Interpretation of Chinese Expert Consensus on Screening and Diagnosis of Familial Hypercholesterolemia

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Chinese Expert Consensus on Screening and Diagnosis of Familial Hypercholesterolemia issued

- «Screening for familial hypercholesterolemia in China» Action-initiated by China Cardiovascular Association, China Heart House and so on.
  - 2016.5 FH Outpatient Screening Program launched by China Cardiovascular Association
  - 2017.5 Holding the awarding ceremony of China FH Excellence Center

- Commissioned by the Academy, the Atherosclerosis and Coronary Heart Disease Society is responsible for this.

- Published on Chinese Journal of Cardiology, 2018; 46(2):99-103

- Providing FH diagnostic screening criteria for Chinese doctors
- Enhancing the concern for FH
- Promoting early diagnosis and early treatment of FH
FH is autosomal dominant disease. Most cases are caused by mutations in **LDLR** gene, apolipoprotein B (ApoB) gene, and the proprotein convertase subtilin/kexin9 (PCSK9) gene, result in disorder of LDL catabolism

- Markedly elevated level of LDL-C
- Premature ASCVD
- skin/tendon xanthoma, corneal arcus

The CAD risk of FH patients is about 20 times that of healthy people. Early detection of FH by screening and active treatment are expected to improve the prognosis of these patients.
Epidemiological features of FH

- FH is the most common genetic dyslipidemia.
- Prevalence of FH are mostly estimated in a particular population or epidemiological study, instead of the census of overall population.
- HoFH is relatively rare, its prevalence is about 1-3/million (1:160,000 - 250,000)
- The prevalence of HeFH is 1/137-500 (mostly in 0.2% - 0.48%)
- The prevalence of Asian population is similar to that of Caucasians.
- Studies have reported that 5-10% of premature CAD patients could be diagnosed with FH; up to 20% survivors of myocardial infarction may have FH
Epidemiological features of FH

- There are relatively few large-scale epidemiological data on FH in China.
- Epidemiological studies in Suzhou in 2014 estimated that the prevalence of FH in China is about 0.31%.
- Prevalence estimation in 9324 general population
  - Diagnosis of FH: LDL-C ≥ 6mmol/L or LDL-C ≥ 3.5mmol/L plus premature CAD history or CAD family history, prevalence of FH: 0.47%.
  - Based on modified DLCN (Dutch Lipid Clinic Network) criteria, prevalence of probable/definite FH: 0.28%.
- Among CAD patients (n=8050), prevalence of definite FH diagnosed by genetic testing is 3.5%.
- The study of 1843 patients with myocardial infarction (MI) by Chinese scholars found that the prevalence of probable/definite FH was 7.1% in patients with premature MI by clinical indicators (according to DLCN criteria), and 0.9% in patients with non-premature myocardial infarction.

The diagnostic rate of FH is seriously low

- FH is a public health issue commonly concerned by international community. But its diagnostic rate is very low, and in most countries is <1%
Clinical characteristics of FH

FH patients can be asymptomatic at the early stage. markedly elevated LDL-C mainly results in premature coronary artery disease. Familial aggregation often occurs.

Markedly elevated serum LDL-C: The serum LDL-C levels in HeFH patients and HoFH patients were 2 times and 4 times higher than those without disease in the same family.

- The level of serum LDL-C of untreated HeFH patients was more than 5 mmol/L (192.3 mg/dL), and that of HoFH patients was higher than 13 mmol/L (500 mg/dL).
- In consideration that the average serum TC level in our population is lower than that in the western population, it is speculated that the overall LDL-C level of Chinese FH patients may be lower than that of Western FH patients.

WHO: global health observatory data repository. Risk factors cholesterol. 2015.
Clinical characteristics of FH (continued)

- Premature ASCVD:
  - Coronary artery disease occurs in male patients<50 years, the onset-age of women is slightly later than male
  - Most HoFH patients could have diffuse atherosclerosis in adolescence, and some even have acute myocardial infarction, sudden death and other events.

In addition to involving the coronary arteries and result in premature ASCVD, FH patients can also affect the aorta, carotid artery and renal artery, and appear the corresponding clinical manifestations.
Clinical characteristics of FH (continued)

- **Xanthomas**: skin and tendon xanthoma are important characteristics for the clinical diagnosis of FH, mostly in the buttocks, elbow joints, knee joints and hands. Achilles tendon hypertrophy is also a manifestation of Xanthomas. Xanthomas is more common in HoFH patients than in HeFH patients. Some HoFH patients may have xanthomas at born.

- **Corneal arcus**: is a lipid deposit in the matrix around the cornea. About 30% of FH patients have corneal arcus.

- **Other**: **Aortic stenosis** may also occur in HoFH patients due to lipid deposition in the aortic valve leaflets and aortic roots.
Screening and diagnosis of FH

- FH is autosomal dominant disease. Early screening, early diagnosis and early treatment will benefit a certain number of FH patients in their family, reducing arteriosclerosis and CAD.
- Every year, 24th September is designated as the International Familial Hypercholesterolemia Publicity Day.

Screening methods:

- Universal screening for all populations
- Targeted screening for target populations
- Once FH patients are found, cascade screening for first-degree relatives of FH patients should be carried out, which is the most cost-effective screening method for FH
Screening criteria on FH from US National Lipid Association

- **Universal screening** for elevated serum cholesterol is recommended. FH should be suspected when untreated, fasting LDL-C meet the following criteria:
  - Adults ≥ 4.9 mmol/L (190mg/dL);
  - Children ≥4.14mmol/L (160mg/dL)

- For subjects meet above criteria, information on family history of hypercholesterolemia and CAD in first-degree relatives should be collected.

- At the LDL cholesterol levels listed below the probability of FH is approximately 80% in the setting of general population screening. These LDL cholesterol levels should prompt obtaining further family information:
  - ≥30 years: LDL-C ≥ 250 mg/dl
  - 20-29 years: LDL-C ≥ 220 mg/dl
  - < 20 years: LDL-C >190 mg/dl
Screening Criteria and Recommendations on FH in this consensus

According to the characteristics of serum cholesterol level of Chinese population and the clinical manifestations of FH, to determine suspected FH population and to prompt early diagnosis and treatment for FH patients, subjects with any one of the following characteristics should be screened for FH:

- Premature ASCVD (ASCVD occurs in men <55 years old or women <65 years old);
- After excluded secondary hypercholesterolaemia, serum LDL-C ≥ 3.8 mmol/L (146.7 mg/dL) in adults, serum LDL-C ≥ 2.92 mmol/L (112.7 mg/dL) in children;
- Presence of skin/tendon xanthoma or corneal arcus (<45 years);
- First-degree relatives with all above three characteristics.

Data from Survey on Nutrition and Health Status of Chinese Residents in 2002 reported:
- The 97.5th percentile of serum LDL-C level for adults and children were 3.8 mmol/L (146.7 mg/dL) and 2.92 mmol/L (112.7 mg/dL).
Contents for FH Screening

- **Family history**: collect information on family history of premature ASCVD and FH, serum LDL-C levels of family members (especially first-degree relatives), and the typical clinical manifestation of xanthomas and corneal arcus, etc.

- **Clinical history**:
  - Whether premature ASCVD
  - Focus on CAD, but do not ignore the history of stroke and peripheral atherosclerosis
  - Ask if there are any other diseases that could increase the level of LDL-C

- **Physical examination**: Standardized physical examination, especially pay more attention to xanthomas and corneal arcus.

- **Serum LDL-C level measurements**: a mandatory item for screening. Although genetic screening is the gold standard for FH diagnosis, LDL-C measurements is required for suspected subjects no matter the results of genetic testing.
**Recommendation for FH diagnosis**

- **Clinical and genetic diagnosis included.** As a genetic disease, the detection of LDLR, ApoB, PCSK9 and LDLRAP1 gene mutations is the gold standard for the diagnosis of FH, but FH could not be excluded without detection of above mutations.

- **There is no universal uniform FH diagnostic criteria**, several commonly used FH clinical diagnostic criteria as following:
  - **UK Simon Broome Register Group criteria:** based on tendon xanthomas and familial history of premature myocardial infarction and/or hypercholesterolemia, subjects could be diagnosed with definite or probable FH, or excluded FH. Tendon xanthomas is one of the necessary diagnostic criteria. TC290, LDL-C190
  - **Dutch Lipid Clinic Network (DLCN) criteria**
  - **USA Make Early Diagnosis-Prevent Early Death (MEDPED) criteria**

- **Japanese and Chinese scholars have proposed diagnostic criteria for FH:**
  - serum TC>7.8mmol/L or LDL-C>4.4mmol/L in adult,
  - serum TC>6.7mmol/L for children under age of 16;
  - Patients or relatives with a tendon xanthomas were diagnosed as HoFH, those who did not meet the homozygous criteria could be diagnosed as HeFH.
# DLCN criteria for diagnosis of FH in adults

<table>
<thead>
<tr>
<th>First: Family history</th>
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<tbody>
<tr>
<td>First-degree relative known with premature CAD (male&lt;55y; female&lt;60y)</td>
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<tr>
<td>First-degree relatives with known LDL-C levels &gt;95th percentile for age and sex in an adult relative</td>
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<tr>
<td>First-degree relative with tendon xanthomas</td>
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<tr>
<td>First-degree relatives with known LDL-C levels &gt;95th percentile for age and sex in a relative &lt; 18 years of age</td>
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<th>Second: clinical history</th>
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<tr>
<td>Presence of premature CAD (male&lt;55y; female&lt;60y)</td>
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<tr>
<td>Presence of premature cerebral/peripheral vascular disease (male&lt;55y; female&lt;60y)</td>
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<tr>
<th>Third: Physical examination</th>
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<tbody>
<tr>
<td>Presence of tendon xanthomas</td>
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<tr>
<td>Presence of corneal arcus in patient &lt; 45 years</td>
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<th>Fourth: LDL-C</th>
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<tr>
<td>Score &gt;8: Definite FH</td>
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<tr>
<td>Score 6-8: Probable FH</td>
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<tr>
<td>Score 3-5: Possible FH</td>
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<tr>
<td>&gt;8.5 mmol/L (&gt;325 mg/dL)</td>
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<tr>
<td>6.5-8.4 mmol/L (251-325 mg/dL)</td>
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<tr>
<td>5.0-6.4 mmol/L (191-250 mg/dL)</td>
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<td>4.0-4.9 mmol/L (155-190 mg/dL)</td>
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<th>Fifth: DNA analysis</th>
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<tr>
<td>Pathogenic mutations in LDLR, APOB, or PCSK9 gene</td>
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</table>
Comprehensive consideration of patients' family history, medical history, physical examination, LDL-C, gene mutation for diagnosis

Adults meeting any two of these criteria could be diagnosed with FH:

1. Untreated serum LDL-C level ≥ 4.65 mmol/L (180 mg/dL);
2. Presence of skin/tendon xanthoma or corneal arcus in subjects < 45 years old;
3. Family history of FH or premature ASCVD, especially CAD within the patient’s first-degree relatives.

Diagnostic criteria for children: Untreated serum LDL-C level ≥ 3.6 mmol/L (140 mg/dL) combined with family history of FH or premature CAD within the patient’s first-degree relatives.

Subjects with gene mutation of LDLR, ApoB, PCSK9 and LDLRAP1 could also be diagnosed with FH.

In patients with clinically diagnosed FH, some may not diagnosed by genetic testing, suggesting that FH may have other pathogenic genes, and the possibility of multi-gene interaction cannot be ruled out.
Differential diagnosis of FH

- Secondary hypercholesterolemia: before the diagnosis of FH, which need to be excluded:
  - Hypothyroidism
  - Nephrotic syndrome, etc.

- Sitosterolemia/phytosterolaemia: FH and phytosterolemia are typical of premature CAD and systemic xanthoma. Phytosterolemia is also caused by gene mutation, but the pathogenic genes of these two are different. These two disease could be differentiated by serum phytosterol level determination or genetic testing.
Flow chart of FH screening and diagnosis

**Screening objects**

1. Premature CAD patients;
2. Family history of premature CAD;
3. Serum LDL-C ≥ 3.8 mmol/L in adults, serum LDL-C ≥ 2.92 mmol/L in children
4. Xanthoma or corneal arcus

**Diagnostic criteria**

**Adults meet 2 of 3 could be diagnosed:**
1. Untreated serum LDL-C ≥ 4.65 mmol/L (180 mg/dL);
2. Xanthoma (Xanthoma on the hand, elbows, knees, buttocks or Achilles tendon hypertrophy) or corneal arcus;
3. Family history of FH or premature CAD within the patient’s first-degree relatives

**Children:** Untreated serum LDL-C ≥ 3.6 mmol/L (140 mg/dL) combined with family history of FH or premature CAD within the patient’s second-degree relatives

**Clinical diagnosis of FH**

**Genetic screening if available**

**Genetic diagnosis of FH**
FH treatment: EAS Recommendations

- Treatment of FH includes lifestyle modification, medication and other treatment.

The target of LDL-C is <1.8mmol/L (70mg/dL) in patients with FH combined with ASCVD.

The target of LDL-C is <2.6mmol/L (100mg/dL) in patients with FH alone.

The target of LDL-C is <3.4mmol/L (130mg/dL) in children with FH.

If it is difficult to achieve the target, it is recommended to reduce the serum LDL-C level of FH patients by at least 50%.

Consistent with “2016 Chinese Guideline for the Management of Dyslipidemia in Adults”
Therapeutic Lifestyle modification

Drug therapy: Start lipid-lowering therapy immediately after the diagnosis

- **Statins**: Recommend to use the maximum tolerated dose of potent statins
- **Combination therapy**: Ezetimibe (10mg/d) may be used in patients with FH who have used a maximum tolerated dose of potent statin, while LDL-C is still not respond to the target or with a statin intolerance
- **PCSK9 inhibitor**: If target could not be achieved with the above treatment, it is recommended to add PCSK9 inhibitor. Repatha (Evolocumab) has been approved for the treatment of homozygous FH in adults or adolescents over 12 years old in China. FDA has approved it for the prevention of MI, stroke, etc. Alirocumab is used in clinical pracabroad for but not yet available in China.

Other treatment:

- Apheresis, surgical treatment, gene therapy, etc., the treatment effect is uncertain
Take Home Messages

- FH is the most common genetic dyslipidemia. The CAD risk of FH patients is about 20 times that of healthy people.
- The main clinical manifestations are markedly elevated serum LDL-C levels, premature ASCVD, especially severe CAD, some patients may have xanthomas and corneal arcus.
- The awareness rate, diagnostic rate and treatment rate of FH is very low, especially the early treatment. Early detection of FH by screening and active treatment are expected to improve the prognosis of these patients.
- FH treatment often requires intensive or combination therapy, in addition to lifestyle interventions.
- PCSK9 inhibitors can not only effectively reduce LDL-C levels of FH patients, but also improve long-term prognosis of non-FH ASC patients.
Thanks to All of the Following Expert

- **Team leaders**: Wei Gao, Hong Chen
- **Expert members**: Yong Huo, Junbo Ge, Yaling Han, Ruiyan Zhang, Dong Zhao, Luya Wang, Weifeng Shen, Ping Ye, Dingyin Zeng, Jiyan Chen, Lixia Yang, Jianhua Zhu, Jian An, Wenliang Che, Shaohong Dong, Zhan Gao, Tao Hong, Ying Huang, Fusui Ji, Xinwei Jia, Jinyu Huang, Qinhua Jin, Jun Jin, Xinjun Lei, Chuanfen Liu, Quan Liu, Hongwei Li, Yu Peng, Liansheng Wang, Linghong Shen, Jinwei Tian, Ye Tian, Min Wang, Yupeng Wang, Bin Wang, Yan Wang, Yong Wang, Hua Wang, Shuangxi Wang, Meng Wei, Ning Wei, Xiaofan Wu, Wei Xie, Biao Xu, Xiaowei Yan, Mei Zhang, Kang Yao, Shaopeng Xu