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**Case Report**

# Severe Familial Hypertriglyceridemia in a Child with Compound Heterozygous Pathogenic APOA5 Variants: A Case Report and Therapeutic Challenge



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**What is already known on this topic?**
Biallelic pathogenic variants in APOA5 are a rare cause of early-onset, severe familial hypertriglyceridemia (FHTG), often associated with recurrent abdominal pain, pancreatitis, and poor response to standard lipid-lowering therapies. Early genetic diagnosis can identify affected individuals and guide tailored management, but long-term pediatric follow-up data remain scarce.

**What this study adds?**
This report expands the phenotypic and therapeutic spectrum of APOA5-related familial hypertriglyceridemia by documenting the long-term metabolic evolution and partial metformin responsiveness in a genetically confirmed pediatric case. It also emphasizes the potential relevance of novel targeted therapies for severe monogenic dyslipidemias in children.

**Abstract**
Familial hypertriglyceridemia (FHTG) is a rare inherited lipid disorder that may present with severe phenotypes when caused by compound heterozygous or biallelic *APOA5* variants. We report a male child diagnosed at 2.5 years of age with severe hypertriglyceridemia, who exhibited serum triglyceride levels persistently above 10 mmol/L (≈ 885 mg/dl) despite adherence to a low-fat diet and pharmacotherapy including fibrates, omega-3 fatty acids, and statins. Representative triglycerides at presentation were 11.6 mmol/L (≈ 1029 mg/dl). During follow-up, the patient experienced an acute abdominal pain episode with triglycerides nearing 20 mmol/L (≈ 1770 mg/dL), managed conservatively under suspicion of pancreatitisOral glucose tolerance testing showed a high-normal insulin response (peak 84.5 mIU/L, below the insulin-resistance threshold of 100–150 mIU/L), which prompted addition of metformin. Over a decade, despite normal growth and clinical well-being, biochemical control remained suboptimal. This case illustrates the clinical utility of early genetic testing in pediatric dyslipidemias and highlights limitations of traditional treatments in monogenic severe FHTG. Emerging therapies, including antisense oligonucleotides and ANGPTL3 inhibitors, may hold future promise.
**Keywords:** APOA5, familial hypertriglyceridemia, pediatric dyslipidemia, compound heterozygosity, metformin, antisense oligonucleotide therapy

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**Introduction**
Hypertriglyceridemia in children is usually an incidental finding, most often mild in severity and secondary rather than primary in origin (1). On the other hand, familial hypertriglyceridemia (FHTG) represents one of the primary genetic causes typically inherited in an autosomal dominant (AD) fashion (2). Elevated levels of triglyceride-rich lipoproteins in FHTG, primarily of very low-density lipoproteins (VLDL), stems from pathogenic variants in the *APOA5* (3). However, when occurring in a recessive or compound heterozygous form, particularly due to loss-of-function variants in the *APOA5*, the phenotype may be markedly more severe (4)The *APOA5* encodes apolipoprotein A-V, a key regulator of plasma triglyceride levels. It enhances lipoprotein lipase activity and facilitates the catabolism of triglyceride-rich lipoproteins (5). Variants in *APOA5* are associated with a wide range of hyperlipidemic phenotypes (6,7). Biallelic pathogenic variants are rarely reported and usually lead to early-onset, severe, and treatment-refractory hypertriglyceridemia (6).
In this case report we present a pediatric patient with a documented history of severe FHTG from early childhood, ultimately diagnosed with compound heterozygous pathogenic variants in APOA5 (NM_052968.4). We provide a detailed longitudinal (ten-year) analysis of his metabolic profile, treatment adjustments, and genetic findings, highlighting the partial biochemical improvement following metformin therapy. The report further discusses genotype–phenotype correlations and places the case in the context of current literature and potential future therapeutic perspectives.

**Case Presentation**

The patient is a boy with a long-standing history of severe hypertriglyceridemia, first documented at the age of 2.5 years. At the time of first evaluation, physical examination revealed a boy in good general health, with no dysmorphic features or stigmata of endocrinopathy. His height was 96.5 cm (−0.9 SDS), weight 16.9 kg (+1.1 SDS) andBMI 18.1 kg/m² (+1.5 SDS). Neurological and systemic examination were unremarkable. Laboratory evaluation was performed due to positive family history for hyperlipidemia. At this age, fasting serum triglycerides were found to be markedly elevated at 11.6 mmol/L (≈ 1028 mg/dL), alongside a total cholesterol of 8.3 mmol/L (≈ 321 mg/dL). He was otherwise well, with no acute symptoms. Both his father and older sister had previously been diagnosed with hyperlipidemia. Given the markedly elevated triglyceride levels, dietary restrictions and omega-3 fatty acid (fish oil preparation, EPA/DHA) supplementation (0.25 g/day) were initiated, followed shortly by the introduction of ciprofibrate (25 mg/day).

During the subsequent years, the boy underwent regular follow-up in a tertiary pediatric clinic. Despite reportedly good adherence to a low-fat diet and consistent pharmacologic therapy, his triglyceride levels remained elevated, fluctuating between 3.1 mmol/L (≈ 275 mg/dL) and 22.8 mmol/L (≈ 2020 mg/dL).. In several instances, laboratory analyses were delayed or invalid due to extreme lipemia of the serum. At the age of 5, the omega-3 dosage was increased from 0.25 g/day to 0.5 g/day, and ciprofibrate was increased from 25 mg/day to 50 mg/day.

Between the ages of 3 and 8 years his condition remained metabolically unstable. On physical examination, there were no dysmorphic features or stigmata of endocrinopathy throughout this period, and systemic examination was unremarkable. However, serial anthropometric measurements demonstrated a progressive increase in body mass index, with a clear trend toward overweight and impending obesity (Figure 1).

Although he was mostly asymptomatic, occasional abdominal pain was reported, and transient elevations in hepatic transaminases (AST up to 100 IU/L, ALT up to 127 IU/L) were noted. Abdominal ultrasound examinations, performed on several occasions, were predominantly normal; however, in a few instances, the findings were reported as potentially consistent with early hepatic steatosis. Pharmacotherapy was modified in multiple cycles, including temporary cessation and reintroduction of ciprofibrate and statins (pravastatin or rosuvastatin), depending on liver enzyme fluctuations and lipid control (Table 1).

At the age of 12, a comprehensive genetic analysis was initiated due to poor therapeutic response. Whole-exome sequencing (WES) with parental segregation confirmed compound heterozygosity in APOA5 (NM_052968.4), identifying two heterozygous pathogenic variants: c.289C>T (p.Gln97Ter) and c.427del (p.Pro143HisfsTer12). Both variants were classified as pathogenic according to ACMG criteria (PVS1, PM2, PP1), consistent with autosomal recessive inheritance. The clinical and biochemical phenotype was concordant with compound heterozygosity for APOA5-related familial hypertriglyceridemia (FHTG). Both variants affect conserved regions of APOA5 and have been previously reported in association with severe hypertriglyceridemia phenotypes.

At the age of 14, the patient was hospitalized at a regional center due to severe abdominal pain and triglyceride levels approaching 20 mmol/L (≈ 1771 mg/dL). Abdominal ultrasound was performed during the acute episode, which did not reveal convincing signs of acute pancreatitis, but early hepatic steatosis was described. Other laboratory parameters during this episode were unremarkable, except for mildly elevated transaminases (AST 112 U/L, ALT 138 U/L). He was managed conservatively, with full clinical recovery and no complications.

By the age of 15, despite continuous treatment with ciprofibrate (100 mg/day) and high-dose omega-3 (2 g/day), the patient's triglyceride levels remained persistently elevated, peaking at 16.78 mmol/L (≈ 1,485 mg/dL). At this age, a comprehensive endocrinological evaluation was performed. The patient's height was 163 cm (−0.8 SDS) and weight 69 kg (+1.9 SDS), yielding a BMI of 26.2 kg/m² (+2.0 SDS), which meets WHO criteria for obesity (Figure 1). On physical examination, he was in good general health, with no dysmorphic features or stigmata of endocrinopathy. Pubertal assessment revealed bilateral testicular enlargement to 14-15 mL (Prader orchidometer), consistent with mid-puberty, along with Tanner stage III pubic hair development. An oral glucose tolerance test (OGTT) showed normoglycemia with a high-normal insulin response (peak 84.5 mIU/L), below commonly cited insulin-resistance thresholds of 100–150 mIU/L; HOMA-IR was 3.12 (borderline) (Table 2). Consequently, metformin (500 mg/day) was introduced in a nightly dose, in an effort to improve insulin sensitivity and reduce hepatic triglyceride output.

Good adherence was reported by parents to both pharmacologic and dietary regimens and continued regular physical activity. Serial abdominal ultrasonography did not reveal hepatomegaly, clear signs of steatosis, or pancreatitis. Despite persistent significant hypertriglyceridemia, the patient's condition remains free of severe clinical complications.

At last evaluation, introduction of metformin (500 mg/day) was associated with early beneficial effects, leading to a notable reduction in serum lipid levels. Further pharmacological options were being considered, including potential off-label use of newer lipid-lowering agents.

**Discussion**

FHTG is a genetically heterogeneous condition characterized by elevated circulating triglyceride levels (1,7). The disorder is most often associated with AD inheritance; however, cases of biallelic pathogenic variants in key lipid-regulating genes such as *APOA5*, *LPL*, or *GPIHBP1* are rare and typically present in early childhood with severe, treatment-refractory hypertriglyceridemia (7). Clinical manifestations are ranging from asymptomatic biochemical findings to life-threatening acute pancreatitis (2).

The *APOA5* encodes apolipoprotein A-V, a key modulator of plasma triglyceride homeostasis. It acts by enhancing lipoprotein lipase (LPL) activity and facilitating hepatic clearance of triglyceride-rich lipoproteins (5). Pathogenic variants in *APOA5* impair this function and result in increased circulating triglyceride levels (4). While heterozygous *APOA5* variants are relatively common in the general population and often asymptomatic, compound heterozygous or homozygous mutations are rare and usually associated with severe phenotypes (8). They typically include triglyceride levels persistently >10 mmol/L (≈ 885 mg/dL) and high risk of potentially life-threatening complications (3).

In our patient, two pathogenic variants in *APOA5* (NM_052968.4) were identified: c.289C>T (p.Gln97Ter), a nonsense loss-of-function variant previously reported in both homozygous and compound heterozygous states in severe familial hypertriglyceridemia, and c.427del (p.Pro143HisfsTer12), a frameshift variant predicted to undergo nonsense-mediated mRNA decay resulting in complete loss of functional apolipoprotein A-V protein (apoA-V)(9). This compound heterozygous state, confirmed by parental segregation analysis, strongly supports a monogenic autosomal recessive etiology underlying the patient's phenotype (10). Beyond severe hypertriglyceridemia, the clinical course was further characterized by progressive weight gain, with BMI rising into the overweight/obesity range and a high-normal insulin response on OGTT (peak 84.5 mIU/L), below commonly cited insulin-resistance thresholds of 100–150 mIU/L; HOMA-IR was 3.12 (borderline).. The poor response to fibrates and omega-3 fatty acids, despite early initiation and dose escalation, is consistent with previous reports of biallelic *APOA5*-related FHTG, where conventional lipid-lowering therapy is often insufficient, necessitating adjunctive measures such as metformin to target insulin resistance and hepatic triglyceride output.

While severe hypertriglyceridemia can also result from familial chylomicronemia syndrome (FCS), our case aligns more closely with familial hypertriglyceridemia (FHTG). FCS, caused by near-complete lipoprotein lipase deficiency, typically manifests in infancy with eruptive xanthomas, recurrent pancreatitis, and poor response to lipid-lowering therapy. In contrast, the absence of these early features in our patient, together with biallelic *APOA5* pathogenic variants and partial therapeutic responsiveness, supports classification within the FHTG spectrum (11,12).At certain points, our patient exhibited markedly poor metabolic control of triglyceride levels, and one episode was highly suggestive of acute pancreatitis. Although acute pancreatitis was not confirmed according to current diagnostic criteria, hypertriglyceridemia is a well-

recognized metabolic cause of acute pancreatitis in adults and is increasingly being identified in children (13). The diagnostic criteria for hypertriglyceridemia-induced pancreatitis are the same as those applied to other etiologies (14). Initial management of this potentially life-threatening complication includes bowel rest, intravenous fluid resuscitation, and symptomatic treatment. In severe cases, insulin therapy or plasmapheresis may be considered for the rapid reduction of triglyceride levels (15,16). Our patient responded favorably to conservative management after suspicion of acute pancreatitis, with gradual clinical improvement and normalization of laboratory markers. While imaging did not confirm pancreatitis, it remains possible that a hypertriglyceridemia-induced pancreatitis was resolved rapidly with supportive care. This observation highlights the importance of maintaining a high index of suspicion for pancreatitis in children presenting with severe hypertriglyceridemia, even in the absence of classical imaging findings.

Furthermore, our patient demonstrated a high-normal insulin response on OGTT and borderline HOMA-IR. This finding aligns with existing data suggesting a bidirectional relationship between hypertriglyceridemia and insulin resistance, particularly in monogenic dyslipidemias (17). In this context, the addition of metformin may be justified, not only to enhance insulin sensitivity but also to reduce hepatic VLDL production, which may contribute to partial triglyceride reduction (18,19). Following metformin initiation (500 mg/day, at bedtime), triglycerides decreased from 16.78 mmol/L (≈ 1485 mg/dL) at the age of 15 years to 4.30 mmol/L (≈ 381 mg/dL) at 15 years and 9 months, alongside ongoing ciprofibrate and omega-3 therapy. This initial improvement supports the potential role of metformin as an adjunctive therapy therapy in obese pediatric patients with familial hypertriglyceridemia. The observed effect likely reflects improved hepatic insulin sensitivity and reduced VLDL secretion rather than a direct triglyceride-lowering mechanism, consistent with metformin's pleiotropic metabolic actions (17,19).

Although current management of familial hypertriglyceridemia relies on dietary modification and fibrate therapy, the response in biallelic APOA5 deficiency is often limited. Recent advances in molecular lipid-lowering therapies — particularly APOC3 antisense oligonucleotides (e.g., volanesorsen, olezarsen) and ANGPTL3 inhibitors — have shown marked triglyceride reductions in adults with monogenic or multifactorial hypertriglyceridemia. These emerging agents may, in the future, provide genotype-tailored options for patients with APOA5-related disease, although their pediatric use remains investigational. (20–24)

This case highlights the importance of early genetic testing in children with unexplained or severe hypertriglyceridemia, particularly when values exceed 10 mmol/L (≈ 885 mg/dL) or remain refractory to standard interventions. Establishing a molecular diagnosis is crucial not only for guiding treatment but also for genetic counseling, family screening, and eligibility for emerging precision therapies (25).

**Conclusion**

This case illustrates the clinical course and therapeutic complexity of a child with severe familial hypertriglyceridemia caused by compound heterozygous pathogenic variants in *APOA5*. The disease manifested in early childhood and remained refractory to standard lipid-lowering therapy, requiring multiple treatment adjustments and the addition of adjunctive metformin therapy

Genetic testing was essential in establishing the molecular diagnosis and understanding the disease mechanism. Identifying biallelic *APOA5* variants provided insight into the severity of the phenotype and enabled more personalized management.

As novel lipid-lowering therapies continue to evolve, genetic characterization of pediatric patients with extreme dyslipidemia may facilitate access to emerging precision medicine options. Early diagnosis, multidisciplinary care, and consideration of emerging therapies are essential to optimize outcomes in monogenic pediatric dyslipidemias.

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**Table 1. Longitudinal lipid profile and therapeutic interventions in the patient**

| Age (years, months) | Triglycerides (mmol/L, mg/dL) | Total Cholesterol (mmol/L, mg/dL) | HDL (mmol/L) | LDL (mmol/L) | Therapy | Comment |
|---|---|---|---|---|---|---|
| 2y 6m | 5.32 (≈ 471) | 3.82 (≈ 148) | – | – | None | Initial evaluation; positive family history |
| 3y 9m | 22.8 (≈ 2020) | 6.0 (≈ 232) | – | – | omega-3 (0.25 g/day), ciprofibrate (25 mg/day) | Postprandial hypertriglyceridemia |
| 5y 3m | 6.4 (≈ 567) | 5.7 (≈ 220) | – | – | omega-3 (0.25 g/day), ciprofibrate (50 mg/day) | Improved lipid profile |
| 7y 9m | 5.1 (≈ 452) | 4.19 (≈ 162) | 0.38 (≈ 15) | 1.49 (≈ 58) | omega-3 (0.25 g/day), ciprofibrate (50 mg/day) | Satisfactory levels |
| 9y 6m | 16.1 (≈ 1426) | 7.08 (≈ 274) | 0.44 (≈ 17) | – | omega-3 (0.5 g/day), ciprofibrate (50 mg/day) | Worsening despite increased Omega-3 dose, dietary supervision advised |
| 11y 1m | 4.3 (≈ 381) | 5.3 (≈ 205) | 0.63 (≈ 24) | 2.71 (≈ 105) | omega-3 (0.5 g/day), ciprofibrate (50 mg/day) | Satisfactory lipid control |
| 13y 2m | 4.62 (≈ 409) | 3.83 (≈ 148) | 0.49 (≈ 19) | – | omega-3 (0.5 g/day), ciprofibrate (100 mg/day) | Moderate TG elevation; ↑ transaminases |
| 14y 4m | 19.81 (≈ 1755) | 7.80 (≈ 301) | 0.63 (≈ 24) | 2.7 (≈ 105) | omega-3 (1 g/day), pravastatin (20 mg/day) | Severe exacerbation |
| 15y 1m | 16.78 (≈ 1485) | 7.35 (≈ 284) | 0.67 (≈ 26) | – | omega-3 (2 g/day), ciprofibrate (100 mg/day) | Exacerbation; incomplete therapy and dietary adherence |

| | | | | | | |
|---|---|---|---|---|---|---|
| 15y 9m | 4.3 (≈ 381) | 4.7 (≈ 181) | - | - | omega-3 (1 g/day), ciprofibrate (100 mg/day) metformin (500 mg/day) | Promising first results after introduction of metformin |
| **Note:** "–" indicates data not available or not measured. | | | | | | |

**Table 2. Oral glucose tolerance test (OGTT) results with corresponding insulin levels and reference ranges**

| Time (min) | Glucose (mmol/L) | Insulin (mIU/L) | Reference insulin range (mIU/L) |
|---|---|---|---|
| 0 | 4.70 | 14.93 | <15 (fasting) |
| 30 | 7.05 | 84.54 | |
| 60 | 4.51 | 45.79 | <100 (peak normal) |
| 90 | 4.51 | 63.31 | |
| 120 | 4.79 | 57.44 | |
| 180 | 3.78 | 8.71 | |

* Reference values: fasting insulin < 15 mIU/L; peak response < 100–150 mIU/L (borderline hyperinsulinemia threshold).

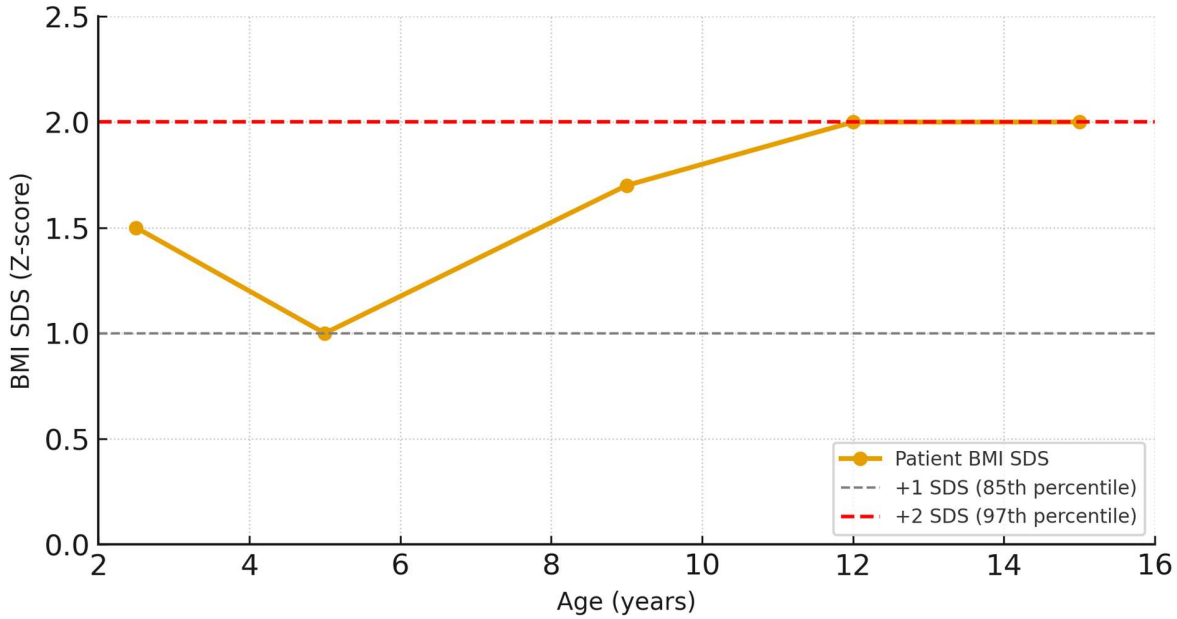


**Figure 1.** BMI SDS trajectory from age 2.5 to 15 years, based on WHO 2007 growth standards. Horizontal dashed lines denote +1 SDS (85th percentile) and +2 SDS (97th percentile).