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ORIGINAL ARTICLE

Early detection of severe hypertriglyceridemia using teleconsultation in a clinical laboratory setting



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KEYWORDS

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Secondary factors;
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Abstract

Background: Teleconsultation in the context of clinical laboratories is a valuable tool for the early detection of dyslipidemia and prevention of cardiovascular risk. Here, we describe a patient who was referred to the Lipid Unit of the Virgen Macarena Hospital due to an alert for severe hypertriglyceridemia through its teleconsultation program.

Case presentation: A comprehensive clinical and biochemical study of the patient was carried out, and genetic testing was performed on the patient and his family. The proband and his family showed mild to severe hypertriglyceridemia and various secondary factors, together with a genetic background associated with a triglyceride-raising effect.

Conclusion: This extensive study has identified a family at high risk of cardiovascular disease and acute pancreatitis. These findings can help maximize lifestyle changes and improve the clinical management of their dyslipidemia.

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PALABRAS CLAVE

Hipertrigliceridemia grave;
Enfermedad cardiovascular;
Laboratorio clínico;
Teleconsulta;
Factores secundarios;
Factores genéticos

Detección precoz de la hipertrigliceridemia grave a través de la teleconsulta en el contexto del laboratorio clínico

Resumen

Antecedentes: En el contexto de los laboratorios clínicos, la teleconsulta es una herramienta útil para la detección temprana de la dislipidemia y el riesgo cardiovascular. En este trabajo se describe el caso de un paciente remitido a la Unidad de Lípidos del Hospital Virgen Macarena por una alerta por hipertrigliceridemia grave dentro del programa de teleconsulta.

Presentación del caso: Se realizó un estudio clínico y bioquímico amplio y un estudio genético del paciente y su familia. El caso índice y los familiares mostraron hipertrigliceridemia de moderada a grave y varios factores secundarios, junto con una carga genética asociada a un efecto elevador de los triglicéridos.

Conclusión: El estudio exhaustivo realizado ha permitido identificar a una familia con riesgo elevado de enfermedad cardiovascular y pancreatitis aguda. Estos hallazgos pueden ayudar a realizar cambios en el estilo de vida y a mejorar el tratamiento clínico de la dislipidemia del paciente y sus familiares.

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Background

Severe hypertriglyceridemia (sHTG) is defined by the Spanish Arteriosclerosis Society as persistent fasting serum triglycerides levels above 1000 mg/dL (11.3 mmol/L).¹ Patients with sHTG are at high risk of premature cardiovascular disease and acute pancreatitis.^{2,3} Unlike rare monogenic cases, such as Familial Chylomicronemia Syndrome, sHTG is polygenic in nature.³

The new important role of clinical laboratories in the early detection of dyslipidemia is well known. This is mainly due to the inclusion of alerts in the analytical reports for cases of familial hypercholesterolemia⁴ and sHTG.⁵ The Clinical Laboratory Service of the Virgen Macarena Hospital, in Seville, Spain, has been a pioneer in our country in implementing a program called ‘‘Laboratory Teleconsultation and Cardiovascular Risk’’. It has designed protocols for the diagnosis of hyperlipidemias⁶ and also favors a multidisciplinary approach that links laboratory members with clinical units.⁷

We present here a case of sHTG that was identified early by our teleconsultation program. This allowed for a rapid and complete phenotypic study and a genetic analysis of the patient and his family.

Case presentation

A sixty-three-year-old man (the proband) was identified through a teleconsultation program due to fasting serum triglycerides levels of 12.1 mmol/L. His extended lipid panel is shown in Table 1. An alert was sent to his general practitioner and the patient was referred to the Lipid Unit at the Virgen Macarena Hospital, Seville, Spain. Clinical and analytical data are shown in Table 2. In summary, the patient was obese and had type 2 diabetes (HbA1c 6.1%) and hypertension. At first visit, he was treated with metformin 1 g/empaglifozine 5 mg every

Table 1 Extended lipid profile of the proband.

Variable	Proband’s value	Normal range
Total cholesterol (mmol/L)	3.9	3.9–5.7
Triglycerides (mmol/L)	12.1	0.8–0.2
HDL cholesterol (mmol/L)	0.6	0.8–1.9
VLDL cholesterol (mmol/L)	1.2	0.4–1.0
Non-HDL cholesterol (mmol/L)	3.3	–
ApoA1 (g/L)	1.2	1.1–2.1
ApoA2 (g/L)	0.3	0.3–0.5
ApoB (g/L)	1.2	0.6–1.4
Lipoprotein (a) (mg/dL)	6.7	0.0–50.0
Homocysteine (μmol/L)	18.9	5–12
TG-QM/TG-VLDL ratio ^a	3.2	–

^a Ratio < 3.8 indicates Type V hyperlipoproteinemia.⁸
100 mg/dL of Lipoprotein (a) = 0.01 g/L

8 h, fenofibrate 145 mg/day, ezetimibe 10 mg/day, Enalapril 20/hydrochlorotiazide 12.5 mg/day, omega-3 1 g/day and aspirin 100 mg/day.

To determine the genetic background of the disease, fasting blood samples were sent to the Lipids and Atherosclerosis Laboratory (CIMES, University of Málaga, Spain). Next generation sequencing was performed using a targeted gene panel including 18 genes involved in triglyceride metabolism, with a target enrichment strategy. The pathogenic and functional genetic variants identified in the proband, his wife and two children are shown in Table 2. The main genetic finding was that the patient and his daughter had a pathogenic variant in the APOA5 gene: rs777046568, c.427delC, p. Arg143AlafsTer57, in exon four, in the heterozygous state. Furthermore, the patient and his relatives also showed several variants that favor TG (triglycerides) raising. Additionally, the patient’s children were obese and exhibited hypertriglyceridemia.

Table 2 Clinical and genetic data of the proband and his family.

Variables	Proband	Son	Daughter	Wife	
Age (years)	63	33	34	66	
TG (mmol/L) ^a	12.1	3.6	3.7	2.0	
BMI (K/m ²)	33.96	30.86	34.15	27.27	
Pancreatitis	No	No	No	No	
Hypertension	Yes	No	No	No	
Diabetes	Yes	No	No	No	
N° pathogenic ^c	1	0	1	0	
N° TG raising ^c	7	6	7	6	
N° VUS ^c	2	1	2	0	
Genetic data					
<i>APOA5</i>	Proband	Son	Daughter	Wife	Functional effect
c.427delC; p.Arg143AlafsTer57 rs777046568 (MA: delC, F: <0.001)	Het	WT	Het	WT	Pathogenic ^b
c.-3G>A rs651821 (MA: G, F: 0.083)	Het	Het	Het	Het	TG raising ⁹
<i>APOC3</i>	Proband	Son	Daughter	Wife	
c.102T>C; p.Gly34= rs4520 (MA: T, F: 0.353)	Hom	Hom	Hom	Hom	TG raising ¹⁰
c.*40G>TC rs5182 (MA: G, F: 0.130)	Het	Het	Het	Het	TG raising ¹⁰
c.*71G>T rs4225 (MA: G; F: 0.371)	Hom	Het	Hom	Het	TG raising ¹⁰
<i>GCKR</i>	Proband	Son	Daughter	Wife	
c.1337T>C; p.Leu446Pro rs1260326 (MA: T; F: 0.410)	Het	WT	Het	Het	TG raising ¹¹

^a Plasma triglyceride level at presentation. VUS: variants of uncertain significance.

^b <https://varsome.com/variant/hg38/rs777046568?annotation-mode=germline>.

^c Number of alleles of each category according to the genetic data. Only variants with at least one pathogenicity criteria or with a reported association with triglyceride levels are shown.

MA: minor allele of each variant. F: frequency. WT: wild type; homozygous for the frequent allele. Het: heterozygous; carrier of both alleles. Homo: homozygous for the minor allele.

Discussion

The goal of teleconsultation is to eliminate the geographical and functional distance between two or more geographically separated health care providers.¹² Teleconsultation improves clinical care by reducing the time taken to refer patients to a specialized clinic and also to alert some busy clinicians who may miss important results that require a change in care, thus preventing errors by acting as a safety net. Our case illustrates the role of our teleconsultation program applied to the clinical laboratory to identify patients with dyslipidemia at high risk of an ischemic event or acute pancreatitis. In addition, it allows patients to be managed by a multidisciplinary team, reducing the time taken to obtain a correct diagnosis and treat.

In this case, we took advantage of the opportunity to include the proband and his family in an ongoing study to screen Familial Chylomicronemia Syndrome among sHTG patients. The findings in our patient confirm the phenotypic and genetic background typically seen in cases

of sHTG. Subjects with this disease are obese or overweight and have hypertension and diabetes, indicating that an insulin-resistant state promotes VLDL overproduction by the liver.¹³ Furthermore, our patient and his relatives have a pathogenic variant in the *APOA5* gene together with several SNPs that raise serum triglycerides. Therefore, our results fit with the polygenic nature of sHTG, with a combination of pathogenic variant and small effect common-variants.³

It is important to note that the polygenic background of the family we studied was similar among its members (at least 6 susceptibility variants). Interestingly, the secondary factors seem to modulate the potential effect of these variants on their TG levels. The proband, who had obesity as well as hypertension and diabetes, exhibited sHTG, whereas his children, with moderate HTG, were obese but not hypertensive or diabetic. Finally, the patient's wife, who was simply overweight, had the lowest TG level. It has been described that obesity modulates the effect of *APOA5* variants.¹⁴ Additionally, it is known that the combination of secondary and

genetic factors, as our findings suggest, increases the risk of disease.¹⁵

As mentioned above, the proband and his daughter had a rare null variant in *APOA5* (Table 2). In a recently published paper, among 363 patients with different levels of HTG (from >2.3 mmol/L) who underwent genetic testing, a pathogenic variant was found in 37 (10%) and 59 (16%) individuals had a high polygenic risk score. As expected, the higher the category of HTG the higher the number of genetic anomalies. Very importantly, the risk for acute pancreatitis increased 5-fold in those subjects who had a combination of a pathogenic variant and a high polygenic score, which is the case of our patient and his daughter, but not when patients had only one genetic anomaly.³

Conclusion

In conclusion, the joint efforts of clinicians, clinical biochemists and geneticists allowed us to identify a family at high risk of developing acute pancreatitis and to maximize lifestyle changes and drugs to control the sHTG. Furthermore, our case supports the idea that teleconsultation applied to clinical laboratories is a feasible and valuable tool that helps physicians identify subjects at risk of disease earlier than in common clinical practice. This improves the prevention of new clinical events, thereby reducing suffering and premature death.

Ethical statement

The subjects described in this work firmed the informed consent for the genetic study performed as participants in the project PIN-0180-2018. This project was approved by the Regional Ethics Committee (CEIm).

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Conflicts of interest

None of the authors has any conflict of interest regarding this manuscript; including sources of support, monetary or other, monetary interests to be regarded as actual conflicts of interest.

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