ScreenPro FH – Screening Project for Familial Hypercholesterolemia in Central, Southern and Eastern Europe: Basic Epidemiology

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Summary

Introduction: Despite great recent progress, familial hypercholesterolemia (FH) is still underestimated, under-diagnosed and thus undertreated worldwide. We have very little information on exact prevalence of patients with FH in the Central, Eastern and Southern Europe (CESE) region. The aim of the study was to describe the epidemiological situation in the CESE region from data available. **Methods**: All local leaders of the ScreenPro FH project were asked to provide local data on (a) expert guess of FH prevalence (b) the medical facilities focused on FH already in place (c)

the diagnostic criteria used (d) the number of patients already evidenced in local database and (e) the availability of therapeutic options (especially plasma apheresis). **Results**: With the guess prevalence of FH around 1 : 500, we estimate the overall population of 588 363 FH heterozygotes in the CESE region. Only 14 108 persons (2.4 %) were depicted in local databases; but the depiction rate varied between 0.1 % and 31.6 %. Only four out of 17 participating countries reported the the LDL apheresis availability. **Conclusion**: Our data point to the large population of heterozygous FH patients in the CESE region but low diagnostic rate. However structures through the ScreenPro FH project are being created and we can hope that the results will appear soon.

Key words: diagnosis – epidemiology – familial hypercholesterolemia – screening

ScreenPro FH – projekt v oblasti screeningu zaměřený na familiární hypercholesterolemii ve střední, jižní a východní Evropě: základní epidemiologie

Souhrn

Úvod: I přes velký pokrok v nedávné době je familiární hypercholesterolemie (FH) stále ještě celosvětově podceňované, nedostatečně diagnostikované, a tedy i nedostatečně léčené onemocnění. O přesné prevalenci pacientů postižených familiární hypercholesterolemií v regionu střední, východní a jižní Evropy (CESE) máme jen velmi málo informací. Cílem studie bylo popsat na základě dostupných údajů epidemiologickou situaci v regionu CESE. **Metody**: Všichni vedoucí představitelé projektu ScreenPro FH v jednotlivých oblastech byli požádáni o poskytnutí lokálních údajů, které se týkají (a) expertního odhadu prevalence FH, (b) již fungujících zdravotnických zařízení, (c) použitých diagnostických kritérií, (d) počtu pacientů již zavedených v místní databázi a konečně (e) dostupnosti možností léčby (zejména plazmaferézy). **Výsledky**: Vzhledem k odhadované prevalenci FH přibližně 1 : 500 odhadujeme, že celková populace FH heterozygotů v regionu CESE zahrnuje 588 363 osob. V místních databázích se však zobrazilo pouze 14 108 osob (2,4 %), přičemž míra zobrazení se lišila v rozmezí od 0,1 % až 31,6 %. Pouze 4 země oznámily dostupnost LDL aferézy. **Závěr**: Naše údaje svědčí o velké populaci pacientů postižených heterozygotní formou FH v regionu CESE a zároveň o nízkých podílech jejich zobrazení. V rámci projektu ScreenPro FH jsou však nyní vytvářeny potřebné struktury a můžeme tak doufat v dosažení příznivějších výsledků.

Klíčová slova: diagnóza – epidemiologie – familiární hypercholesterolemie – screening

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder with well-known genetic transmission and clinical course [1]. Despite great recent progress, FH is still underestimated, under-diagnosed and thus undertreated [2]. Furthermore it represents a significant healthcare challenge as a common risk factor for the premature development of coronary heart disease [3].

The prevalence of FH in a given population can be only estimated. The estimated global number of patients with FH is at least 15 million people [4]. FH is an autosomal dominant disease that occurs naturally in two forms: homozygous and heterozygous. FH homozygotes are rare and their frequency in the general population is about 1 : 1 000 000. In specific populations the "founder effect" increases the prevalence (i.e. increased frequency of FH or a predominant mutation in a specific population because a new population was founded by a very small subset of the original population "bottle necking") [5]. The population prevalence of FH homozygotes based on the founder effect is between 1 : 10 000 and 1 : 100 000. The highest prevalence rates are found in the Afrikaner population in South Africa (1 : 10 000), and high rates have also been observed in French Canadians (mainly in the province of Quebec). In Europe, the highest prevalence of homozygous FH is in north-western Europe. In heterozygotes, the highest prevalence is found also in the Afrikaner population in South Africa (as high as 1 : 70) and in French Canadians (1 : 270) [6–8]. The Netherlands reports an prevalence of 1 : 300–1 : 400 [9]. We have very little information on exact prevalence of patients with FH in the Central, Eastern and Southern Europe (CESE) region. With regard to the Czech population from CESE region (which is similar to the American population), the more commonly cited heterozygote prevalence of 1 : 500 is still valid [1]. There are other populations with a higher prevalence of FH that have not yet been precisely specified via epidemiological investigations (e.g. Lithuanian Jews, the Lebanese) [10,11]. The prevalence is also higher in preselected population, e.g. in the setting of coronary care unit [12].

The aim of the study was to map the epidemiological situation in the CESE region.

Methods

ScreenPro FH project

The ScreenPro FH Project is an international network project aiming at improving complex care – from timely screening, through diagnosis to up-to-date treatment of familial hypercholesterolemia in Central, Eastern and Southern Europe including some countries of the Middle Asia.

Data acquisition

All local leaders were asked to provide local data on

- expert guess of FH prevalence
- the medical facilities focused on FH already in place
- the diagnostic criteria
- the number of patient already in database
- the availability of therapeutic options (especially plasma apheresis)

Statistics

We used descriptive statistics only. Relative rates were used where appropriate.

Results

The total population of the CESE regions counts 430 361 839 persons. In the majority of states the guess prevalence of FH is around 1 : 500, which translates to an overall population of 588 363 FH heterozygotes. Nevertheless only 14 108 persons (2.4 %) are evidenced in local databases, where the diagnostic rate varies considerably between countries from 0.1 % to 31.6 % (tab).

All countries used the Dutch lipid clinic network diagnostic criteria as primary diagnostic tool. Besides these MedPed criteria are being used in the Czech Republic, Latvia, Lithuania, Slovakia and the Simon Broome diagnostic criteria are being used in Lithuania, Poland, Slovakia and Ukraine.

Only four countries reported the availability of LDL apheresis (Czech Republic, Greece, Russia and Turkey).

Discussion

The prevalence of patients with heterozygous FH was estimated mostly as 1 : 500, as the prevalence in community derived from symptomatic FH patients (from hospital patients, registries, and from models estimating also homozygous FH [13–16]. Nevertheless the epidemiological studies from unselected populations in last years, that combined also genetic analysis and cascade screening, led to higher FH prevalence. In a huge unselected Danish general population the prevalence of FH was 1 : 223 FH was defined as Dutch lipid clinic network score higher than 5 [17]. The data derived from United States National Health and Nutrition Examination Surveys led to an estimated US prevalence of probable/definite FH 1 : 250. Probable and definite diagnosis was defined according to Dutch lipid clinic network score 6–8 points and more than 8 points, respectively. The probable FH prevalence was 1 : 267 and definite 1 : 4 023. In China the estimated FH prevalence was 1 : 357 [18] and in Australia 1 : 353 and 1 : 229 [19]. In Poland, one of the countries from the CESE region, the pooled data from several studies the FH prevalence was also higher than expected: 1 : 248 [20]. These results correspond to the finding of Wald et al, who performed a FH screening among children during routine immunization visits. In these 1–2 years old children detected newly diagnosed FH in 4 in 1 000 children, which translates to a prevalence rate of 1 : 250 [21]. If we assume this higher prevalence, this would lead to doubling the number of patients affected by FH in the CESE region.

In the countries of the CESE region the predominantly used diagnostic criteria are Dutch lipid clinic network diagnostic criteria. The genetic testing is not necessary for the diagnosis of FH, as in approximately 20 % of patients with a clinical FH diagnosis we are unable to find a genetic mutation [3]. Nevertheless when a genetic mutation is demonstrated the diagnosis of FH is established [1]. On the other hand not all patients with a heterozygous FH mutation have LDL-cholesterol high enough to make the clinical diagnosis [1]. That is why the recommended screening criteria in the ScreenPro FH project are the Dutch lipid clinic network diagnostic criteria, which combines both possibilities: genetic and clinical diagnosis.

The number of patients already followed in databases is very low from the target FH population (2.4 %) and varies from country to country. Unfortunately this is in accordance with the worldwide situation. In most countries the estimated diagnosed FH is less than 1 % from the number of FH patients predicted from the prevalence of 1 : 500 [2]. The highest diagnosis rates are in the Netherland and Norway, where the diagnostic process received a governmental support and in countries with dedicated physicians [1].

LDL apheresis is indicated in homozygous FH patients and severe heterozygous FH patients [1]. LDL apheresis is available only in few countries (Czech Republic, Greece, Russia, Turkey).

Conclusion

Our data point out to the large population of heterozygous FH patients in the CESE region but low diagnostic rates. However structures through the ScreenPro FH project are being created and we can hope that the results will appears soon.

Financial support

To increase our financial resources we´ve applied for the IAS independent grant: IAS/Pfizer IGLC Grant Request: Lipid Management in High-Risk Patients.
The project is financially supported by Amgen and Sanofi. Local activities in different countries are also supported by local grants and sponsors.

Conflict of interest

Authors expressed these conflicts of interest:

- *grants/research supports – Amgen, Sanofi*
- *honoraria or consultation fees – MSD, Bayer, Aegerion, Amgen, Sanofi, AstraZeneca, AOP orphan, Teva, Pfizer,*

Tab. Overview of participating countries

country	national coordinator	national center	other centers	population	FH prevalence	estimated number of FH patients
Bosnia and Herzegovina	prof. Belma Pojskic, MD	Cantonal hospital Zenica	0	3 825 334	1 : 500	7 652
Bulgaria	prof. Assen Goudev, MD, FESC	N/A	N/A	7 202 198	1 : 500	14 404
Croatia	Ivan Pecin, MD, PhD	University Hospital Center Zagreb	4 (planned)	4 225 316	1 : 500	8 450
Czech Republic	Tomas Freiberger, MD, PhD	General University Hospital in Prague, St. Anne's University Hospital in Brno	62	10 538 275	1 : 500	21 077
Greece	prof. Alexandros D. Tselepis, MD, PhD	University Hospital of Ioannina	8	10 812 467	1 : 500	21 625
Hungary	prof. György Paragh, MD	Medical Center, University of Debrecen (prof. György Paragh), Semmelweis University, Budapest (prof. István Karádi)	20	9 849 000	1 : 500	19 698
Kyrgyzstan	prof. Erkin M. Mirrakhimov, MD, PhD prof. Tolkun Murataliev Muratalievic, MD	The National Centre of Cardiology and Therapy	2	5 850 687	1 : 500	11 700
Latvia	assoc. prof. Gustavs Latkovskis, MD	Latvian Institute of Cardiology and Regenerative Medicine, Riga	0	1 986 096	1 : 500	3 972
Lithuania	prof. Zaneta Petrulioniene, MD, PhD	Vilnius University Hospital Santariskiu Klinikos, Center of Cardiology and Angiology				
Poland	prof. Andrzej Rynkiewicz, MD, PhD, DSc	University of Warmia and Mazury (prof. Andrzej Rynkiewicz), Medical University of Gdansk (prof. Marcin Gruchala)	7	38 005 614	1 : 500	76 011
Romania	prof. Gheorghe-Andrei Dan, MD, PhD prof. Dan Gaita, MD, PhD	N/A	N/A	19 861 408	1 : 500	39 723
Russia	prof. Marat V. Ezhov , MD	Cardiology Research Center, Moscow	16	146 267 288	1 : 500	292 535
Serbia	prof. Nebojsa Tasic, MD, MSc	N/A	N/A	7 111 973	1 : 500	14 224
Slovakia	Branislav Vohnout MD, PhD	Slovak Medical University, Bratislava	19	5 421 340	1 : 500	10 843
Slovenia	prof. Zlatko Fras, MD, PhD, FESC, FACC	N/A	N/A	2 062 874	1 : 500	4 126
Turkey	prof. Meral Kayıkcıoglu, MD	Ege University, Cardiology Dep, Lipid Clinic, Izmir	none yet	84,000,000	1 : 200–1 : 300	280 000–420 000
Ukraine	prof. Olena Mitchenko, MD	National Scientific Center, Kyiv	4 (in development)	45 245 894	1 : 500	90 492
Uzbekistan	prof. Alexander B. Shek, MD	Republican Specialised Center of Cardiology (RSCC), Tashkent, Osyo	RSCC had 12 branches in 13 regions of Uzbekistan	31 025 500	1 : 500	62 051

FH – familial hypercholesterolemia **N/A** – not available

FH program	criteria for diagnosis	network	number of patients in the database (percent of estimated number of FH patients)	LDL apheresis
identifying and screening patients with high LDL from hospital database collecting patients' data in database educational activities for GPs, pediatricians, internists, ophthalmologists	Dutch lipid clinic network diagnostic criteria	functional	900 (11.8 %)	
N/A	N/A	N/A	N/A	
based on the MedPed FH approach with national co-ordinating center and network of lipid clinics involved in MedPed	Dutch lipid clinic network diagnostic criteria	based on MedPed – functional	130 (1.5 %)	
based on MedPed approach, functional network of centres, support of Czech Atherosclerosis Society, online nationwide database, activity of coordinator who keeps centres informed and helps them with inserting patients' data into database, availability of DNA diagnostics	MedPed, Dutch lipid clinic network diagnostic criteria might be applied as well	based on MedPed – functional	6 652 (31.6 %)	available
based on national coordinating centre and network of lipid clinics involved in FH registry, Hellas FH registry (database)	Dutch lipid clinic network diagnostic criteria	expected 2 000 within one year	40 (0.2 %) (expected 2 000 patients within 1 year)	available
2 national centres are able to perform genetical examination, the examinations are sponsored from scientific grant	Dutch lipid clinic network diagnostic criteria	doesn't exist, but it's in development, FH registry was just developed – next step will be a pilot study and according to the experience of the study the programme will be applied in country or modified if needed		
analysis of the FH prevalence in patients with "premature" CHD and metabolic syndrome and related management of primary and secondary prevention	Dutch lipid clinic network diagnostic criteria	at the beginning	13 (0.1 %)	
FH registry – initiated in February 2015, run by the Latvian Institute of Cardiology and Regenerative Medicine, University of Latvia	Dutch lipid clinic network diagnostic criteria, (MedPed also calculated)	functional/in development	162 (4.1 %)	
Polish national programme for the diagnosis and treatment of FH	Dutch lipid clinic network diagnostic criteria and Simon Broome diagnostic criteria	functional/in development	1 884 (2.5 %)	
N/A	N/A	N/A	N/A	
focussed on detection and treatment of FH, population study, molecular biology all criteria for FH used	Dutch lipid clinic network diagnostic criteria	functional/in development	700 (0.2 %)	available in some centers (rare)
N/A	N/A	N/A	N/A	
MedPed FH Slovakia based on the MedPed FH approach with national coordinating centre and network of lipid clinics involved in MedPed, molecular genetics is performed – covered by grants	Dutch lipid clinic network diagnostic criteria, Simon Broome diagnostic criteria, MedPed US	based on MedPed – functional	2 000 (18.4 %)	
N/A	N/A	N/A	N/A	
under development	Dutch Lipid Network	no but with the new registry we will establish new lipid centers connected to FH network	> 1 000 (0.2–0.4 %)	18
active detection of patients with suspected FH, with the further definition of the family history, lipid profile, the identification of markers of subclinical atherosclerosis, conducting stress tests, computer tomography coronary angiography (if the diagnosis is confirmed, patients' family is included)	Dutch lipid clinic network diagnostic criteria, Simon Broome diagnostic criteria	doesn't exist/in development	81 (0.1 %)	
in development	Dutch lipid clinic network diagnostic criteria	doesn't exist/in development	46 (0.1 %)	

Servier Laboratories, Abbott Laboratories, GlaxoSmith-Kline, Berlin Chemie, novo Nordisk, Boehringer Ingelheim, Mylan, Krka

- *participation in a company sponsored speaker's bureau – MSD, Bayer, Sanofi, Boehringer Ingelheim, Pfizer*
- *other support – advisory boards, clinical studies – MSD, Bayer, Aegerion, Amgen, Sanofi, AstraZeneca, AOP Orphan, Pfizer, Teva, Regeneron*

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Doručeno do redakce 22. 12. 2016