Think Tank: Severe hypertriglyceridaemia

This year's VMAC (Vascular Medicine and Atherosclerosis Congress) took place from 22–24 February 2024 at the Augsburg Congress Centre. It is jointly organised by the D.A.CH Gesellschaft Prävention von Herz- Kreislauf-Erkrankungen e.V., the Lipidliga (DGFF) and the Dt. Gesellschaft für Arteriosklerosеforschung e.V. (DGAF). This year's Sobi Symposium "ThinkTank: Severe Hypertriglyceridaemia (sHTG)" focused on new developments in the interpretation of genetic findings, the management of acute HTG-related pancreatitis and the prevention of pancreatitis in severe hypertriglyceridaemia. This was discussed in a lively and practical manner by an interdisciplinary panel of experts.

Interdisciplinary and practical

ThinkTank: sHTG

Chairwoman and current D.A.CH President Dr Ulrike Schatz (Dresden) introduced the well-attended Sobi Symposium at this year's VMAC with the classic tasks of a think tank: Proven, interdisciplinary experts develop solutions for forward-looking issues in a closed room.

Fig. 1: Under the chairmanship of Dr Ulrike Schatz, the interdisciplinary ThinkTank team intensively discussed future issues relating to the diagnosis, consequences and management of severe hypertriglyceridaemia. (from left to right: Dr U. Schatz, Prof U. Laufs, Prof A. Madisch, Prof W. März)
Source: Sobi

Dr Schatz emphasised the importance of interdisciplinary collaboration, particularly in the case of severe hypertriglyceridaemia (sHTG) and its consequences, and introduced Professor März (laboratory medicine and genetics), Professor Madisch (gastroenterologist) and Professor Laufs (cardiologist/lipidologist). (Fig. 1)

Understand Genetics

Nomenclature and new genes in sHTG

Prof. W. März (Mannheim)

The level of triglyceride (TG) concentration is determined by exogenous (secondary) factors, which include certain diseases such as obesity and diabetes mellitus or certain medications such as oestrogens and antihypertensives, as well as genetic (primary) factors.

Difficult: Interpretation of the gene dose-response relationship for mixed forms

In terms of genetic factors, a distinction is made between common genetic variants (formerly known as polymorphisms) and rarer monogenetic variants (formerly known as mutations). Classically, the latter include variants that influence the activity of lipoprotein lipase (LPL), i.e. the breakdown of triglycerides (LPL, ApoA5, ApoC2, GPIHBP-1, LMF-1). The difficulty in interpreting genetic findings is that the penetrance of rare variants can be modulated by common variants. There is therefore a gene dose-response relationship with mixed forms. (Fig. 2)

Established entities: Monogenetic versus polygenetic hypertriglyceridaemia

According to Prof. März, the previous terminology with the distinction between familial (FCS) and multifactorial chylomicronaemia syndrome (MCS) is misleading: both forms have a familial (genetic) component that can be influenced by secondary causes (multifactorial). Chylomicrons occur in both diseases, the detection of which is not established, in contrast to the measurement of TG. He therefore recommends differentiating between monogenetic and polygenetic HTG.

In **monogenetic HTG, the genetic load is high enough to cause constant HTG**, regardless of other factors such as additional mutations or lifestyle factors.

In **polygenetic HTG, a single mutation is not sufficient** to cause a clinical phenotype. The severity of HTG is determined by the cumulative/interactive effects of several genetic risk variants.

Patients with predominantly autosomal recessive, monogenetic HTG usually have homozygous or combined heterozygous variants with a major effect on TG.

In the case of polygenetic HTG, such variants occur in combination with TG-increasing single nucleotide polymorphisms (SNPs) are present. Even a large number of SNPs with a small effect on the TG alone can result in a polygenetic HTG.[1]

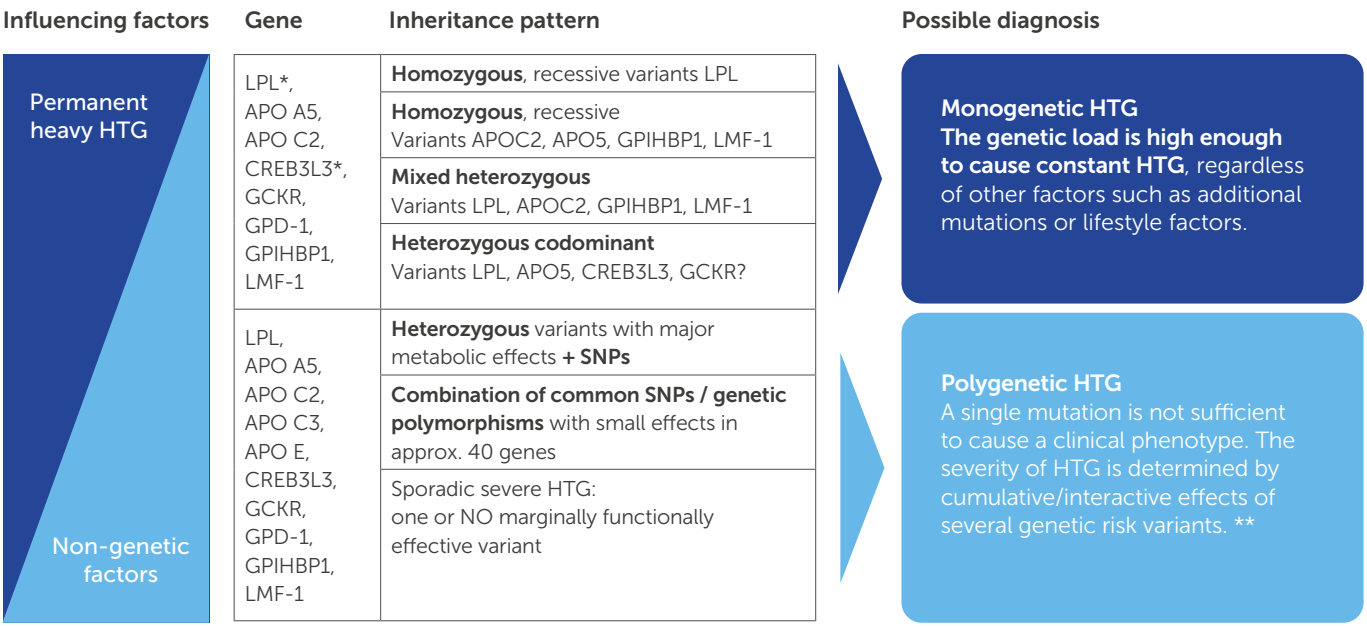

Fig. 2: Genetic causes and gene dose-response relationship in severe sHTG (mod. after Moulin et al, 2018)[1] ; abbr.: see p. 4

*In the case of mutations with major metabolic effects, heterozygous codominant inheritance is also possible **Risk variants for HTG include both heterozygous rare variants with major metabolic effects and common variants with minor effects. A large number of common variants with low penetrance (SNPs) alone can also lead to polygenetic HTG.

To summarise, this means that each variant must be evaluated individually with regard to its effect on the phenotype.

HTG Genetics Panel: Measurement also of GCKR, CREB3L3 and GPD-1

In contrast to the classic genes, there are also loss-of-function (LoF) variants in the glucokinase regulator protein (GCKR), which reduce glucose and increase the "output of triglycerides" from the liver cells, according to Prof. März.[2] LoF variants of CREB3L3/CREB-H (cyclic AMP-responsive element binding protein H) lead to increased lipid absorption from the intestine, increased lipid synthesis in the liver and a reduction in lipoprotein lipase activity.[3,4] A deficiency of GPD-1 (glycerol-3-phosphate dehydrogenase) can lead to infantile, transient hypertriglyceridaemia.

Conclusion

If a genetic cause of sHTG is clinically suspected, the entire panel of TG-influencing genes should always be requested. This also helps the geneticist to differentiate between monogenetic and polygenetic HTG.

Save the pancreas

Management of HTG pancreatitis

Prof. A. Madisch (Frankfurt)

The incidence of acute pancreatitis (AP) is increasing worldwide, particularly in the western world. The increase in metabolic syndrome and alcohol abuse are seen as the main reasons for this. The most common causes of AP are gallstones (50 %) and alcohol (20-25 %), followed by HTG as the third most common cause with around 10 %.

Acute pancreatitis is a potentially lifethreatening disease

While the mortality rate for AP was still >20 % in the 1980s, it has now been reduced to approx. 5 %, with the mortality rate for severe pancreatitis - particularly in the case of infected necrosis - being between 17 % and 30 %. The course of the disease within the first 48 hours determines whether the patient must be admitted to the intensive care unit.

A high initial TG concentration is a negative prognostic factor for the course of the disease

It is important to correctly assess the patient's risk factors and this includes - even in the emergency department - the initial determination of the TG concentration, as HTG increases the risk of a more severe course of acute pancreatitis.[5,6] The data here is very clear, says Professor Madisch. (Fig. 3)

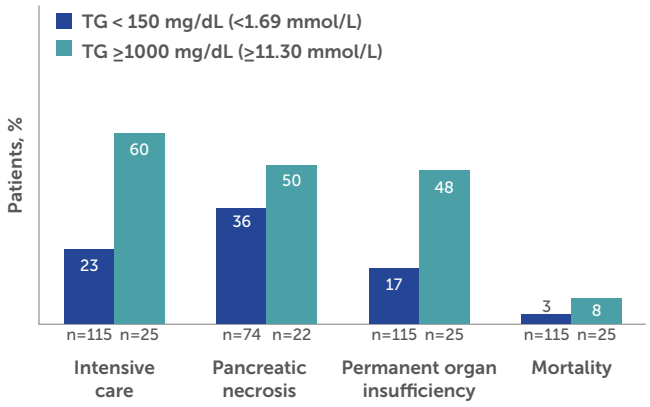

Fig. 3: Clinical course of acute pancreatitis with normal or high triglyceride (TG) levels (mod. after Nawaz H et al, 2015)[6]

Lipoprotein apheresis: no positive effect on clinical outcome proven

Prof Madisch presented a current algorithm for the diagnosis and treatment of acute pancreatitis, which could also form part of a possible SOP in emergency departments.[7] As soon as the clinical diagnosis of AP has been confirmed, the TG should also be determined. If these are above 11.3 mmol/l, conventional lipid-lowering therapies (such as fibrates, statins, insulin, heparin, etc.) should be used to lower the TG <5.7 mmol/l. In the acute situation, the use of lipoprotein apheresis has not shown any positive effect on the outcome of patients; if necessary, plasma exchange can be used for acute TG reduction. It is therefore important that patients are referred to a lipidologist for further diagnosis and treatment after the acute event.

Conclusion

Every episode of acute pancreatitis is potentially lifethreatening, so prevention and effective control of TG is essential.

Source: Gildemeister Photography

Prevent pancreatitis

Triglyceride management from a lipidological perspective

Prof U. Laufs (Leipzig)

From the point of view of cardiovascular medicine, it is not only the reduction in the risk of pancreatitis that is relevant. The much more common aspect is that lipoproteins containing TG or apoB also represent a risk factor for atherosclerosis.[8]

Exclusion of secondary causes and lifestyle changes

Therefore, secondary causes, above all metabolic syndrome and diabetes mellitus, must always be in second place are lifestyle changes.

From the perspective of pancreatitis prevention, these primarily include abstinence from alcohol.

Reduction of non-HDL/ApoB for cardiovascular risk prevention

In moderate HTG, statins, ezetimibe, bempedoic acid or PCSK9 inhibitors can be used to reduce the risk of atherosclerosis. These lower the non-HDL or apoB levels, have but no major effect on the TG concentration.

Fibrates: No evidence for reducing the risk of cardiovascular disease or pancreatitis

The use of fibrates was discussed critically in relation to other outcome parameters: „According to a review of the literature, there is no evidence that fibrates can reduce the cardiovascular risk or the risk of pancreatitis, nor that fibrates have a favourable effect on the course of pancreatitis," Professor Laufs stated. „In the FIELD study, the occurrence of pancreatitis was even more frequent with fenofibrate than with placebo.[9] According to the information for healthcare professionals, chronic pancreatitis is even a contraindication for fenofibrate. In addition, fibrates are not particularly effective in severe HTGs with an expected TG reduction of 20 %," emphasised Prof Laufs.

ApoC3 inhibition - a promising target

Inhibition of ApoC3 by highly specific antisense oligonucleotide (ASO) technology is an interesting approach as it may play a mechanistic role at the interface between TG-rich lipoproteins and the inflammasome in the context of the development of sterile inflammation.

Table 1: Incidence of pancreatitis 5 years before treatment with volanesorsen and during the long-term open study over 104 weeks.[10]

Confirmed acute Pancreatitis (AP)	Total (n=68)	
Time of the AP	**n (%) Patients**	**n Events**
Before therapy[a]	33 (48.5)	82
in connection with the therapy[b]	5 (7.4)	5
during therapy[c]	4 (5.9)	4
After the therapy[d]	0	0

[a]A pre-therapy pancreatitis event was defined as any confirmed event that began before the first dose of study drug. [b]A therapy-related event was defined as any confirmed event that began on or after the first dose of study drug. [c]An on-treatment event was defined as any adjudicated event that began between the first and last dose of study drug + 28 days. [d]A posttreatment event was defined as any confirmed event that began on or after the last dose of study drug + 29 days to the last dose of study drug + 90 days.

Volanesorsen resulted in an effective TG reduction and less pancreatitis.

In patients with monogenetic sHTG, TG could be reduced by up to 70 % depending on the dose of ASO volanesorsen 300 mg.[11] The APPROACH study included 66 FCS patients, 76 % of whom had a history of pancreatitis. Here, too, a TG reduction of between 50–70 % was observed over time and this was associated with a numerical reduction in the risk of pancreatitis.[12,13] This was also confirmed in the open long-term observation[10] (Table 1) and is consistent with Prof Laufs' own experience in Leipzig.[14] Prof. Laufs concluded his presentation with an outlook on the development of further drugs with the target ApoC3, ANGPTL-3 or FGF21.

Conclusion

Lifestyle changes are the first priority for moderate TG values. In the case of persistently severe HTG, a genetic cause and treatment with volanesorsen should be considered.

Further information on severe hypertriglyceridaemia or familial chylomicronaemia syndrome:

www.spotlightfcs.com

Literature:

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Abbreviations:
ANGPTL-3,angiopoietin-like3protein;**AP**,acutepancreatitis;**Apo**,apolipoprotein;**Chol**, cholesterol; **ASO**, antisense oligonucleotide **CREBH**, cyclic adenosine monophosphate (cAMP)-responsive element-binding protein H; **CREB3L3**, CAMP-responsive elementbinding protein-3-Like-3; **FC3**, cyclic adenosine monophosphate (cAMP)-responsive element-binding protein H. cyclic adenosine monophosphate (c A M P)-responsive element-binding protein H); **CREB3L3**, CAMP-responsive element-binding protein-3-like-3; **FCS**, familial chylomicronaemia syndrome; **FGF**, fibroblast growth factor; **GKCR**, glucokinase regulatory protein; **GPD-1**, glycerol-3-phosphate dehydrogenase-1; **GPIHBP-1**, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein-1; **HDL**, highdensity lipoprotein high density lipoprotein); **HTG**, hypertriglyceridaemia; **LDL**, low density lipoprotein; **LoF**, loss of function; **LPL**, lipoprotein lipase; **sHTG**, severe hypertriglyceridaemia; **MCS**, multifactorial chylomicronaemia syndrome; **SNPs**, single nucleotide polymorphisms. Single nucleotide polymorphism; **LMF-1**, lipase maturation factor 1; **TG**, triglycerides; **VLDL**, very low density lipoprotein;

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