Lowe syndrome identified in the offspring of an oocyte donor who was an unknown carrier of a de novo mutation: a case report and review of the literature

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Abstract

Background: Oculocerebrorenal syndrome of Lowe is an X-linked disorder with very low prevalence in the general population. The OCRL gene encodes the protein phosphatidylinositol 4,5-bisphosphate-5-phosphatase, a lipid phosphatase, located in the trans-Golgi network. Point mutations in the OCRL gene cause Lowe syndrome and Dent disease, which are characterized as a multisystemic disorder. The symptoms of Lowe syndrome are expressed primarily as dysfunction of the eyes, kidneys, and the central nervous system.

Case presentation: This report describes a case of a 31-year-old Georgian woman with a de novo pathogenic mutation causing oculocerebrorenal syndrome of Lowe, who was a volunteer in an oocyte donation program for in vitro fertilization purposes, and the outcome of the treatments of this particular donor’s oocyte receivers, describing the implications of the mutation for the children born as a result of the treatments. It raises important medical and ethical issues about the necessity of genetic testing of oocyte donors and the possibility of rare genetic disorders being inherited by the offspring of donors.

Conclusion: This particular case indicates the legal, medical, and emotional risks of utilizing donor oocytes from phenotypically healthy women, whose genetic constitution is unknown in terms of being silent carriers of rare diseases. In addition, all the necessary actions were followed; the further examinations that are required are mentioned. The donor and the offspring should be further tested. The remaining cryopreserved embryos should be destroyed or preimplantation genetic testing should be performed before they are utilized. Finally, all the people involved, the treated couples and the donor, alongside her family, should follow genetic and psychological counselling.

Keywords: Lowe syndrome, Dent disease, Assisted reproduction, Rare genetic disease, X-linked disease, Oocyte donation program, De novo mutation, IVF, Genetic screening

Introduction

Oculocerebrorenal syndrome of Lowe (OCRL) or Lowe syndrome is an X-linked disorder [1], first described in 1952 [2]. The syndrome is extremely rare; its estimated prevalence is 1 out of 500,000 individuals in the general population [3].

Lowe syndrome is related to a combination of: (i) ocular anomalies (cataracts, glaucoma); (ii) renal disorders; and (iii) central nervous system defects (hypotonia, hyporeflexia, intellectual disability). It is also correlated with oral manifestations: delayed eruption, crowding, and constricted palate; taurodontism of the molars; hypoplastic enamel; dental caries; and large pericoronal radiolucencies [4].

Genetic and molecular basis of the syndrome

Lowe syndrome is caused by mutations in the OCRL gene (Figs. 1 and 2), which is located on chromosome Xq26 (#300535) [5, 6]. To date, more than 200 mutations in the OCRL gene (2680 bp) have been described. The genetic
basis could be nonsense mutations, splice site mutations, missense mutations, insertions, and deletions [7]. Normally, the OCRL gene encodes the protein phosphatidylinositol 4, 5-bisphosphate-5-phosphatase (OCRL-1), which is a lipid phosphatase, localized in the trans-Golgi network [8, 9]. The importance of the protein relies on the fact that it controls the cellular levels of a critical metabolite, phosphatidylinositol 4,5-bisphosphate (PIP2). Thus, the mutated gene, which results in the deficiency of the enzyme, causes the protein manifestations of the syndrome. In fact, cells affected by Lowe syndrome, and consequently tissues and organs, are characterized by disturbed metabolism because PIP2 is crucial in intracellular signaling, protein trafficking, and polymerization of actin cytoskeleton [3, 9, 10]. It is suggested that the accumulation of the metabolite, caused by the enzyme insufficiency, along with a mutual disequilibrium of the phosphoinositides lead to the clinical picture of the affected infants.

Mutations in the OCRL gene also result in Dent disease type 2 (#300555). Dent disease type 2 is characterized by a broad phenotypic spectrum, depending on the OCRL mutations that are responsible, implying that this particular disease may be a mild variant/phenotype of Lowe syndrome [11].

**Diagnostic criteria – differential diagnosis**

Point mutations in the OCRL gene cause the multisystemic disorder Lowe syndrome, affecting the eyes, kidneys, and the central nervous system [2, 9]. All patients suffering from Lowe syndrome show dense bilateral cataracts present at birth. Half of the cases develop glaucoma, which can be detected within the first year of life or, in some cases, later in life [3]. The renal dysfuncion is expressed as Fanconi syndrome, which can be detected during the first months of life and shows a wide range of severity among the population. The symptoms include proteinuria, proximal renal tubular acidosis, bicarbonaturia, phosphaturia, hypercalciuria, aminoaciduria, and hypokalemia [12]. The above symptoms may lead during the second decade of life to chronic renal failure [3].

The first picture of the syndrome is apparent at birth, as serious hypotonia and hyporeflexia are observed. A general delay in neuropsychomotor development is also observed. Approximately 10% of the patients with Lowe syndrome show mild to severe intellectual disability [3]. Lowe syndrome is associated with maladaptive behavior, including auto-aggressive and hetero-aggressive behaviors, anger, and obsessive-compulsive behavior [13]. Approximately 50% of the adult patients show seizures and 9% of the patients present febrile convulsions [14, 15].

Among the reported symptoms of Dent disease type 2, patients usually display low molecular weight proteinuria and hypercalciuria and in some cases nephrocalcinosis. Additional symptoms may include increased lactate dehydrogenase, increased creatine kinase, short stature, and umbilical hernia [11]. At least six different mutations of the OCRL gene have been described and it is estimated that 59.7% of families showing a Dent disease phenotype have mutations of the OCRL gene [11].

**Case presentation**

**Oocyte donation program**

The Georgian donor at the age of 31 years visited Assisting Nature in vitro fertilization (IVF) clinic and expressed her desire to donate her oocytes to infertile couples. According to Greek law, thorough medical screening of all female donors is required: (i) blood group, Rh, Rhesus type, hemoglobin (Hb)-electrophoresis; (ii) genetic tests for cystic fibrosis, α thalassemia, β thalassemia, δβ thalassemia and Fragile X syndrome, and full karyotype testing; and (iii) testing for infectious diseases is also mandatory, that is, human immunodeficiency virus (HIV), Venereal Disease Research Laboratory (VDRL) antigen,
hazard of misidentifying the donor. The genetic testing revealed that the donor’s genetic origin of the disease indicating Lowe syndrome. At this point, the couple informed us about the case and the chance that the biological mother-donor might be the carrier of a mutation that causes Lowe syndrome.

The fifth couple who received oocytes from this donor had already undergone embryo transfer by the time we were informed about the possible Lowe syndrome from the previous couple. They also achieved a twin pregnancy, leading to delivery of twins: a healthy baby girl and a boy that suffers from some of the optical symptoms of Lowe syndrome. The parents informed us that the boy had already been operated on for cataracts. We are expecting the genetic analysis of the potentially affected boy.

In conclusion, 41 metaphase II (MII) oocytes were used from this particular donor and 31 utilizable blastocysts were formed. Nine offspring were delivered by the treated couples resulting in a live birth rate of 75% since 12 blastocysts were embryo transferred. All the children delivered seven were male and two were female. The two female children were unaffected by the mutation; out of the nine male offspring, two were diagnosed with Lowe syndrome and one died, its diagnosis remains unknown, and, finally, the rest of them were healthy and unaffected by the disease.

Genetic counselling of the donor
The donor was immediately informed, and after discussion about protecting her anonymity, she agreed to undergo additional genetic analysis. Supplementary counseling was offered: first, with regard to her female offspring’s future family planning; and, second, regarding her wish for a possible future pregnancy. The extra genetic tests that the donor underwent proved that a de novo mutation in the OCRL gene of the X chromosome exists, despite the absence of any previous family medical history of Lowe syndrome, and it is responsible for Lowe syndrome and Dent disease (Fig. 3 Hereditary tree).

Genetic analysis
A genetic laboratory conducted the analysis from genomic deoxyribonucleic acid (DNA) isolated from a peripheral blood sample. The analysis included sequencing
of the whole coding region and all of the splicing regions of exons and introns (±8 bp) of the gene OCRL (NM_000276.3, chr. X). The amplification of the examined regions was completed by oligonucleotide-based target capture (QXT, Agilent Technologies) followed by next generation sequencing (MiSeq, Illumina). Alignment and variant calling were performed using Burrows-Wheeler Aligner (BWA, MiSeq reporter) and Genome Analysis Toolkit (GATK). Sanger sequencing was performed in order to confirm any detected variant. Results from this analysis were evaluated according to international standards [16] and included all mutations with known clinical significance, mutations non-reported in the literature, and mutations with unknown clinical significance.

The genetic analysis proved c.940-11G>A p.? mutation in OCRL gene in heterozygous condition. According to international literature, pathogenic mutations to OCRL gene cause Lowe syndrome (#309000) and Dent disease (#300555) in an X-linked recessive inheritance pattern. The c.940-11G>A p.? mutation is reported in patients with Lowe syndrome and affects splicing procedure resulting in the premature termination codon (p.Lys313_Val314insAsnSer*) that alters the structure and function of the produced protein.

By the time we received the genetic results of the donor the Greek National Authority of Assisted Reproduction was informed for further actions to be implemented. In addition, we communicated with all the couples involved with this donor to ask them to inform us about the health status of their children, whether they are affected by Lowe syndrome or not and to provide genetic counseling (Table 1).

**Discussion**

The above case signifies the legal and emotional risks of utilizing donor oocytes from phenotypically healthy women, whose genetic constitution is unknown in terms of being silent carriers of rare diseases. First, such genetic risks cannot be avoided, and second, although the couples who receive the donor eggs are extensively consulted, it is difficult for them to realize or even accept taking such a risk [17, 18].

Procreation with donor oocytes is expected to be as safe as the natural conception of fertile couples. Therefore, although the possibility of having a child with an inherited disorder is still present, oocyte acceptor couples underestimate such a risk. On the other hand, currently, extensive genetic testing of gamete donors is not recommended for economic or ethical reasons, unless there is a family history or other specific reason [18]. In our specific donor, the mutation is very rare (1 out of 500,000) and, moreover, none of her male family members were affected, indicating the de novo origin of the mutation.

Since Lowe syndrome is an X-linked disease, it is usually inherited by sons from the mother. Asymptomatic female individuals may be carriers of the mutated gene and carry 25% probability of having a child (boy) with the syndrome. Carriers of Lowe syndrome can be reliably (94%) diagnosed by an ophthalmological evaluation [19], as they display specific lens opacities on slit-lamp examination [20]. However, such a diagnostic tool is usually used only in cases of women with a family history of the syndrome because they are at greater risk of having an affected child. The family of this particular

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**Table 1** Summary of the cases treated with the affected donor’s oocytes

| Cases | MII oocytes | Blasts available | Fresh ET | Result | FRET ET | Live birth | Gender | Affected | Outcome |
|-------|-------------|-----------------|----------|--------|---------|------------|--------|----------|---------|
| Couple 1 | 10 | 7 | 2DS | Pregnant | – | 2 | Male-male | Unaffected | Healthy-healthy |
| Couple 2 | 9 | 7 | 2DS | Terminated | 2DS | 1 | Male | Unaffected | Healthy |
| Couple 3 | 6 | 4 | 2DS | – | – | 2 | Male-female | Unaffected | Healthy-healthy |
| Couple 4 | 4 | 4 | 2DS | Pregnant | – | 2 | Male-male | Unknown-affected | 1 boy died, 1 alive |
| Couple 5 | 12 | 9 | 2DS | Pregnant | – | 2 | Male-female | female unaffected, male affected | Boy operated cataracts |

2DS 2 embryos day 5, ET embryo transfer, FRET frozen embryo transfer, MII metaphase II
donor had never shown any relevant symptoms and, as a consequence, no such examination took place.

Cases of de novo mutations have been reported in 30% of male individuals with Lowe syndrome. In this case, the mother is not a carrier and the possibility of having another affected child is equal to that of the general population, as proved to happen in this specific case. Similarly, somatic/germline mosaicism may be identified and should be considered and mentioned in genetic counseling (4.5% of the patients) [21]. In cases of women with a germline mosaicism, no molecular, enzymatic, or slit-lamp testing can be used for identification of the situation and the women are perfectly healthy. In cases of female carriers, measurement of the activity of the enzyme is not usually accurate because of the random X-chromosome inactivation [22]. In any case, mothers of affected boys or women with a family history of Lowe syndrome should undergo prenatal testing.

It is obvious that if all the necessary examinations and tests of a candidate donor are negative and the donor has a normal status, no family record of any syndrome exists, and is considered healthy, then she is thus suitable for an oocyte donation program. Syndromes with extremely rare emergence, such as Lowe syndrome, can practically only be diagnosed at a preimplantation or prenatal level in families with a known history of the disease. Otherwise, in cases in which prenatal testing is required, it can be performed with DNA analysis and ultrasound examination. In the latter case, ultrasonography aims to detect the early presence of fetal cataracts. The fetal lenses can be identified from 14 weeks and high attention should be given to the orbital region during the ultrasound [23]. Alternatively, fetal cells obtained either by chorionic villus sampling or by amniocentesis can be used for DNA analysis for the OCRL1 gene.

In the unfortunate coincidence that the prenatal diagnosis of the syndrome has not been done and an ailing child is born, then the treatment of Lowe syndrome is mainly symptomatic, aiming to improve the clinical condition and the evolution of the disease. One of the major goals of the treatment is to postpone the terminal renal disease, which is the most frequent reason for death [3] and limits the lifespan of the patients to a maximum of 40 years. Management of the ocular dysfunctions includes surgical cataract removal (as already happened in one of the cases), use of glasses, and frequent testing for early glaucoma diagnosis. In addition, rehabilitation therapy and seizure drugs are required to treat the complications of the syndrome, while other drugs such as neuroleptics, stimulants, anti-depressives, and so on can be used, but their efficiency is limited. Renal dysfunctions may be treated with different supplements and vitamin D is needed to treat rickets. In any case, the right treatment should be decided according to the clinical status of the patient. Only a minority of patients are recorded to have had a successful renal transplantation [3].

The importance of psychological counseling in fertility care has been acknowledged for many years because infertility treatment is stressful and may result in multiple losses that provoke feelings of sadness, grief, depression, anxiety, and isolation. IVF treatment with donor eggs is highly successful but social, legal, and ethical issues arise. Screening and educating patients about the possible implications of gamete donation have become central recommendations for pretreatment counseling in guidelines issued in the USA, UK, Australia, New Zealand, and Germany among other countries. Internationally, considerable variation remains in recipient counseling, ranging from legislated, recommended, to minimal [24, 25].

Conclusions
The aforementioned realistic case indicates that, in the near future, carrier screening of oocyte or sperm donors might become fundamental. Ropers in 2012 stated that 1–2% of all couples are carriers of genetic diseases and in this case a 25% risk of having an affected child exists [26]. In the extreme scenario that a full genetic screening (WGS) should be performed, oocyte donors may be excluded from egg donation programs for possible risks that may never emerge. All donors are plausible carriers of such conditions so targeted carrier testing might be preferable to extended screening.

Thorough genetic consultation is of paramount importance for: (i) donors, to scrutinize their hereditary history and provide useful information about family members and therefore early identification of possible genetic diseases; and (ii) acceptors of genetic material in order to realize the risks that such procedures render. The current case of a rare disease – Lowe syndrome – is such an excellent paradigm that carrier screening of donors in the future, although still controversial for ethical reasons due to genetic selectivity, might gain a lot of popularity.

Abbreviations
AMH: Anti-Müllerian hormone; FRET: Frozen embryo transfer; FSH: Follicle-stimulating hormone; GATK: Genome Analysis Toolkit; GnRH: Gonadotropin-releasing hormone; Hb: Hemoglobin; HBV: Hepatitis B virus; hCG: Human chorionic gonadotropin; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HMG: Human menopausal gonadotropin; IVF: In vitro fertilization; LH: Luteinizing hormone; MII: Metaphase II; OCRL: OCRL gene; OCRL: Oculocerebrorenal syndrome of Lowe; PIP2: Phosphatidylinositol 4,5-bisphosphate; protein OCRL-1: Phosphatidylinositol 4,5-bisphosphate-5-phosphatase; rec-FSH: Recombinant follicle-stimulating hormone; rec-hCG: Recombinant human chorionic gonadotropin; VDRL: Venereal Disease Research Laboratory; WGS: Full genetic screening.

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Authors’ contributions
PT, TC, and ET performed all embryological laboratory work including oocyte pick-ups, denudation of oocytes, fertilization, embryo evaluation and selection, vitrification, and thawing. EP, RN, and AA were responsible for the
donor’s and the patients’ treatment, follow-up, and welfare. They administered the necessary medication during IVF therapy and informed the patients and the donor of the implications and the success rates of the treatment. IP performed all necessary genetic analysis and tests. All authors contributed to the writing of this manuscript and read and approved the final manuscript. Written informed consent was obtained from the patient for publication of this case report.

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Competing interests
The authors declare that they have no competing interests.

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