avoids risk factors such as cigarette smoking. Many affected individuals have a very fulfilled life, including high-level paid employment.

Legal Advice

1.21. 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.

1.22. The committee had regard to its decision tree, Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, Regulation 8(a)(ii). The committee considered whether there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease.

Mitochondrial Donation using Pronuclear Transfer (PNT)

1.23. The committee noted that Mitochondrial DNA (mtDNA) mutations are collectively a relatively common cause of genetic disease. Mitochondrial donation can be used as treatment for patients with a severe mitochondrial disease in order to reduce the risk of passing this maternally inherited condition on to their children. 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.

Reversion

1.24. 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

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

2. Decision

Mitochondrial Donation Explanatory Note and

Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015,

Regulations 8(a)(i), 8(a)(ii) and 8(b)

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

Pre-implantation Genetic Diagnosis (PGD) - Patient selection criteria

2.2. The committee considered the advice that PGD would not be suitable in this case.

Particular Risk

2.3. On the basis of the information presented, 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.

Significant Risk

2.4. On the basis of the information presented, the committee was satisfied that there was a significant risk that a person with those mitochondrial abnormalities caused by a pathogenic mtDNA mutation will have or develop serious mitochondrial disease.

2.5. The committee considered the patient's family history and the manifestation of the disease along with her medical history, which indicates that any child conceived by her is likely to be at risk of being affected by this disease which in the worst case scenario could cause blindness, Multiple Sclerosis-like syndrome, cardiac and neurological disorders and severely impact on the quality of life. The committee also considered the psychological impact of living with the possibility of going blind. The committee acknowledged that men are more likely to be affected by the condition than women.

Peer Review & Specialist Advice

2.6. The committee considered the information provided by the centre. The committee also considered advice from the Peer Reviewer and the Specialist Adviser to the committee.

Authorised Treatment

2.7. 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), caused by a mutation in the MT-ND1 gene (m.3460G>A) for the patient named in the application. The committee recognised the right of the patient not to be identified.

HFEA Code of Practice

2.8. 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

2.9. 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.

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

Welfare of a child

2.11. 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.

2.12. The committee also had regard to the patient and the progressive nature of this condition, which may affect her health further in the future. The committee acknowledged that the centre is responsible for providing the patient with relevant information concerning her treatment to make fully informed ongoing decisions.

Follow up to mitochondrial donation

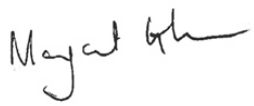
2.13. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical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

2.14. 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

27 November 2018