Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)
Mitochondrial Donation using Pronuclear Transfer (PNT)
Application Reference: M0011
Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m.11778 G>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 statement from a relative affected by the condition)
- Peer Review
- PR response to peer review
- Figure to accompany PR response to peer review
- Peer review response to rebuttal
- Written advice from Statutory Approvals Committee Specialist Adviser
- Person Responsible response to written advice from Statutory Approvals Committee Specialist Adviser
- SAC 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 and agreed with the Peer Reviewer's point below that mutation levels can drift up or down.

1.2. The committee noted that the description in the application for Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m. 11778 G>A) is consistent with the peer review, with one exception, the applicant states that 'mutation levels tend to drift to homoplasmy' – the Peer Reviewer states that this is incorrect and that the levels can drift up or down and there is no evidence of selection for/against the m.11778A>G mutation during transmission (PMID 26740552).

1.3. The Peer Reviewer also commented that the application emphasises the extra-ocular features of LHON. These have been known about for some time, and are vanishingly rare. The Peer Reviewer estimated that they affect 1% or less of affected individuals.

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-ND4 gene (m. 11778 G>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.

Peer Review Advice

1.8. The Peer Reviewer did not agree that PGD would be inappropriate in this case, arguing that there is a significant chance that some oocytes will have less than 60% of the m.11778A>G mutation and be at low risk of developing the disorder.

Specialist Advice

1.9. The Specialist Adviser stated that the application did not contain sufficient information to conclude whether PGD would be inappropriate in this case and outlined some important factors necessary to make a determination.

1.10. The Specialist Adviser stated that the threshold of expression is not clear. This is a prequisite for determining whether PGD would be inappropriate in this case, however the applicant does not mention a threshold. The paper which the Reviewer refers to in their rebuttal (Wilson et al 2016) shows that there is a proband with a mutation load close to 50%. Based on the meta-analysis compiled in this paper on the m.11778G>A mutation, it should be possible to define this threshold accurately, although intuitively 50% does not seem unlikely. The Specialist Adviser agreed with the Reviewer that the mutation load may go up or down as genetic drift is likely to occur. This is also shown in this same paper. There is a possibility that the patient produces oocytes below the threshold. In the responses of the centre of October 18, 2018 to the comments of the Specialist Adviser they refer to a threshold of 18%, but this threshold only applies to fully penetrant mutations and excludes the LHON mutations, like the m.11778G>A mutation. In the application it is claimed that it is likely that this woman's mutation load is consistent across all tissues including her eggs, however no evidence was provided on which this conclusion was based. From the meta-analysis in the Wilson paper, it should be evident how the mutation percentage can differ among the oocytes of a single heteroplasmic carrier. This distribution is important to judge the frequency of oocyte below the threshold. Based on this patient's mutation load, it is not unlikely that she will have oocytes below the threshold in numbers which can be selected in a regular PGD procedure. It should be noted that this likelihood should be calculated on available data and does not require a real PGD cycle, as suggested by the centre.

Committee Consideration

1.11. The committee noted that the patient is heteroplasmic for the m.11778G>A mutation.

1.12. The committee noted that, based on the information provided, the Specialist Adviser confirmed that it could not be concluded whether PGD is inappropriate in this case and that there is existing data available to complete an evaluation for presentation to the committee for consideration.

1.13. The committee took account of the particulars of this patient's case in favour of mitochondrial donation (PNT) rather than PGD. The committee was advised by its Legal Adviser that this factor would form only a part of the information it considered on the specific patient in making its decision and, of itself, would not be sufficient to be a determining factor for approval of this application.

Particular Risk

1.14. 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.

1.15. The committee noted that the application sets out information about LHON, caused by a mutation in the MT-ND4 gene (m. 11778 G>A), including the patient's clinical history and family history of affected individuals, their mutation load and clinical manifestations of the disease.

1.16. The committee noted that this patient is asymptomatic. A relative of the patient manifests clinically. The patient has no preceding pregnancy history as she opted not to conceive until now due to the potential risk of serious mitochondrial disease to her off-spring.

1.17. 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

1.18. The application describes that LHON mutations are typically homoplasmic, although heteroplasmic patients have been reported, as in this case, and demonstrate incomplete penetrance and variable expression.

1.19. LHON is the most common form of mitochondrial disease and results in often devastating inherited visual loss. Individuals present with acute/subacute, bilateral, painless, visual loss often in early adult life. Men are four to five times more often affected than women. The spectrum of visual loss may vary with the worse possible outcome of an individual registered legally blind. However, most patients who develop visual impairment are profoundly affected with a major impact on their mental, social and economic well-being. There is emerging evidence to suggest more widespread multi-system involvement in 11778G>A-related LHON including; cardiac arrhythmia, cardiomyopathy and extra neurological features such as progressive global dystonia [muscle spasms and contractions] and a multiple sclerosis (MS)-like illness referred to as Harding-disease. While the co-occurrence of MS and LHON may be due to chance, Harding Disease has a more aggressive course. 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.

1.20. 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.

1.21. 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

1.22. 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.

1.23. 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.

1.24. The Peer Reviewer predicted 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, and therefore the recurrence risks in this family will be lower than the figures provided above. If an individual is affected this has a profound effect on quality of life, however, it should also be noted that many affected individuals have a very fulfilled life, including high-level employment. Once the vision is impaired, there is no progression. There is, however, a (~10%) chance of spontaneous visual recovery.

1.25. The committee noted the information provided by the Person Responsible to address some of the points raised.

Legal Advice

1.26. 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.

1.27. 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)

1.28. 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

1.29. 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

1.30. 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

2.1. The committee agreed to adjourn its decision on whether to allow mitochondrial donation (PNT) treatment in this case and urged the centre to provide the required information listed below in order to continue consideration of this application.

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

2.2. The committee had regard to its Mitochondrial Donation Explanatory Note 2.5 and 7.1. The committee highlighted that it may only approve applications for patients who are (or are predicted to be) highly heteroplasmic or homoplasmic for a particular mtDNA mutation in their germ line and who have undergone assessment that deems pre-implantation genetic diagnosis (PGD) inappropriate or likely to be unsuccessful.

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

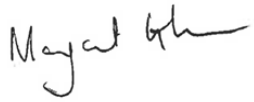
2.4. The committee agreed that the questions raised by the Specialist Adviser which outlined some factors necessary to make a determination on whether PGD would be inappropriate or likely to be unsuccessful were important. The committee had regard to its decision tree and agreed that the applicant should have the opportunity to answer the following questions raised by the Specialist Adviser:

- what is the threshold of expression of clinical manifestation?
- what is the likelihood of this woman producing embryos below the threshold of expression of clinical manifestation?

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