EARLY DETECTION OF FAMILIAL HYPERCHOLESTEROLEMIA IN CHILDREN

Acronym: DECOPIN

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INTRODUCTION

The most prevalent cause of hypercholesterolemia in childhood is Heterozygous Familial Hypercholesterolemia (HeFH).

It is a monogenic disorder that is transmitted of autosomal dominant way and affects 50% of offspring. It is characterized by the increase of low-density lipoproteins (LDL-C), which can be detected from birth. It is mostly caused by mutations in the gene that encodes the LDL receptor (LDLr) located in the short arm of chromosome 19. Nowadays, more than 1500 different mutations have been described worldwide. Less common are the ApoB3500 Family Defect, caused by the mutation of the Apolipoprotein B gene (APOB) that is located on chromosome 2, and the mutation of the gene encoding PCSK9 (proprotein convertase subtilisin-kexin type 9) located on the chromosome 1p32.2. These three entities are clinically expressed in the same way and only the genetic study will allow us to differentiate them.

HeFH has a prevalence of 1 for every 250 individuals in the European population, therefore it is the most frequent genetic disease, which is a major public health problem as it is associated with high cardiovascular risk (CVR). In spite of the current knowledge and the diagnostic techniques, it continues being an unknown disease and therefore is underdiagnosed and under-treated. In countries with active screening projects of HeFH detection, only 20% are diagnosed. In Catalonia, in order to get free access to lipid lowering therapy, a register was started in 2004. In November 2012, a total of 2,981 patients were registered in Catalonia, representing 19.53% of expected HeFH patients in Catalonia. Only 108 children were included, in the age group 0 to 14 years,

In clinical practice, DLCN criteria (clinical criteria of Dutch Lipids Units) is used as a diagnostic tool, but these clinical criteria cannot be applied to the children. The criteria are based on family history, personal history, physical examination and LDL-C levels. A definite clinical diagnosis of HeFH is considered when the score obtained is equal to or greater than 8 points, it’s probable when the score obtained is between 6-7 points and possible when it is between 3-5 points (table 1). In these clinical criteria, the presence of tendinous xanthomas and the corneal arch are very important. These two stigmas are not present in HeFH children, and we will only find xanthomas in Homozygous Familial Hypercholesterolemia (HoFH). This form of the disease is very serious and the prevalence
is low, 1 per 300,000-400,000 habitants.

We suspect HeFH when we observe LDL levels >135 mg/dL in children with a family history of premature cardiovascular disease (men < 55 y/o and women < 65 y/o) in first-degree relatives, or a parent with LDL levels > 240 mg/dL (according to data published in adult HeFH population in the Spanish population)\(^1\).

At present, there are clear evidences that high LDL-C levels in children induce the formation and development of atheromatous lesion\(^2\). This lesion can be initiated during the first years of life by cholesterol deposit, causing an increase in the carotid intima-medium thickness (cIMT), progressing silently until adulthood.

It has been observed in children over 5 years of age that high cholesterol levels cause alterations in endothelial function of the arterial wall, measured by flow-mediated dilation (FMD)\(^3\). Wigman and colleagues observed that cIMT of HeFH children between 8 - 18 years \(H\) was higher than the control children population, estimating cIMT growth in around 0.0047 mm/year; in front of 0.0003 mm/year in the control group\(^4\). Dalmau and colleagues evaluated the cIMT of 88 HeFH children between 2 and 19 years and described a faster cIMT increase with age particularly after 12 years old, regardless of gender and other analytical parameters related to CVR\(^5\).

Statin intervention studies, have described that reductions between 30 and 40% in LDL-C levels lead to an improvement in endothelial function measured by FMD\(^6,7\) and cIMT\(^8,9\). Núñez et al, have also observed that arterial stiffness was increased in children with CVR compared to children without CVR\(^10\).

There is evidence suggesting that HeFH children have a pro-inflammatory and pro-oxidant state that could accelerate the atherosclerosis process and increase CVR\(^11\). Recent studies from our group have shown that E-selectin, sVCAM or oxLDL/LDL are associated with lower post-ischemia reactivity in small arteries in patients with high CVR\(^12\).

Statin intervention studies in HeFH children have proven that these drugs are safe and effective. LDL-C reduction is associated to a reduction in cIMT\(^13\). An early lipid lowering therapy decrease the lifelong CVR\(^14\).

The first clinical guidelines addressing familial hypercholesterolemia (FH) in children were published in 1992 by National Cholesterol Education Program (NCEP)\(^15\). Since then, many Scientific Societies have given recommendations about detection, diagnosis and treatment\(^16-21\). All guides reinforce the importance of an early detection.
The most conflicting point between the different panels of experts is the type of screening. The National Heart Lung and Blood Institute (NHLBI) recommends universal screening between 9 and 11 years, in the context of the comprehensive management of CVR factors in childhood, and selective screening between 2 and 8 years\textsuperscript{17}. Other guidelines recommend selective screening based on family history and the presence of CVR factors\textsuperscript{18-21}.

A recent study has shown that screening based on lipid profile may be insufficient to detect HeFH population. A genetic study of 215 members of 24 families with RLDDL mutations showed that 7% of the members wear the mutation despite a normal lipid profile\textsuperscript{22}.

The Netherlands is one of the countries with a more active health policies to detect the HeFH population. For many years, they have established a National Program based in cascade screening of all first-degree relatives of diagnosed FH patients. They propose a general screening of the children population between 1 and 9 years. This type of screening has a greater sensitivity and specificity\textsuperscript{23}. Universal screening together with selective screening would be the most efficient method to detect FH patients, but this goal can only be achieved by activating specific healthcare strategies in the usual clinical practice.

Avis et al. assessed the degree of control and follow-up of 207 HeFH children (0-18 y/o) from January 2007 to May 2008. Only 62% had received a lifestyle change advice, 16% took functional foods every day with stanols or sterols and only 26% were taking statin therapy. Their conclusions were that a screening program is necessary but this programme should be accompanied by a proper follow-up with a multidisciplinary health group (nurses, pediatricians, dietitians and specialists involved in the management of severe hypercholesterolemia)\textsuperscript{24}.

Previously, different studies had observed that 50% of men and 20% of woman with FH don’t received adequate treatment increasing the risk of coronary episodes before 50 years old\textsuperscript{25}. Nowadays, it has been shown that the intensive treatment of FH patients reduce cardiovascular mortality, reaching the same proportion as the general population\textsuperscript{26}.

According the official data from the “Generalitat of Catalonia” the province of Tarragona has a population of 71,186 children between the ages of 0 and 14. The aim of this project is detecting FH children early to improve their CVR in adulthood.
HYPOTHESIS

HeFH is an underdiagnosed disease in the paediatric population. Its early detection, would allow us to initiate lifestyle therapeutical changes and early pharmacological therapy if necessary. This is a key fact to reduce atherosclerosis progression and CVR in adulthood. Moreover, it will allow, detecting the first and second degree affected relatives.

1-OBJECTIVES:

Main

1- Early detection of FH in the children population by:
   • Increasing paediatric awareness and cholesterol measurements (oportunistic screening).
   • Reverse cascade screening: Confirmation of FH in one of the progenitors of suspicious children, by positive mutation or clinical criteria (DLCN ≥8 points).
   • Direct cascade screening: Studing children from FH families

2- Comprehensive phenotype characterization. Including new plasma biomarkers of cardiometabolic risk

3- Follow-up of FH children to assess the impact of lifestyle therapeutic changes or lipid lowering therapy if indicated.

Secondary aims

1- To study subclinical atherosclerosis parameters of the FH child population and compare it with non-FH child population, using non-invasive techniques such as the measurement of the cIMT and the rigidity determination of the arterial wall at baseline. This study will be repeated every two years, at the fifth year and later every 5 years, in FH children and in children with Polygenic Hypercholesterolaemia (PHC). This follow-up will allow study the progression of two lipid disorders and study the relation with atherosclerosis.

2- To determinate the Achilles tendons thickness of FH children and compare it with the non-FH children at basal time. This study will be repeated over the next year,
after two years, at the fifth year and every 5 years after. This study only will do in FH and PHC children. This follow-up will allow seeing if there are differences between the two pathologies.

3- To determine biochemical parameters and complete lipid profile by NMR and new biomarkers of children at basal time. Annual and follow-up will be determinate in FH and PHC children.

4- To collect the anthropometric and clinical data of all children at baseline. FH and PHC children will be monitored annually.

5- To study the pro inflammatory and oxidant status of the FH children and compare it with the non-FH children at basal time. This study will be repeated in the fifth year to children diagnosed with FH and PHC.

6- To study the parameters of aortic arterial elasticity in all the children at basal time. This study will be repeated over the next year, after two years, at the fifth year and every 5 years after children diagnosed with FH and PHC. This follow-up will allow to study if there are differences between the two pathologies.

7- To study the lifestyle of all the children before explanations about recommendations of lifestyle changes and verify their compliance after one year. Every year we will study the healthy patterns of children with FH and PHC.

8- To start selective screening cascade of the first and second degree relatives after receiving the results of the genetic study in the index patient (progenitor).

9- To compare all the results of FH children at basal time and follow-up.

2- MATERIAL AND METHODS

2.1-Patients of the study:

Inclusion criteria:

Children between 2 and 18 years of age who have a LDL-C level above 135 mg/dL will be referred to the Unit of Vascular Medicine and Metabolism (UVASMET) of the Sant Joan University Hospital. Previously, the pediatrician will have discarded secondary causes of hypercholesterolaemia such as hypothyroidism, nephrotic syndrome, diabetes, renal insufficiency (table 2).

After confirmation that one of the parents has a genetic mutation
(Lipoxip/Liponext) or clinical diagnosis (DLCN ≥ 8), the child will be studied. The progenitor with hypercholesterolemia will be considered as an index case, in this way we will demonstrate the vertical transmission of the genetic disease.

**Exclusion criteria**

The child population under 2 and over the age of 18 and children with secondary hypercholesterolaemia.

**Procedures:**

The detailed clinical history of the index case, including the history of cardiovascular disease in first and second degree relatives, personal history of cardiovascular disease as well as the presence of other CVR factors, anthropometric data and usual treatment will be collected.

The family history, personal, anthropometric data, CVR factors of all affected or unfocused children of FH related in first or second degree will be collected.

A semi-quantitative assessment of the consumption of different food groups and physical activity (Minnesota Test) will be done.

To all of them, carotid ultrasound will be performed to determine the cIMT at the level of the common, bulb and internal portion of the right and left side (a total of six determinations).

The rigidity of the arterial wall, determined by the central velocity of the pole wave (PWV), the distensibility and the rate of increase (IAx) at the level of the common portion of the carotid artery will be studied.

For ultrasound, the Achilles tendon thickness will be measured and the presence of hypo-echogenic areas compatible with tendon xanthomas will be recorded.

For transthoracic echocardiography, the parameters of aortic arterial elasticity will be measured.

Control population will be considered to all those relatives of the case that do not present diagnostic criteria of the disease and are in the age of inclusion of the study or those candidates with relevant age who are referred to the UVASMET for suspicion of FH in which the diagnosis is not confirmed.
2- Assessment of the lifestyle

A semi-quantitative assessment of the consumption of different food groups will be carried out using a frequency questionnaire validated by the Spanish population\textsuperscript{27}. This questionnaire consists of 137 food items and will be obtained by the dietitian of our Unit (see annex). A review will be added for those foods enriched with phytosterols and that can influence the levels of cholesterol. These data, we can assess the effect of different groups of foods or specific foods on cholesterol levels. In addition, it will allow us to see which patterns of food consumption can influence, positively or negatively, on the levels of cholesterol in the child population carrying the genetic alteration.

The child population and/or their parents will be instructed on how to fill the data in the food diary for a period of 3 days, in order to be able to analyse the nutritional composition of the intake and the effect on the lipid profile. The first food register, will be obtained at the collection visit before starting any type of treatment. Another food diary will be included after one year.

Physical activity will be collected from the Minnesota Test and we will ask about the consumption of tobacco.

2.3-Biochemical analysis

A fasting analysis will be performed which will include blood count, glycemia, total cholesterol, HDL-C, LDL-C, triglycerides, ApoA, ApoB, Lp(a), ApoE genotype, GOT, GPT, GGT, alkaline phosphatases, total and direct bilirubin, calcium, CPK, TSH, Vitamin D, creatinine and proteinuria.

Complete lipid profile by NMR will be also determined.

Selective determination of specific mutation (RLDL, ApoB, PCSK9) in the case of a positive outcome of the index case.

Plasma concentrations of E-selectin and oxLDL will be determined by commercial ELISA kit: E-selectin (R & D Systems) and oxLDL (Mercodia).

2.4-Collection of samples

An additional sample of 10cc of venous blood will be collected that will be processed in plasma and serum aliquots according to the protocol of the METBANC-HFH collection that is part of the BIOBANC of the Pere Virgili Health Research Institute (IISPV).
In the child population diagnosed with FH and PHC a new additional sample will be included in the follow-up year, at two and five years and later every five years.

3- DETERMINATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHILDREN'S POPULATION WITH AND WITHOUT FH.

3.1 Determination of the intima-medium thickness of the carotid artery (cIMT).

The cIMT determination is a reliable, standardized, reproducible and validated method that use ultrasounds, allows quantitative measurements of the bulk of the carotid artery wall. It is a non-invasive technique that has proven to be directly associated with CVR factors and to be useful in predicting the future incidence of cardiovascular events. This measure allows quantifying the vascular damage caused by CVR factors over time. The technique will be carried out according to the recommendations of the Consensus of the American Society of Ecography. It will be carried out in the external consultations (UVASMET) of the Sant Joan University Hospital, by the same operator to minimize the variability and we use Esaote My-Lab 60 X-Vision (Esaote SpA, Italy) that allows to determine the cIMT for a semi-automatic method in live and radio frequency images. Images of the posterior wall of the common carotid artery, 1 cm proximal to the carotid bifurcation and 1 cm distal to the division corresponding to the internal carotid will be obtained.

The existence of an atheroma plaque will be considered when protrusion of the wall towards the light that is higher than 1.5 mm thick or when the thickness is greater than 50% of the surrounding area. The average cIMT will be the result of the average of both cIMT of the common carotids and the maximum cIMT will be the one that corresponds to the maximum of cIMT of the 6 studied territories (the two common carotids, the 2 branches and the 2 internal carotids).

3.2. Measurement of the elasticity of the carotid arterial wall:

The loss of arterial elasticity is one of the mechanisms that most alarmingly warn of damage to the arteries. There are several parameters that evaluate the arterial elasticity:

The pulse wave velocity (PWV) is one in which the energy wave caused by the cardiac systole travels through the arterial wall. At higher speeds, greater rigidity of the
wall and also higher pulse wave transmission speed. This variable corresponds mainly to the rigidity of large arteries, such as the aorta and its main forks, which are the main responsible for the damping of the energy caused by cardiac contraction. It is expressed in m/sec, the values of normality vary according to age, gender and blood pressure.

The increase index (AIx) corresponds to the interaction between the incident pulse wave that comes from the cardiac systole and the reflex wave, which occurs when the incident bounces in the middle artery divisions and small diameter and arterioles. The pulse wave detected by tonometry is the result of the interaction of these two. It is defined as the percentage of the distance between the inflection point corresponding to the confluence of the incident wave and the one that returns with respect to the distance between the maximum point of the pulse wave (systolic blood pressure) and the base of the wave (diastolic blood pressure). This measure correlates with the cardiovascular risk and expresses the rigidity not only of large arteries but also of those of small size, which reflects the elasticity of the entire arterial tree.

The arterial distensibility is the fluctuation of the size of the arterial light when receiving the impulse of the blood column mobilized by the cardiac contraction. Increased arterial stiffness less complacency or viscoelasticity of the arterial wall.

All these variables are measured by arterial tonometry and radio frequency. In the present study, they will be measured using the My-Lab 60 X-Vision device (Esaote S.p.A., Italy) at the level of the common portion of the carotid arteries.

3.3 Determination of the thickness of the Achilles tendons:

The determination of the thickness of the Achilles tendons will be carried out in the HFH child population and in the non-HFH child population participating in the study.

To measure the Achilles tendons, the participants will be placed in a position with a folded ankle beyond the test bed and with the feet at 90° of flexion. The high resolution linear probe will be placed perpendicular to the tendon at 2 cm from the proximal zone of the insertion of the calcaneus. Once the image is obtained, it will freeze and be measured in a transverse manner in the tendon. When the upper and lower limits of the tendon walls are clearly observed, three determinations will be made at the maximum thickness point and separated by 0.5 cm. The Achilles tendon thickness of each foot will be the result of the average of the three determinations. We will consider that there is an
increase in the thickness of the tendon when it is greater than 5.3 mm in men <45 years of age and more than 5.7 mm in men over 45 years of age. In women, we will consider xanthomas when the thickness of the aquiline tendon is greater than 4.8 mm in age under 50 and 4.9 mm in over 50 years. At the same time, the presence of xanthomas will be assessed for the presence of hypo-echogenic areas and for the ecological deconstruction of the tendon. In the child population, the values of normality of the Achilles tendon thickness are described based on age and sex.

3.4 Determination of aortic arterial elasticity by transthoracic echocardiography:

The echocardiography is an innocuous, painless technique that does not require sedation for its realization.

The echocardiography will be performed with a General Electrocardiograph E9, with a 5 Mhz transducer suitable for paediatrics. The measures will be carried out with the patient placed in the left lateral position, and in the absence thereof, if by age of the patient it is not possible, in supine order.

The measures of structures and standard flows will be carried out as well as measures to determine the arterial elasticity. The standard measures will be carried out as described in the paediatric echocardiography guides.

The diameters of the aorta will be carried out in three locations:

1. In the long parasternal axis, with M mode, 0.5 cm above the sinus-tubular junction.
2. From the super sternal axis to the ascending aorta just before the exit of the first brachiocephalic trunk, both by 2D and by mode M.
3. Short axis at the level of the right pulmonary artery.

The systolic diameter will be measured at the point of maximum previous movement of the aorta, and the diastolic diameter will be measured at the peak of the QRS in the simultaneous ECG.

Aortic distensibility (DA) will be calculated according to the formula: \( DA = 2 \times (AoS - AoD) \times \frac{AoD \times PP}{(AoS - AoD) \times (AoD)} \times 10^{-6} \).

Aortic rigidity will be calculated according to the formula: \( RA = \frac{\ln (PAS / PAD)}{(AoS - AoD) / (AoD)} \).
Likewise, a determination of the blood pressure will be made with the supine patients, after a rest period of 15 minutes. The measurement will be done with an automatic tensiometer with a handle adapted to its age and condition.

Pressure of dust (PP) will be calculated with the difference between systolic and diastolic blood pressure.

In the event that any structural or functional anomaly is detected, the patient will be referred to the pediatric cardiology questionnaire for appropriate follow-up.

4. SIZE OF THE SAMPLE AND STATISTICAL ANALYSIS:

The population of the demarcation of Tarragona between 2 and 18 years old is 71,186 children. We know that the prevalence of HeFH is 1/200-300 habitants, therefore we have a population of 355 to 237 HeFH children in the province of Tarragona.

Statistical analysis will be carried out through the SPSS statistical program (version 19.0) through a specific database for this study.

The normal distribution of the continuous variables by the Kolmogorov-Smirnoff test will be studied. For the categorical variables and comparisons of frequencies between groups, the chi square test will be used to compare continuous variables between groups and with normal distribution the Student T test or the U Mann-Whitney test in the case of Non-normal distribution variables. In order to associate variables, Pearson or Spearman correlations will be made between normal or non-normal continuous variables respectively. Multivariate analysis will be done with logistic or linear regressions depending on whether the variables are dichotomous or continuous.

5. INFORMED CONSENT:

The study procedure will be explained to the parents of FH and non-FH children. Parents, as legal guardians, must sign the consent informed and confidentiality procedures will be given a patient information sheet detailing all the procedures of the study. A copy of the informed consent will also be given (see annex). This study has been approved by the clinical research ethics committee (CEIC) of the Sant Joan University Hospital.

6. GOOD CLINICAL PRACTICE:

All the clinical procedures will be in accordance with the current international
regulations on good clinical practices, in accordance with the Provisions of the International Conference Harmonization on Good Clinical Practices (ICH-GCP) and the principles established by the 18th International Medical Association (Helsinki, 1964).

7. WORK PLANNING

Clinical visit:

The child population between 2 to 18 years old with LDL-C levels >135 mg/dL and/or progenitor with cholesterol levels >300 mg/dL or with hypolipemiant treatment, or a history of premature cardiovascular disease in relatives of first or second degree (<55 years men and <65 years in women), will be referred to external consultations of endocrinology with Dr. Feliu.

Dr. Feliu is responsible to assess the inclusion criteria and if the child and the parent can be FH, they will be sent to UVASMET. In there, the responsible staff will explain the reasons for the study again and insisting on the importance of early detection to reduce CV risk. The informed consent will be collected, filed and kept under key in the Clinical Investigation Unit (UIC). Family history, personal history, anthropometric data, physical examination and current treatment data will be collected under the supervision of Dr. Plana.

All researchers will participate in the analysis and discussion of the results.

Evaluation of the lifestyle:

The semi-quantitative assessment of the consumption of the different food groups will be carried out in UVASMET (Sant Joan University Hospital, Reus). Children and his families will be informed about foods with low cholesterol content. Recommendations will be made and "cardiosaludable" habits will be stimulated. Support documentation will be provided.

The annual follow-up visit will evaluate compliance with the recommendations made and the frequency questionnaire for food consumption will be collected again. Mrs. Cèlia Rodríguez will be the nutritionist-dietician in charge of this task. All researchers will participate in the analysis and discussion of the results.

Vascular study:
The study of subclinical arteriosclerosis will be carried out in UVASMET (Sant Joan University Hospital, Reus). An ultrasound will be performed at levels of the carotid arteries and levels of Achilles tendons. Team work will be supervised by Dr. Ferré and Dr. Ibarretxe.

Echocardiography will be carried out by Dr. Marimon.

All researchers will participate in the analysis and discussion of the results.

**Blood extraction:**

Blood samples will be obtained after 8-hours fasting in UVASMET (Sant Joan University Hospital, Reus) premises. Mrs. Anna Varela will be the nurse in charge of processing and distributing samples. Several plasma, serum and WBC aliquots will be stored in the BioBanc of the Hospital Research Institute (IISPV).

An aliquot will be sent to the laboratory of the San Juan Hospital for routine biochemical parameters measurement.

A complete lipid profile by NMR will be analysed in Biosfer Teslab. (www.biosferteslab.com)

If the genetic study is indicated, a DNA sample will be sent to the Hospital de Sant Pau in Barcelona, that centralize these genetic studies in Catalonia.

All the members of the team of researchers will participate in the analysis of the results.

**Determination of inflammatory parameters:**

Inflammation, oxidation and other biomarkers determination will be carried out in the Research Unit on Lipids and Arteriosclerosis (URLA) located at the Faculty of Medicine of Reus of the Rovira i Virgili University (URV) at the end of the recruitment of the child population. Dra. Josefa Girona will be responsible.

All the members of the team of researchers will participate in the analysis of the results.

The Dra. Plana and Dr. Feliu will be in charge of supervising and coordinating the team of researchers as well as analyzing the results and the possible publication. Drs NP,
AF, RF, DI, JG, CR, CM, LM will participate actively in the elaboration of manuscripts derived from the study.

All pediatricians involved in the DECOPIN group will be present in all the publications derived from the study.
8-REFERENCES


17-Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction


26-Avishay E, Rong Z, Evan A, Stein MD. Effect of lipid-lowering treatment on natural


## Table 1. Clinical criteria diagnosis of HFH according to DLCN

<table>
<thead>
<tr>
<th>Family History:</th>
<th>Score if is affirmative</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. First-degree family with precocious disease and / or vascular</td>
<td>..... 1 point</td>
</tr>
<tr>
<td>II. First-degree family member with c-LDL ≥210 mg/dL</td>
<td>..... 1 point</td>
</tr>
<tr>
<td>III. First degree family with xanthoma and / or corneal arch</td>
<td>..... 2 points</td>
</tr>
<tr>
<td>IV. Child under 18 with c-LDL ≥150 mg/dL</td>
<td>..... 2 points</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal History:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Antecedent of precocious coronary disease</td>
<td>..... 2 points</td>
</tr>
<tr>
<td>II. Antecedent of peripheral vascular disease and/or precocious cerebral</td>
<td>..... 1 point</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Tendinous Xanthome</td>
<td>... 6 points</td>
</tr>
<tr>
<td>II. Corneal arc before age 45</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting analytics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I. LDL-C ≥ 330 mg/dL</td>
<td>...... 8 points</td>
</tr>
<tr>
<td>II. LDL-C 250 - 329 mg/dL</td>
<td>...... 5 points</td>
</tr>
<tr>
<td>III. LDL-C 190 - 249 mg/dL</td>
<td>...... 3 points</td>
</tr>
<tr>
<td>IV. LDL-C 155 - 189 mg/dL</td>
<td>...... 1 point</td>
</tr>
</tbody>
</table>

**TRUE DIAGNOSIS:** ≥8 points, **PROBABLE DIAGNOSIS:** 6-7, **POSIBLE DIAGNOSIS:** 3-5 Points
Table 2. Causes of secondary dyslipidemia in the child population

<table>
<thead>
<tr>
<th>Pure Hypercholesterolemia</th>
<th>Mixed dyslipemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nephrotic syndrome</td>
<td>• Diabetes type 1 and type 2, metabolic syndrome, obesity, lipodystrophy</td>
</tr>
<tr>
<td>• Hypothyroidism, hypopituitarism, idiopathic hypercalcemia</td>
<td>• Drugs: antiretrovirals, oral contraceptives, anabolizers</td>
</tr>
<tr>
<td>• Drugs: corticosteroids, retinoic acid</td>
<td>• Ketogenic diets, alcohol.</td>
</tr>
<tr>
<td>• Anorexia nervosa, Kawasaki's disease</td>
<td>• Chronic renal or hepatic insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy</td>
</tr>
<tr>
<td></td>
<td>• Turner Syndrome or Klinefelter</td>
</tr>
<tr>
<td></td>
<td>• Lupus erythematosus, rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>• Glucogenosis (type I), sphingolipidosis (Niemann-Pick)</td>
</tr>
</tbody>
</table>
SUSPECT CRITERIA IN HeFH CHILDREN'S POPULATION

- Child with LDLC ≥ 135 mg / dL.
- Antecedents of early cardiovascular disease (<55 years in men or <65 years of age in women) in relatives of first or second degree.
- Progenitor with CT levels> 300 mg / dL or in hypolipemiant treatment.
- Progenitors of unknown origin (Child adopted).

CRITERIA OF DERIVATION TO PEDIATRIC ENDOCRINOLOGY

- Child with confirmed hypercholesterolaemia.
- Discard causes of secondary hypercholesterolaemia.
- Confirmation of hypercholesterolemia in progenitor.
How will we do universal screening?

- We will take the opportunity to request CT and TG in all analyzes that ask the child population between 2 and 14 years.
- If CT levels > 200 mg / dL, we will repeat the analytic after one month to confirm the finding and we will request a complete lipid profile (CT, HDL, LDL, TG), TSH to rule out hypothyroidism, liver profile and kidney. We will discard proteinuria in urine.

Lipid Profile

If LDL-C <135 mg/dL
Lifestyle changes

If LDL-C >135 mg/dL
Lifestyle changes
Family screening

Yes, cLDL > 135 mg / dL
+ Parents with CT > 300 mg / dL
or
History of precocious CV disease
or
Unknown progenitors

Send to Pediatric Endocrinology Service

UVASMET
DE: Dra. Mª. Teresa Auguet
A: Dra. Núria Planas Gil

Presidenta del CEIm
Hospital Universitari Sant Joan de Reus

Assumpt: DECOPIN
Ref. CEIm: 176/2018

Benvolgut,

Li comunico que amb data 25/10/2018, el CEIm ha avaluat l’esmena presentada a l’estudi titulat “DETECCIÓN PRECOZ DE LA HIPERCOLESTEROLEMIA FAMILIAR HETEROCIGOTA EN LA POBLACIÓN INFANTIL”

El dictamen del CEIm respecte a l’anomenat projecte en el format actual és favorable.

Cordialment,

Dra. Mª. Teresa Auguet
Presidenta Comité Étic d’Investigació amb medicaments
Institut d’Investigació Sanitaria Pere Virgili

Reus, 25 d’octubre de 2018
DICTAMEN COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS

DOÑA Mª TERESA AUGUET QUINTILLA, PRESIDENTA DEL COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS DEL INSTITUT D'INVESTIGACIÓ SANITÀRIA PERE VIRGILI.

HACE CONSTAR QUE:

Este Comité, en su reunión de fecha 25/10/2018 acta número 9 se ha evaluado y decidido emitir Informe Favorable para la enmienda presentada al estudio titulado:

"DETECCIÓN PRECOZ DE LA HIPERCOLESTEROLEMIA FAMILIAR HETEROCIGOTA EN LA POBLACIÓN INFANTIL"

Código: DECOPTN
Versión HIP y Cl: Versión 3.0 10 d'octubre de 2018
Ref. CEIM: 176/2018

CONSIDERA QUE:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.

La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.

El alcance de las compensaciones económicas previstas no interfiera con el respeto a los postulados éticos.

Este comité acepta que dicho estudio sea realizado en el Hospital Universitari Sant Joan de Reus por la Dra. Núria Plana Gil del Servicio de Medicina Interna

En el caso que se evalúe algún proyecto en el que participe como investigador/collaborador algún miembro de este comité, se ausentará de la reunión durante la discusión del estudio.

La composición actual del CEIm del Instituto d'Investigació Sanitària Pere Virgili es la siguiente:

Presidente
Dra. Maria Teresa Auguet Quintilla
Servicio de Medicina Interna. Hospital Universitari Joan XXIII. Representante de la Comisión de Investigación.

Secretario
Dr. Josep Mª Alegret Colomé
Cardiólogo. Hospital Universitari Sant Joan de Reus
Vocales

Dr. Xavier Ruiz Plazas
Urólogo. Servicio de Medicina Interna del Hospital Universitari Joan XXIII.

Sra. Montserrat Boj Borbonés
Servicio de Farmacia del Hospital Universitari Sant Joan de Reus.

Sra. Anna Borruel Llovera
Diplomada Universitaria en Enfermería. UAU

Sra. Immaculada de Molina Fernández
Diplomada Universitaria en Enfermería. Hospital Universitari Joan XXIII.

Dr. Joaquín Escribano Súbias.
Médico del Servicio de Pediatría. Representante de la Comisión de Bioética Asistencial. Miembro de la Comisión de Investigación.

Dr. Joan Fernández Ballart
Catedrático de Medicina Preventiva y Salud Pública. Facultad de Medicina y Ciencias de la Salud. Universitat Rovira i Virgili.

Sra. M. Mar Granell Barceló
Abogada y Asesora Jurídica del Comité.

Dr. Josep M. Crespo Bernabeu
Servicio de Farmacia del Hospital Universitari Joan XXIII.

Dr. Jesús Miguel López-Dupla
Servicio de Medicina Interna Hospital Universitari Joan XXIII

Sr. Jordi Mallol Mirón
Catedrático de Farmacología, Facultad de Medicina, Universitat Rovira i Virgili.

Sra. Isabel Rosich Martí
Farmacéutica Atenció Primària

Sr. Francesc Xavier Sureda Batlle
Profesor Titular de Farmacología. Universitat Rovira i Virgili.

Dr. Vicente Valenti Moreno
Oncólogo. Hospital Sant Pau i Santa Tecla.

Dra. Elisabet Vilella Cuadrada
Departamento de Formación e Investigación del Hospital Psiquiátric Universitari Institut Pere Mata. Representante de la Comisión de Investigación.

Sra. Mercè Vilella Papasii
Representante de la Sociedad Civil.

Firma

Dra. Mª Teresa Auguet
Presidenta CEIm IISPV

Reus, 25 de octubre de 2018