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Incidental finding of lipaemia retinalis on diabetic retinal screening

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Summary

A 37-year-old female of South Asian origin was referred to our diabetes clinic for evaluation of an unusual finding during her retinal screening. Her retinal blood vessels appeared white in contrast to the normal pink-red colour. She had type I hyperlipidaemia, confirmed by genotype, and was recently diagnosed with diabetes, secondary to pancreatic insufficiency, for which she had suboptimal control and multiple hospitalisations with recurrent pancreatitis. On examination, she had multiple naevi on her skin; the rest of the examination was unremarkable. The patient did not report any visual disturbances and had intact visual acuity. Investigations showed raised total cholesterol (12.5 mmol/L) and triglycerides (57.7 mmol/L). Following evaluation, the patient was diagnosed with lipaemia retinalis, secondary to type I hyperlipidaemia. The patient was managed conservatively to reduce the cholesterol and triglyceride burdens. However, therapies with orlistat, statin, fibrates and cholestyramine failed. Only a prudent diet, omega-3 fish oil, medium-chain triglycerides oil and glycaemic control optimised with insulin showed some improvements in her lipid profile. Unfortunately, this led her to becoming fat-soluble vitamin deficient; hence, she was treated with appropriate supplementation. She was also recently started on treatment with volanesorsen. Following this, her lipid parameters improved and lipaemia retinalis resolved.

Learning points:

- Lipaemia retinalis is an uncommon incidental finding of type I hyperlipidaemia that may not affect vision.
- Management of associated dyslipidaemia is challenging with minimal response to conventional treatment.
- Increased awareness of lipaemia retinalis and specialist management is needed as part of regular patient monitoring and personalised management.

Background

Hyperlipidaemia is a metabolic syndrome defined as elevated serum triglyceride and cholesterol levels, with disturbances to low- and high-density lipoprotein concentrations. It can be primary, also called familial, or acquired and is common in patients with diabetes mellitus who present with hypertriglyceridaemia

and/or hypercholesterolaemia (1, 2). Secondary causes of hyperlipidaemia include drugs, chronic alcohol abuse, uncontrolled diabetes mellitus, hypothyroidism and obesity (1, 3). It is the most common disorder of lipoprotein metabolism, affecting an estimated 10% of US children and adolescents (4). It increases the risk of



atherosclerosis, with multisystem involvement including the gastrointestinal system, skin and eyes. Five subgroups of primary hyperlipidaemia have been defined based on the type of lipoproteins involved (Table 1) (5). Of these, types I, IV and V are characterised by hypertriglyceridaemia. Chylomicronaemia occurs with a triglyceride level >25.9 mmol/L and is defined as chylomicronaemia syndrome associated with systemic signs and symptoms, such as eruptive xanthomas, recurrent episodes of abdominal pain, hypertriglyceridaemia and lipaemia retinalis (6, 7).

Lipaemia retinalis is a rare ocular manifestation and clinical sign of hypertriglyceridaemia and chylomicronaemia. It can occur in both children and adults (2). Its incidence correlates approximately with the level of plasma triglycerides; however, the key factor is the level of chylomicrons (6). It presents with creamy-white retinal blood vessels and a salmon-pink retina on fundoscopic examination, due to an increased chylomicron level in circulating retinal blood (6). Most cases do not affect visual acuity. Although described as rare, Brunzell and Bierman

reported that lipaemia retinalis is underdiagnosed and occurs in 23% of patients with chylomicronaemia, which may be explained by the lack of routine fundoscopic examination (7). Herein, we describe a patient with grade III lipaemia retinalis and the complexities of the patient management.

Case presentation

A 37-year-old South Asian woman with a 19-year history of genotype-confirmed type I hyperlipidaemia was referred to our diabetes clinic from the NHS Diabetic Eye Screening Programme for evaluation of an unusual finding during her retinal screening. Her retinal blood vessels appeared white, in contrast to the normal pink-red colour (Fig. 1).

The patient was diagnosed with diabetes mellitus, secondary to pancreatic insufficiency due to chronic pancreatitis nearly a year prior to this index presentation, for which she was on metformin and long-acting insulin but had suboptimal control and multiple hospitalisations

Table 1 Fredrickson–WHO classification for hyperlipidaemia (5). The five subgroups of hyperlipoproteinaemia and their common alternative names, the molecular abnormalities involved, the specific lipoproteins that are significantly elevated, the associated symptoms, the appropriate evidence-based treatments and the relative occurrence rates of the subgroups are presented.

Hyperlipoproteinaemia, type/synonyms	Defect	Increased serum lipoprotein	Symptoms	Treatment	Occurrence
Type I		Chylomicron	Pancreatitis, lipaemia retinalis, xanthomas, hepatosplenomegaly	Diet	Rare
Familial hyperchylomicronaemia	↓LPL				
Familial APOC2 deficiency	Altered APOC2				
Buerger–Gruetz syndrome	LPL inhibitor in blood				
Type II			Xanthelasma, arcus senilis, corneal arcus, tendon xanthomas		
Familial hypercholesterolaemia	↓LPL receptor	LDL		Bile acid sequestrants, statins, niacin	Common
Familial combined hyperlipidaemia	↓LDL receptor; ↑APOB	LDL, VLDL		Statins, niacin, fibrate	Most common
Type III			Tubo-eruptive xanthomas, palmar xanthoma	Fibrate, statins	Rare
Familial dysbetalipoproteinaemia	APOE2 synthesis defect	IDL			
Type IV			Lipaemia retinalis, pancreatitis, xanthomas	Fibrate, niacin, statins	Common
Familial hypertriglyceridaemia	↑VLDL production, ↓Elimination	VLDL			
Type V			Lipaemia retinalis, xanthomas	Niacin, fibrate	Rare
Combined hypertriglyceridaemia	↑VLDL production, ↓LPL	VLDL, chylomicron			

APOB, apoprotein B; APOC2, apoprotein C2; APOE2, apoprotein E2; IDL, intermediate-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.

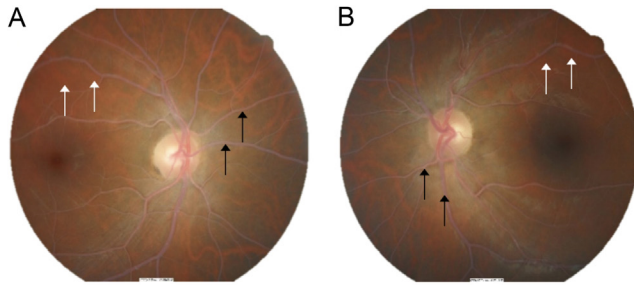


Figure 1
Retinal images of a patient's right (A) and left (B) eyes before treatment, showing normal optic discs with white retinal vessels (black arrows) in the posterior poles and peripheral retina. All the retinal vessels have a similar pale colour and are only distinguishable by size. The choroidal vessels have a similar pallor, giving the fundus a salmon-pink appearance (white arrows). These findings are suggestive of grade III lipaemia retinalis.

with recurrent pancreatitis. She had no significant family history. Her marriage was non-consanguineous, and she had five children, none of whom struggled with lipid abnormalities. She was a lifelong non-smoker and did not consume alcohol.

Investigation

Upon examination, the patient had multiple naevi on her skin, for which she was being managed conservatively by dermatologists. The rest of her examination was unremarkable. Laboratory investigations showed a raised triglyceride level of 57.7 mmol/L (reference range: <2.0 mmol/L) and total cholesterol level of 12.5 mmol/L (reference range: <5.0 mmol/L), markedly higher than previous readings. Her diabetes control was suboptimal, with an HbA1c of 74 mmol/mol (8.9%). The remaining blood tests were within the normal limits. Following evaluation, the patient was diagnosed with grade III lipaemia retinalis, secondary to type I hyperlipidaemia.

Treatment

Following her diagnosis with severe hypertriglyceridemia and type I hyperlipidaemia, she was initially managed under a specialist multidisciplinary team (including diabetologist, lipid specialist and dietician) with various stand-alone and combination therapies with fibrates, cholestyramine, orlistat and statin over the years; however, these proved to be ineffective. Dietary interventions with dietician input consisting of fruits, vegetables, whole grains, legumes, nuts, fish, and low-fat dairy products rather than refined or processed foods, red meats, high concentrated sweets, eggs, and butter, strict glycaemic control, optimised with

a combination of short- and long-acting insulin, omega-3 fish oil, and the use of medium-chain triglyceride oil led to some improvements in her lipid profile. The latter resulted in fat-soluble vitamin deficiency, confirmed by laboratory blood tests, which was subsequently treated with vitamins D and E supplementation following multidisciplinary team guidance. She was also started on volanesorsen, which was well-tolerated, to lower the serum triglyceride level. This lowered her serum triglycerides to single figures with no further admission with pancreatitis. However, there were some elevations of triglycerides depending on her glycaemic control as poor glycaemic control increases very low-density lipoprotein (VLDL) production.

Outcome and follow-up

Following significant changes, her lipid parameters improved, with a triglyceride level of 27.4 mmol/L and total cholesterol level of 7.6 mmol/L (Fig. 2; Supplementary materials, see section on [supplementary materials](#) given at the end of this article). These were further lowered to single figures (7.5–10.5 mmol/L) following introduction of volanesorsen. At the last follow-up, over 3 years after the first presentation, retinal images showed a complete resolution of lipaemia retinalis and normalisation of the retina (Fig. 3). She was genetically tested, and her family offered screening.

Discussion

Lipaemia retinalis is a rare manifestation of hyperlipidaemia and a direct consequence of elevated triglyceride and/or chylomicron levels in retinal vessels (6, 7, 8). In secondary

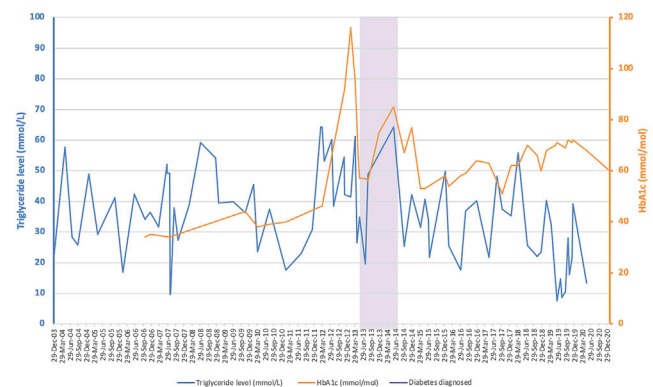


Figure 2
Blood samples were collected at intervals over the case period when the patient consulted. The results show fluctuations in triglyceride (blue), and total cholesterol (orange) levels over time. Purple shaded area illustrates the period when the patient was diagnosed with diabetes mellitus.

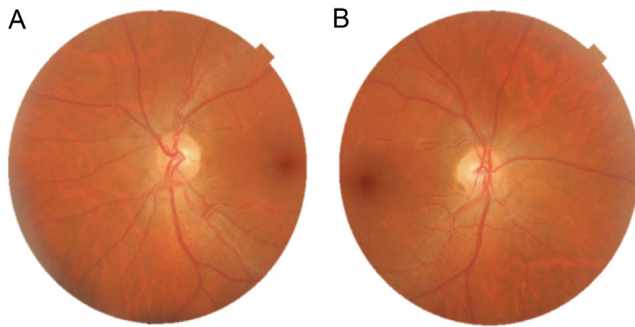


Figure 3 Retinal images of the patient's right (A) and left (B) eyes after treatment, showing a complete resolution of the ocular findings of lipaemia retinalis, with the retinal vessels and retina restored to their normal appearances.

hyperlipidaemia, a major cause of lipaemia retinalis is chylomicronaemia which results from uncontrolled diabetes mellitus (6). As for primary hyperlipidaemia, lipaemia retinalis is only observed in patients with type I, IV and V hyperlipidaemia without hypertriglyceridaemia, and is not commonly associated with lipaemia retinalis (2, 9).

The pathological appearance of lipaemia retinalis is due to the visualisation of triglyceride-laden chylomicrons circulating in the retinal vessels, which have a light-scattering effect and produce a turbid appearance (3, 6). As chylomicrons contain a high proportion of triglycerides (95%), a raised triglyceride level is observed in lipaemia retinalis (6). Characteristic fundus changes, namely discolouration of the retinal vessels are primarily observed when plasma triglyceride levels are >50 mmol/L. This varies from a salmon-pink to creamy-white colour, depending on the plasma triglyceride level (6).

Early signs of lipaemia retinalis, at a triglyceride level of 50–90 mmol/L, are confined to the peripheral retina, where the vessels appear thin and creamy (6). As the triglyceride level increases to 91–129 mmol/L, vessels in the posterior pole become creamy as the lipaemia extends towards the optic disc (6). At a triglyceride level >130 mmol/L, retinal arteries and veins adopt a similar creamy-white appearance and are only distinguishable by size (6). Similar changes in

the choroidal vessels gives the fundus a salmon-coloured appearance (6).

A grading system describes the stages of lipaemia retinalis (Table 2), of which grade III has rarely been described (6, 9). Based on this classification, our patient had grade III changes. This is particularly interesting as our patient had a relatively low triglyceride level of 57.7 mmol/L. It must be noted that not all patients with elevated triglyceride or chylomicron levels show lipaemia retinalis, suggesting other influencing factors, such as haematocrit and translucency of vessels (9). We also considered the impact of ethnicity as Asian populations have been shown to have more severe manifestations of metabolic syndrome (10). More studies are needed to confirm this, perhaps, with a new grading system specifically for Asian populations.

Vision is initially normal, but may be affected by advanced lipaemia or in the presence of age-related macular degeneration (6). However, persistent lipaemia retinalis can lead to extensive, irreversible vision loss (6). Hence, rapid recognition and reversal are needed and have been shown to improve prognosis (6). A low-fat diet can be used for management as well as primary and secondary prevention of lipaemia retinalis in high-risk individuals (11). Currently, there are no specific medications that can be used to treat lipaemia retinalis. Lipid-lowering therapies with fibrates, nicotinic acid and n-3 polyunsaturated fatty acid can reduce triglycerides levels by up to 50%, which may cause rapid reversal of abnormal findings (12, 13, 14). Volanesorsen, a new pharmacological drug received by our patient, inhibits hepatic *APOC3* mRNA and has been shown to significantly reduce triglyceride levels. *APOC3* glycoprotein is synthesised in the liver and to a lesser extent in the small intestine and has recently being recognised as a key regulator of plasma triglyceride levels. *APOC3* is a potent inhibitor of lipoprotein lipase resulting in inhibition of lipolysis, hence reducing triglyceride levels. It has also been reported to inhibit hepatic lipase activity, promoting VLDL production and secretion, as well as inhibiting the clearance of triglyceride-rich lipoproteins (15). Injection site reactions and thrombocytopenia were the most commonly reported adverse events of volanesorsen – fortunately, this was well-tolerated by our patient. Improvement of the lipid profile might also prevent acute complications of hypertriglyceridemia, such as acute pancreatitis and cardiovascular events. Optimisation of glycaemic control in patients with poorly-controlled diabetes is essential for diabetes management (16). As in this case, optimal management lowered the plasma triglyceride levels and lead to a complete resolution of fundoscopic findings alongside the other signs and

Table 2 Clinical features of lipaemia retinalis (9). To view the full dataset for the blood results within the ScholarOne system please click the 'Files' tab to download the documents.

Grade	Intensity	Clinical appearance
I	Early	White and creamy peripheral vessels
II	Moderate	Creamy-coloured vessels extending towards optic disc
III	Marked	Salmon-coloured retina, all vessels having milky aspect



symptoms of chylomicronaemia syndrome (4, 6, 7). This highlights the importance of involving dieticians and wider multidisciplinary team as our patient was initially resistant to conventional lipid-lowering agents. Earlier dietician input could have prevented both chronic pancreatitis and the development of lipaemia retinalis. Exchange transfusion has been proposed as a management option for patients with severe hypertriglyceridaemia (17, 18). Furthermore, surgical management such as ileal bypass surgery has also been shown to be effective in improving the lipid profile. However, surgical interventions should only be opted for in cases where the patient does not respond to conventional medical therapies.

In the UK, the National Institute for Health and Care Excellence provides a clear guidance for genetic testing, identification and management of familial hypercholesterolemia (19). This includes a structured annual review for any symptoms of coronary heart disease, smoking status, fasting lipid profile and current management options with no specific emphasis on signs and symptoms of lipaemia retinalis. Given the potential visual deficits and systemic complications of lipaemia retinalis and severe hypertriglyceridemia, we suggest regular screening for lipaemia retinalis in all patients with familial hypercholesterolaemia to prevent morbidity and mortality from this condition.

Conclusion

Lipaemia retinalis is an initially asymptomatic condition, which is an important clinical indicator, with high specificity, for elevated triglyceride and chylomicron levels. Because it does not typically cause visual symptoms and presents first in the peripheral retina, lipaemia retinalis is underdiagnosed. It can be rapidly resolved by lipid-lowering measures; however, persistent lipaemia retinalis and hypertriglyceridaemia may lead to irreversible visual deficits and more severe systemic complications. Given that lipaemia retinalis is an important ocular finding of potential cardiovascular disease, it is essential that clinicians recognise the signs and symptoms so that treatment can be rapidly commenced.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EDM-21-0051>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient (or patient's guardian) for publication of the submitted article and accompanying images.

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