Original paper

Simvastatin in Familial Hypercholesterolemia

Karim O. Al-Naffi[1*]

[1]Department of Internal Medicine, College of Medicine, University of Kerbala, Kerbala, Iraq

Abstract

Background: Familial Hypercholesterolemia is hereditary disease which needs different type of treatment modalities, all are lifelong & some of it are either not promising or expensive**.**

Aim: The aim of the study has three disciplines one is to assess the effect of simvastatin in lowering cholesterol level in patient with familial hypercholesterolemia, the second discipline is to study the use of the simvastatin in children starting from age of 4 years . The third is to monitor the expectable side effect if it happens.

Patient and method: Eighteen persons of three families with consanguineous marriage, age 4 - 48 years with familial hypercholesterolemia was diagnosed in Karbala governorate at 2009 and started on dietary control & simvastatin in increasing dose up to the maximum allowed dose , they were followed between august 2009-January 2012 for clinical, biochemical response & any drug side effects. They are still under follow up.

Results and Discussion: Simvastatin showed significant decrease in cholesterol level in the first six months with 20% reduction with a P value of 0.001, then the response decrease with rebound increment. There is no significant drug side effect reported neither in adults nor in the children. The result of the study is coinciding with similar studies regarding the limited effectiveness of statin in FH, also the safety of its usage in children

Conclusion: Statin usage alone is not as effective as along run treatment for FH, other treatment modalities are required; although it is save with minimal side effect even in children

Keywords: Familial hypercholesterolemia, simvastatins, Children.

Abbreviations*:* FH: Familial Hypercholesterolemia, LDL: Low density lippprotein.TG: triglyceride., ECG: electrocardiography, ECHO: Echocardiography

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder that causes severe elevations in total cholesterol and low-density lipoprotein cholesterol (LDLc). Although moderate hypercholesterol-emia is a common finding in industrialized countries, heterozygous FH occurs in approximately 1 per 500 persons worldwide.[1,23]

The prevalence has been reported to be ten times higher in certain populations with a presumed founder effect, such as the Lebanese, the French Canadians, and the South Afrikaners(2)

FH is a disorder of absent or grossly malfunctioning low-density lipoprotein (LDL) receptors. In 1986, the LDL receptor (LDLR) was discovered as the cause of Autosomal Dominant Hypercholesterolemia (ADH) (3).

*For Correspondence: Email to karimalnaffi@yahoo.com

The LDL receptor gene is located on the short arm of chromosome 19, It is the primary determinant of hepatic LDL uptake, which normally processes approximately 70% of circulating LDL. Two ligands on LDL bind to the receptor, apolipoprotein B-100 (apoB-100) and apoE. The LDL receptor also binds another ligand, apoE, and is, therefore, more accurately termed the B,E receptor.[4,5]

LDL cholesterol normally circulates in the body for 2.5 days, and subsequently binds to the LDL receptor on the liver cells, undergoes endocytosis, and is digested. LDL is removed, and synthesis of cholesterol by the liver is suppressed in the HMG-CoA reductase pathway.[7] In FH, LDL receptor function is reduced or absent, and LDL circulates for an average duration of 4.5 days, resulting in significantly increased level of LDL cholesterol in the blood with normal levels of other lipoproteins.[6] In mutations of *ApoB*, reduced binding of LDL particles to the receptor causes the increased level of LDL cholesterol.

A major change in the number or functional status of LDL receptors directly affects serum cholesterol levels. If the liver does not take up LDL particles, serum LDLc levels increase. Also, when LDL is not internalized by hepatocytes, hepatic synthesis of cholesterol is not suppressed. This leads to further cholesterol production despite high levels of circulating cholesterol. Therefore, circulating cholesterol levels are increased dramatically

Although atherosclerosis occurs to a certain degree in all people, FH patients may develop accelerated atherosclerosis due to the excess level of LDL. The degree of atherosclerosis approximately depends of the number of LDL receptors still expressed and the functionality of these receptors. In many heterozygous forms of FH, the receptor function is only mildly impaired, and LDL levels will remain relatively low. In the more serious homozygous forms, the receptor is not expressed at all.[4,6]

Homozygous FH may have cutaneous xanthoma at birth or by early childhood. Several types of xanthoma are usually obvious in the first decade of life, and they include (1) planar xanthoma (on hands, elbows, buttocks, or knees), which are diagnostic for the homozygous state and are distinct from other cutaneous xanthoma because of their yellow-to-orange coloration; (2) tuberous xanthoma (on hands, elbows, or knees); and (3) tendon xanthoma (especially on extensor tendons of hands or Achilles tendon) will occur somewhat later. The presence of tendon xanthoma is often stated to be pathognomonic for FH [22]

Children may have corneal arcus, which is sometimes circumferential. While occasionally present in older adults with normal cholesterol levels, corneal arcus is highly unusual in children, and this finding should prompt a workup for homozygous FH. The murmur of aortic stenosis may be heard also.

In regard of treatment, homozygous FH is harder to treat. The LDL receptors are minimally functional, if at all. Only high doses of statins, often in combination with other medications, are modestly effective in improving lipid levels.[21] If medical therapy is not successful at reducing cholesterol levels, LDL apheresis may be used; this filters LDL from the bloodstream in a process reminiscent of dialysis.[4] Very severe cases may be considered for a liver transplant; this provides a liver with normally functional LDL receptors, and leads to rapid improvement of the

cholesterol levels, but at the risk of complications from any solid organ transplant (such as rejection, infections, or side-effects of the medication required to suppress rejection).[8,9] Other surgical techniques include partial ileal bypass surgery, in which part of the small bowel is bypassed to decrease the absorption of nutrients and hence cholesterol, and portacaval shunt surgery, in which the portal vein is connected to the vena cava to allowing blood with nutrients from the intestine to bypass the liver.,(10,11,12) Inhibition of the microsomal triglyceride transfer protein, for example with the investigational drug AEGR-733, and infusion of recombinant human apolipoprotein A1 are being explored as medical treatment options.13 (13,14). Gene therapy is a possible future alternative.(15)

In Iraq the only available medication is the statin, the simvastatin is delivered freely in popular health clinics for the patients so we use it in our patient. The other cholesterol lowering medication is not available only cholyestramine is available on limited scale & it was costive so not used.

Aim

The study has three aims:

1. To assess the biochemical response to simvastatin in FH patients and if we use the maximum tolerable dose, how much It can reduce serum cholesterol?
2. What are the side effects in using these medications if we use it in its maximal dose?
3. How is it safe to use the simvastatin in children?

Patient and Method

This is a case series study done in Karbala Governorate over 30 months from June 2009-January 2012 on18 person of 4-48 yrs. old, ten females & eight males of three families with consanguineous marriages

After the presentation of 15 year boy with big xanthoma on the buttock causing difficulty for him to sit on the school chair, as seen in figure-**1**,he was found to have arcus as well and high serum cholesterol (690 mg/dl) & normal TG (74mg/dl). The whole family was examined clinically for xanthomas & their lipid profile was studied As seen in table-1., two other families who were the near relative from the father & mother side having variable form of xanthoma in their babies as in figure -**2**,

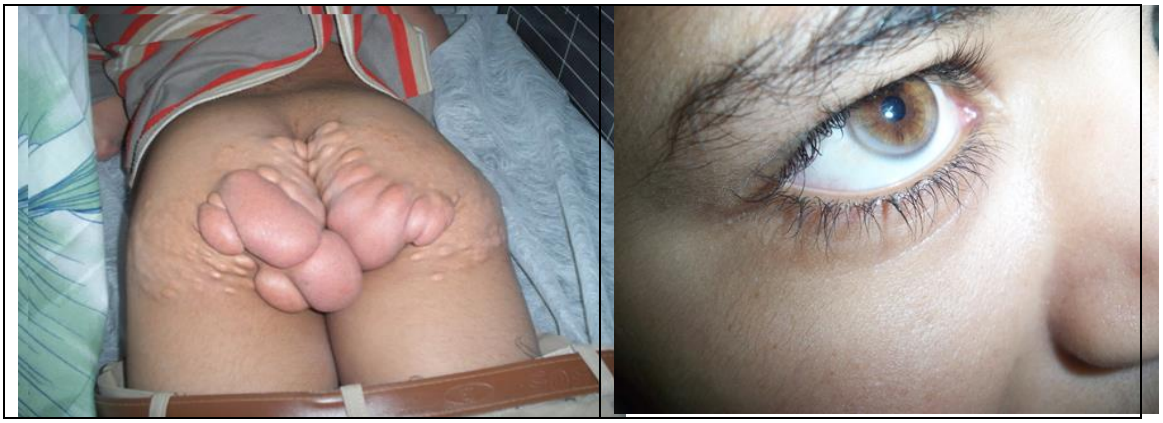
The members of the three families, their family pedigree, age & sex depicted in figure- **3**

The 1st family is formed of the parent with three boys, the second family is formed of the parent with one boy &fife girls, the third family is formed of the parent with three girls.

Initial full history was done interrogating concentrating on the expected complications of hypercholesterolemia especially any chest pain suggestive of ischemia heart disease, dyspnoea, intermittent claudication or any neurological complaint, and history of sudden death in their families.

Full clinical examination was done for the whole members of the three families. The basic data as body weight, height, skin examination for xanthoma, the eyes for arcus & cardiovascular examination was done.

All the member of the three families have normal blood pressure ,not diabetic and have normal cardiovascular system examination but the babies have variable form of xanthoma.



A B

Figure-1 A-Xanthoma of the buttock. B- Arcus in 13 year old boy with FH (case number-11)

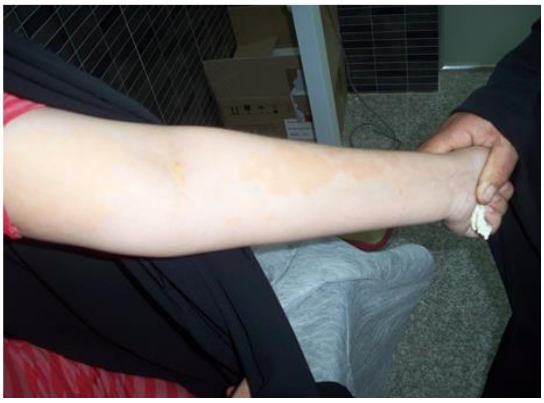


Figure-2 Xanthoma of forearm in 18 yr old girl with FH (case number-3)

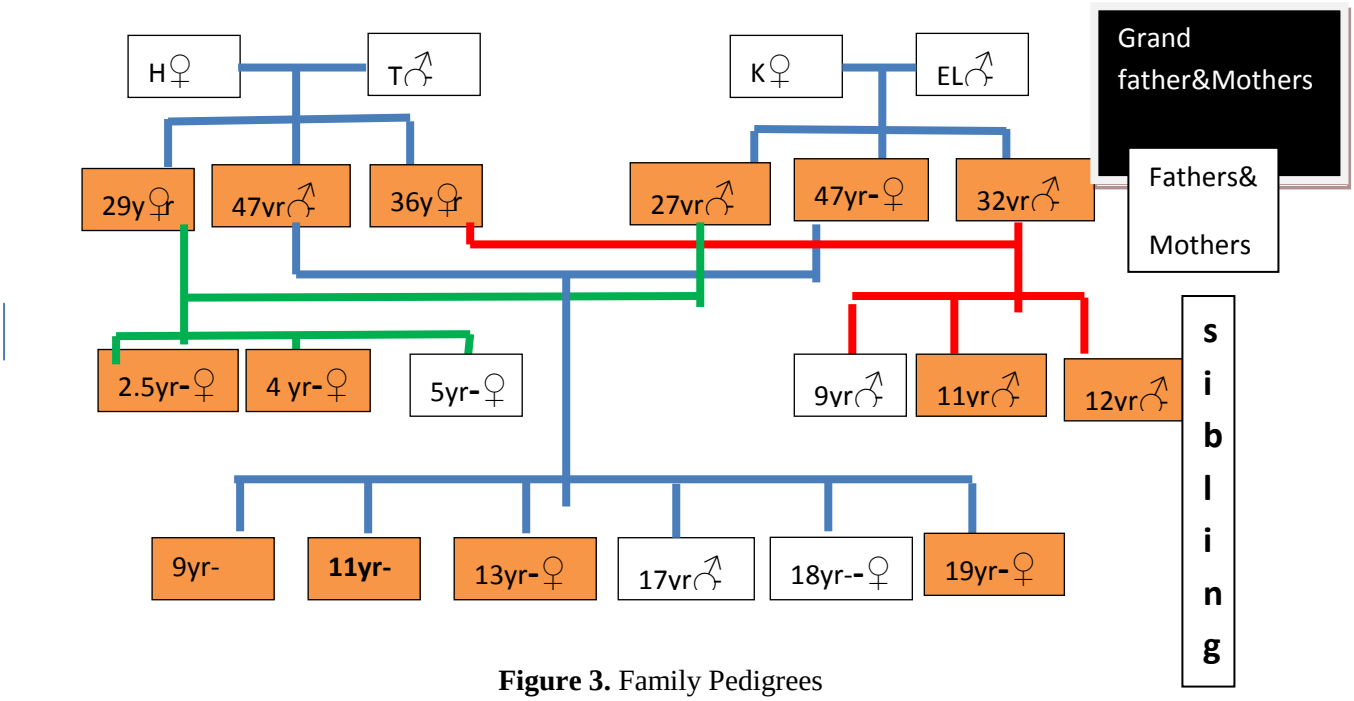


Figure 3. Family Pedigrees

ECG & ECHO was done for all of them. Baseline blood samples after at least a 12-hour overnight fast was collected to measure lipid profile and serum transaminases as a basic first reading as seen in table-1.

Explanation for the parents about the their clinical condition & their affected sibling, what are the treatment options &which one is available in Iraq. Since the only medication which is available is the statin and the freely dispensed statin brand in the Popular Health Clinics (Which is Governmental clinics) is simvastatin. Because of many members of the families need long term treatment , the other more effective statin brand is costive &the families have limited income to buy it, so the simvastatin is chosen .

Other medication as cholestramine or nicotinic acid is not available so also other modality of treatment as lipopharesis.

The consent of the families is taken to start the affected members on simvastatin.to be dispensed freely every month on special certificate issued from Al-Hussain Teaching Hospital directed to the Popular Health Clinics.

Table 1. The member of the three families with their age and first reading of lipid level. **A**-1st family, **B**-2nd family,**C**-3rd family, the white rows are normal, yellow rows have moderate elevation of serum cholesterol &orange rows have high serum cholesterol

Case No.&Family	Sex	Age(yr)	S.Cholesterol(mg/dl)	S.Triglyceride(mg/dl)
1-A	M	47	314	125
2 -A	F	47	248	82
3 -A	F	20	603	87
4-A	**F**	**18**	**102**	107
5-A	**M**	**17**	**147**	103
6-A	F	12	510	84
7-A	F	11	600	70
8-A	M	8	355	78
9-B	M	36	284	145
10-B	F	32	255	80
11-B	M	12	690	74
12-B	M	11	351	158
13-B	M	9	145	100
14-C	M	29	245	161
15-C	F	27	239	115
16-C	**F**	**5**	**121**	77
17-C	F	5	687	168
18-C	F	1	520	106

The three families got instruction concerning feeding as avoidance of fatty meals & encouragement of exercise. Whole cases except the four normal cases were started on simvastatin in a dose started with 10 mg for those under 10 yrs, 20 mg for those 10- 18yr & 40 mg for those over18 yrs.

Repeated blood samples test for serum lipoprotein after overnight fasting & transaminases was measured every two months, interview with the patient& interrogation concerning any unwanted side effect due to drugs as muscle pains

or any other side effects, also by checking the transaminases frequently. Meanwhile we follow them for any complication from the disease itself by history, physical examination, ECG & ECHO. follow up of lipid profile and transaminases was studied, then after 8 months the dose increased to 80mg in adult and 20 mg for kids below 10y & 40mg for those 10-18yrs of age.

Ideal level of serum cholesterol varies according to cardiovascular risk. The following value which was described by the European Atherosclerosis Society is used for grading of hypercholesterolemia was used for grading as in table 2:

Table 2.

Mild increase	
5.2-6.5 mmol/	200-250 mg/dL
Moderate increase	
6.5-7.8 mmol/L	250-300 mg/dL
Severe increase	
> 7.8 mmol/L	> 300 mg/dL

Data management and statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 19.0 software. Results were expressed as means ± standard deviation (SD); The one-way ANOVA and F-test was used to test the strength of the relationship between the means of categorical variables. All statistical analyses were done at 95% confidence level. Statistical significance was accepted when $P < 0.05$.

Results

The positive history of the families is only their consanguineous marriages, no history of diabetes, hypertension or any cardiovascular disease or sudden death. the physical examination is positive for variable form of cutaneous xanthoma in the sibling only some of them has arcus as seen in figure1&2.

The parent having moderate elevation of serum cholesterol (mean=264mg/dl) with mild TG (mean=185mg/dl) while the sibling have high level of cholesterol (mean=524mg/dl). The level of serum triglycerides is normal.as seen in table-1 (Mean=116 mg/dl), within the 1st year of treatment with simvastatin in dose of 20-80 mg/dl according to the age. the mean of serum cholesterol drops after three months by 20.7% and after 6 month it continue to drop reaching around 30%., table-3&4, this is near to similar study results done by de Jongh S, Ose L, Szamosi which found 31% reduction in cholesterol.[26]The mean of their first cholesterol=370.6mg/dl then after two months the mean cholesterol drop to 292 mg/dl which is statically significant (P value is less than .001) &after 6 months it drops to 230 mg/dl which also statistically significant. Thereafter no further drop in the cholesterol level over the next year on the contrary in the kids there is elevation in the level with mean level of cholesterol (429mg/dl) after two years as seen in figure- 4. There is no significant effect on triglycerides level as seen in table5&6 .Repeated transaminases measurement shows no elevation over two years and for all age groups, no any muscular complaint was reported from all the patients.

Clinical follow up of the cutaneous xanthoma shows no significant regression. The big gluteal xanthoma of the index case number one was later removed surgically as seen in figure -5.

Patient number (3A) who is a female age 20 year got heart attack at the end

of the second year of treatment for which coronary angiography done which shows critical lesion of left anterior descending artery & circumflex artery, stent put in &she is doing well.

At the end of the second year her father developed dyspnoea, his ECG shows LBBB and his ECHO shows systolic dysfunction with EF of 45%.

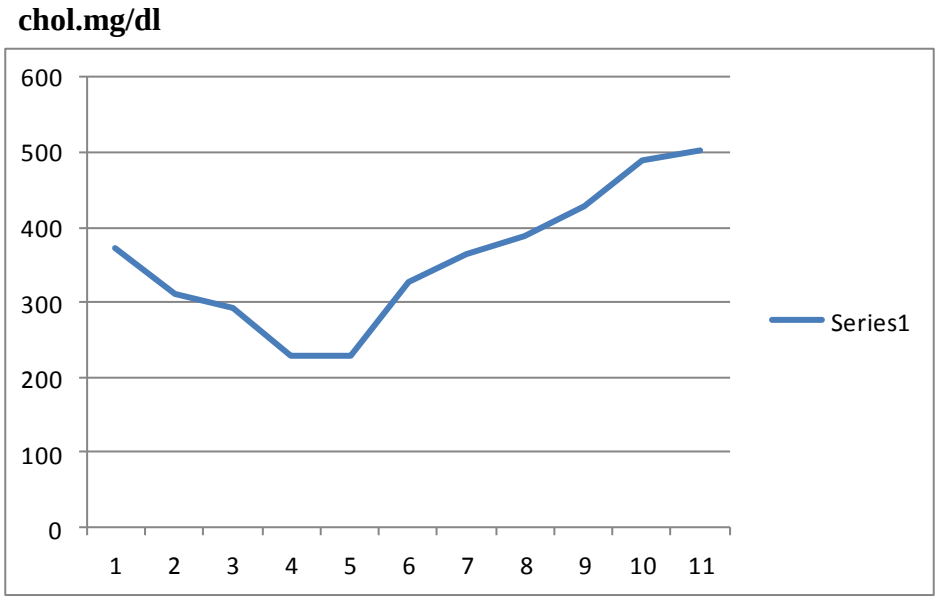


Figure 4. Change of mean cholesterol level every two months

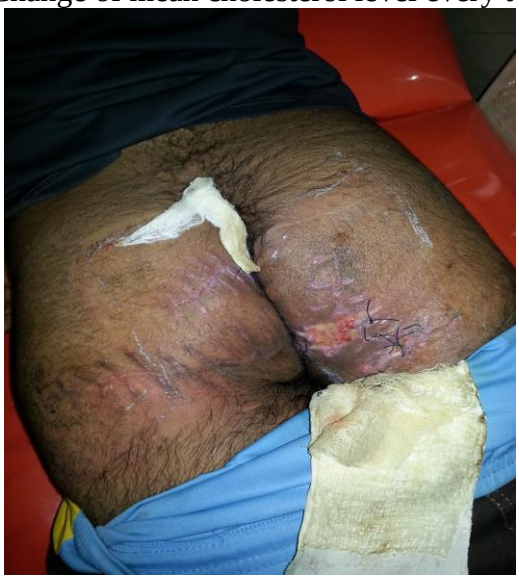


Figure 5. Case 1 after removal of the buttock xanthoma

Discussion

The diagnosis of the cases as FH done on clinical &biochemical measures which fulfil the criteria for diagnosis which they have: [16 ,19]

1) Severe hypercholesterolemia that is not explained by secondary causes.

2) A strong personal or family history of premature atherosclerotic cardio-vascular disease (CVD) or familial hyperlipidaemia

3) Tendon Xanthoma.

The parents who are near relative and have consanguineous marriage have moderate elevation of serum

cholesterol mean = (264mgldl) mostly to the classification of FH [18,19] they have heterozygous trait according

Table 3. Serum cholesterol levels according to the time of measurement

Descriptives

Chol

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
6/2009	9	370.5556	90.97542	30.32514	300.6257	440.4855	248.00	500.00
8/2009	8	369.0000	118.95257	42.05609	269.5532	468.4468	183.00	560.00
9/2009	7	292.1429	58.81731	22.23085	237.7459	346.5398	195.00	373.00
11/2009	7	230.7143	52.50624	19.84549	182.1541	279.2745	175.00	316.00
12/2009	6	272.0000	112.31385	45.85194	154.1338	389.8662	190.00	488.00
3/2010	5	326.6000	78.14602	34.94796	229.5689	423.6311	210.00	390.00
8/2010	8	507.7500	201.68416	71.30612	339.1378	676.3622	276.00	859.00
1/2011	8	480.7500	154.02945	54.45763	351.9782	609.5218	189.00	680.00
3/2011	10	468.0000	227.43302	71.92064	305.3042	630.6958	183.00	874.00
7/2011	8	439.1250	214.96939	76.00316	259.4061	618.8439	33.00	681.00
1/2012	10	545.7000	172.08076	54.41672	422.6008	668.7992	330.00	833.00
Total	86	404.3023	176.01411	18.98009	366.5648	442.0398	33.00	874.00

Table 4. Statistical siginficant of the drop in serum cholesterol

ANOVA

Chol

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	836992.5	10	83699.246	3.494	.001
Within Groups	1796390	75	23951.862		
Total	2633382	85			

Descriptives

TG

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
6/2009	9	114.0000	79.19754	26.39918	53.1234	174.8766	70.00	313.00
8/2009	6	133.8333	104.55509	42.68444	24.1095	243.5572	62.00	335.00
9/2009	6	138.8333	44.16975	18.03222	92.4800	185.1866	108.00	211.00
11/2009	1	105.0000	.	.	.	.	105.00	105.00
12/2009	5	109.8000	42.62276	19.06148	56.8768	162.7232	66.00	171.00
3/2010	4	169.7500	123.87460	61.93730	-27.3621	366.8621	98.00	355.00
8/2010	8	133.3750	35.57663	12.57824	103.6322	163.1178	74.00	184.00
1/2011	7	109.0000	32.77702	12.38855	78.6863	139.3137	78.00	173.00
3/2011	9	173.6667	96.28863	32.09621	99.6527	247.6807	94.00	400.00
7/2011	7	173.4286	132.05663	49.91271	51.2966	295.5606	63.00	376.00
1/2012	8	129.0000	77.96153	27.56356	63.8225	194.1775	65.00	309.00
Total	70	137.6286	80.38606	9.60797	118.4612	156.7959	62.00	400.00

ANOVA

Tal **des**

TG

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	41321.537	10	4132.154	.603	.805
Within Groups	404550.8	59	6856.793		
Total	445872.3	69			

While their sibling have high serum cholesterol (mean=524mg/dl) this indicate that they got homozygous gene expression according to Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia [17,18,]

These families have a pattern is typically compatible with hyperlipo-proteinemia type IIa on the Fredrickson classification: raised level of total cholesterol, markedly raised level of low-density lipoprotein (LDL), normal level of high-density lipoprotein (HDL), and normal level of triglycerides [4]

It has become clear that atherosclerotic cardiovascular disease begins in childhood and is progressive &that what happened in one of our patient age 19 year with homozygous FH. This provides the strongest rationale for aggressive treatment of risk factors in individuals at greater risk for cardiovascular disease at an early age. [24]

The response of the cholesterol level to statin therapy shows good initial response as seen in the curve, then the level is flattened for a while then the level increased in spite of treatment. This is expected in homozygous hypercholesterolemia because Statins act by inhibiting the enzyme hydroxymethylglutaryl CoA reductase (HMG-CoA-reductase) in the liver. In response, in normal the liver produces more LDL receptors, which remove circulating LDL from the blood but this is not happened in homozygous FH because these receptors are deficient.

The elevation in serum cholesterol observed after the first where initial response was seen possibly is related to the progression of the condition with the age.

In most of other studies it is mentioned that homozygous FH is much more resistant to medical therapy. In homozygous FH both LDL receptor alleles are affected so that there is little to no LDL receptor activity to be up-regulated. Do the statins work in homozygous FH? Initially, with the less potent statins, it was rather discouraging. [26] In other study However, with the advent of the more potent statins, a clinically meaningful effect began to be observed in homozygous FH. In a study of eight homozygous FH patients treated with simvastatin 80 mg and 160 mg, the 80-mg dose produced a 25% reduction in LDL and the160-mg dose, 31%.Seven of the eight patients were receptor defective, but in one receptor-negative patient, there was a 30% reduction in LDL.[27]

In other studies it was found that homozygous FH is harder to treat. The LDL receptors are minimally functional, if at all. Only high doses of statins, often in combination with other medications, are modestly effective in improving lipid levels.[9] & that is what we found in our patients.

Although there has been a general reluctance to use drug therapy to treat lipid abnormalities in children, increasing evidence suggests effective-ness and short-term safety similar to those in adult.

In heterozygous FH There are data indicate that early initiation of statin treatment delays the progression of carotid IMT in adolescents and young adults & that early initiation of statin therapy in children with familial hypercholesterolemia of heterozygous type might be beneficial in the prevention of atherosclerosis in adolescence. [21]

There is no remarkable drug side effect recoded in our patient over the last three years of management, although our sample is small but they are mostly children, neither GIT symptom or muscle problem, also the repeated measurement of serum transaminase were normal & this is

also shown in previous multiple studies which shows minor elevation in serum transaminases

Conclusion

FH although is rare but it is difficult to treat by drugs only, it need more sophisticated treatment like lipophresis or liver transplantation. The limited side effect of usage of statin even in children is encouraging to extend its usage in children with Familial hypercholesterolemia or other causes of hypercholesterolemia.
Early diagnosis of FH whether heterozygous or homozygous with proper treatment according to its type will hinder the progression of atherosclerosis & cardiovascular complications.

References

1. National Institute for Health and Clinical Excellence. Clinical guideline 71: Familial hypercholesterolaemia. London, 2008.
2. Khachadurian AK: The Inheritance of Essential Familial Hypercholesterolemia. The American journal of medicine 1964, 37:402-7.
3. Brown M, Goldstein J: A receptor-mediated pathway for cholesterol homeostasis. Science 1986, 232:34-47.
4. Rader DJ, Cohen J, Hobbs HH (2003). "Monogenic hypercholesterolemia: new insights in pathogenesis and treatment". *J. Clin. Invest.* 111 : 1795–803. doi:10.1172/JCI18925. PMID 12813012. Full text at PMC: 161432.
5. Hobbs HH, Brown MS, Goldstein JL (1992). "Molecular genetics of the LDLR gene in familial hypercholesterolemia". *Hum. Mutat.* 1 : 445–66. doi:10.1002/humu.1380010602. PMID 1301956.
6. Durrington P (2003). "Dyslipidaemia". *Lancet* 362 (9385): 717–31. doi:10.1016/S0140-6736 14234-1. PMID 12957096.
7. Brown MS, Goldstein JL (1974). "Familial hypercholesterolemia: defective binding of lipoproteins to cultured fibroblasts associated with impaired regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity". *Proc. Natl. Acad. Sci. U.S.A.* 71: 788–92.doi: 10.1073/ pnas. 71.3.788.
8. Arch. Intern. Med. 158 : 1253–61. doi:10.1001/archinte.158.11.1253. PMID.
9. Marais AD, Blom DJ, Firth JC (January 2002). "Statins in homozygous familial hypercholesterolemia". Curr Atheroscler Rep 4 : 19–25. doi:10.1007/s11883-002-0058-7. PMID 11772418.
10. Bilheimer DW, Goldstein JL, Grundy SM, Starzl TE, Brown MS (December 1984). "Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia". N. Engl. J. Med. 311: 1658–64. PMID 6390206.
11. Revell SP, Noble-Jamieson G, Johnston P, Rasmussen A, Jamieson N, Barnes ND (November 1995). "Liver transplantation for homozygous familial hypercholesterolaemia". Arch. Dis. Child. 73 : 456–8. doi:10.1136/adc.73.5.456. PMID 8554367. Full text at PMC: 1511367.
12. López-Santamaria M, Migliazza L, Gamez M, *et al.* (April 2000). "Liver transplantation in patients with homozygotic familial hypercholesterolemia previously treated by end-to-side portocaval shunt and ileal bypass". *J. Pediatr. Surg.* 35: 630–3. doi:10.1053/jpsu.2000.0350630. PMID 10770402. http://linkinghub.elsevier.com/retrieve/pii/S0022-3468-56892-4.
13. Buchwald H, Varco RL, Boen JR, *et al.* (June 1998). "Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Program on the Surgical Control of the Hyperlipidemias 9625405. http://archinte.ama-assn.org/cgi/content/full/158/11/1253.
14. Bilheimer DW, Goldstein JL, Grundy SM, Brown MS (December 1975). "Reduction in cholesterol and low density lipoprotein synthesis after portacaval shunt surgery in a patient with homozygous familial hypercholesterolemia". *J. Clin. Invest.* 56 : 1420–30. doi:10.1172/JCI108223. PMID 172531. http://www.jci.org/articles/view/108223. Full text at PMC: 333120
15. Cuchel M, Bloedon LT, Szapary PO, *et al.* (January 2007). "Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia". *N. Engl. J. Med.*

356: 148–156. doi:10.1056/ NEJMoa 061189. PMID 17215532. http://content.nejm.org/cgi/content/full/356/2/148.
16. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic basis of inherited disease, vol. 120. New York: McGraw-Hill; 2001
17. Williams et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol 1993;72:171–6.
18. Melissa A. Austin,Carolyn M. Hutter, , Ron L. Zimmern2 and Steve E. Humphries .American Journal of EPIDEMIOLOGY September 1, 2004 p. 2863–913.
19. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolemia Atherosclerosis 1999;142:105–112. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991;303:893–6; Mortality in treated heterozygous familial hypercholesterolaemia: implica-tions for clinical management.
20. Steinberger, Albert P. Rocchini, Laura L. Hayman and Stephen R. Daniels Brian W. McCrindle, Elaine M. Urbina, Barbara A. Dennison, Marc S. Jacobson, Julia Disease in the Young, , With the Council on Cardiovascular Nursing. Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents Circulation published online Mar 21, 2007;
21. Jessica Rodenburg, Maud N. Vissers, Albert Wiegman, A. S. Paul van Trotsenburg, Anouk van der Graaf, Eric de Groot, Frits A. Wijburg, John J.P. Kastelein and Barbara A. Hutten Statin Treatment in Children With Familial Hypercholesterolemia : The Younger the Better, the Circulation. 2007;116:664-668;
22. Elena Citkowitz, Hypercholesterolemia, Familial MEDESCAPE Updated: Oct 16,2008.
23. George Yuan, Jian Wang, Robert A. Hegele,Canadian Med.Ass.Jpurnal(CMAJ) Heterozygous familial hypercholesterolemia:an underrecognized cause of early cardiovascular disease.
24. Brian W. McCrindle, Elaine M. Urbina, Barbara A. Dennison, Marc S. Jacobson, Julia *Circulation* published online Mar 21, 2007;
25. De Jongh S, Ose L, Szamosi T, Gagne C, Lambert M, Scott R, Perron P,Dobbelaere D, Saborio M, Tuohy MB, Stepanavage M, Sapre A,Gumbiner B, Mercuri M, van Trotsenburg AS, Bakker HD, Kastelein JJ,for the Simvastatin in Children Study Group. Efficacy and safety ofstatin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation.2002;106:2231–2237.
26. Linda C. Hemphill, Journal of Clinical Lipidology (2010) 4, 346–349.
27. Cobb MM, Teitelbaum HS, Breslow JL. Lovastatin efficacy in reducing low-density lipoprotein cholesterol levels on high- vs low-fat diets. JAMA. 1991;265:997–1001