Statutory Approvals Committee – minutes

Centre 0102 (Guy's Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for MEGDEL Syndrome (3-Methylglutaconic Aciduria with Deafness, Encephalopathy, and Leigh-Like Syndrome), OMIM #614739

Thursday, 28 June 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Anthony Rutherford Ruth Wilde	
Members of the Executive	Bernice Ash Dee Knoyle Paula Robinson Catherine Burwood Richard Chamberlain	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer) Temporary Committee Clerk (Induction)
Specialist Adviser	Dr Alan Fryer	
Legal Adviser	Tom Rider	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.

The following papers were considered by the committee:

- Executive Summary
- PGD Application Form
- Redacted Peer Review
- Genetic Alliance UK Statement
- A summary of Barth syndrome (OMIM #302060) presented to the Licence Committee.
- SAC minutes 24 November 2016, Applications to add Methylmalonic Acidemia (multiple types), OMIMs #251000, #251100 and #251110, to the PGD list.
- SAC minutes 27 February 2014, Application to add Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) (OMIM #231680) to the PGD list.
- LC minutes 25 November 2010, Application to add Methylmalonic Aciduria and Homocystinuria (OMIM #277400) to the PGD list.
- LC minutes 29 July 2010, Application to add Propionic Acidemia, (OMIM #606054) to the PGD list.

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Dr Alan Fryer who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application for PGD for MEGDEL syndrome (3-Methylglutaconic Aciduria with Deafness, Encephalopathy, and Leigh-Like Syndrome), OMIM #614739, is consistent with the peer review.

1.3. The committee noted that the Genetic Alliance opinion provided a patient perspective and supported the application.

1.4. The committee had regard to its decision tree. The committee noted that the centre is licensed to carry out PGD. The committee was also satisfied that the centre has experience of carrying out PGD and that generic patient information about its PGD programme and associated consent forms had previously been received by the HFEA.

1.5. The committee noted that the condition being applied for is not on the list of approved PGD conditions.

1.6. The committee noted that the proposed purpose of testing the embryos was as set out in paragraph 1ZA(1)(b) of Schedule 2 of the Act, i.e. 'where there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality, establishing whether it has that abnormality or any other gene, chromosome or mitochondrion abnormality'.

1.7. The committee noted that the condition is inherited in an autosomal recessive pattern which means there is a 25% chance of an embryo being affected with the condition in each pregnancy, if both parents have a relevant mutation.

1.8. The committee noted that MEGDEL syndrome is primarily a disorder of the biosynthesis of phospholipid, with secondary mitochondrial dysfunction and rapid regression and progressive multi-organ disorder

1.9. The committee noted that a recent academic study cited in the application found that in 67 individuals with MEGDEL syndrome:

- 70% presented in the neonatal period;
- 27% had died, with an average age of death of 9 years (main cause of death was respiratory infections);
- Many survived to adulthood but 100% of them had intellectual disability which was graded in 51 patients, and was severe in 73%, moderate in 16% and mild in 12%;
- 35% presented with epilepsy;
- 78% never learned to walk;
- 39% developed scoliosis;
- 93% were completely dependent on others for daily living activities;

1.10. MEGDEL syndrome is an extremely rare disorder, but from the limited clinical information available, the Peer Reviewer expects the penetrance of the condition to be effectively 100%.

1.11. The committee noted there is no treatment available that is curative, or which modifies the course of the disease. Treatment is supportive aimed at keeping an affected individual as comfortable as possible. Most patients will be completely dependent on others for daily living activities.

1.12. The committee noted that the Peer Reviewer stated that MEGDEL syndrome is one of a group of disorders affecting biosynthesis and remodelling of complex lipids, along with Sengers syndrome (OMIM #212350) and Barth syndrome (OMIM #302060). It was noted that Barth syndrome was first licensed for PGD in January 2004.

1.13. The panel noted that Sengers syndrome is not currently on the list of conditions for which PGD can be applied, but is an autosomal recessive mitochondrial disorder characterized by congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, exercise intolerance, and lactic acidosis. The condition has two forms, a lethal neonatal form and a chronic form. In the neonatal form, hypertrophic cardiomyopathy is diagnosed at birth in half of patients, sometimes with encephalopathy, and death in the first year often occurs due to cardiac failure. Marked lactic acidemia is seen with even limited muscular exertion. Patients with the chronic form have stable cardiomyopathy and myopathy with normal mental development. Sengers syndrome is caused by homozygous or compound heterozygous mutation in the AGK or the SLC25A4 genes. The AGK gene encodes the mitochondrial acylglycerol kinase, which plays a role in the assembly of adenine nucleotide translocator. The SLC25A4 gene encodes the heart and muscle specific isoform 1 of the mitochondrial adenine nucleotide translocator. Some of the symptoms of Sengers syndrome appear very similar to those of Barth syndrome, which is already approved for PGD, e.g. hypertrophic cardiomyopathy and skeletal myopathy, resulting in early death in some cases.

1.14. The committee noted the inspectorate's request to consider whether MEGDEL syndrome (3-Methylglutaconic Aciduria with Deafness, Encephalopathy, and Leigh-Like Syndrome), OMIM #614739, should be approved for inclusion on the PGD List. The inspectorate also requested that the committee considers approving Sengers syndrome, OMIM #212350, since the condition is similar in symptoms and severity in the worst case (i.e. death in infancy) to Barth syndrome, which is already on the PGD approved list. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario, MEGDEL syndrome (3-Methylglutaconic Aciduria with Deafness, Encephalopathy, and Leigh-Like Syndrome), OMIM #614739 is serious, with symptoms developing soon after birth, causing devastating multi-organ disease and death in infancy. The committee had also agreed that in the worst case scenario, Sengers syndrome is a severe condition, which can result in neo-natal death. The committee considered the impact of these syndromes on the individual's quality of life and the family.

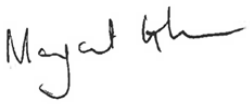
2.2. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormalities in question and that there is a significant risk, given the conditions' worst symptoms, that a person with the abnormality will have or develop a serious physical or mental disability, a serious illness or any other serious medical condition. The committee was therefore satisfied that the following conditions meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise testing for:

- MEGDEL syndrome (3-Methylglutaconic Aciduria with Deafness, Encephalopathy, and Leigh-Like Syndrome), OMIM #614739
- Sengers syndrome, OMIM #212350

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

30 July 2018