Child-Parent Screening for Familial Hypercholesterolemia

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A pilot study of child-parent screening for familial hypercholesterolemia was undertaken in children aged 1 to 2 years coming for immunization. Of 214 parents asked, 200 agreed to screening (94%). Simultaneous immunization-cholesterol measurement was successful in all children. Population child-parent screening is feasible and acceptable when combined with pediatric immunization. (J Pediatr 2011;159:865-7)

Familial hypercholesterolemia (FH) results in raised serum cholesterol levels and about a 100-fold higher risk of coronary heart disease before age 40 years.1,2 Cholesterol-lowering medications reduce risk, so screening would be worthwhile if an effective method of distinguishing people with and without FH were available.3

Child-parent FH screening is a means of achieving this. It involves measuring total cholesterol in children aged 1 to 2 years.4 A meta-analysis indicated that at this age cholesterol measurement discriminates best between individuals with and without FH, identifying about 88% of affected children and 0.1% of unaffected children.5 As an autosomal dominant disorder, each affected child has one affected parent, identifiable as the parent with the higher cholesterol level. Child-parent screening screens two generations simultaneously; both parent and child can be identified before the onset of disease, providing an early opportunity for preventive treatment.

Immunization clinics could provide a convenient and timely setting for screening. The feasibility and acceptability of the method is untested, so we undertook this pilot study.

Methods

Children aged 1 to 2 years requiring routine immunization were identified from the register of a London general practice. Parents were asked whether their child could be screened for FH. To avoid distressing children twice, once from the immunization and again from the blood sampling, the immunization (left thigh) and blood spot (left heel, with 2-mm Tenderfoot lancet; ITC, Edison, New Jersey) were performed simultaneously by two clinical staff members. Blood was collected with capillary tubes, and cholesterol level was measured with the point-of-care Cholestech analyzer (Hayward, California). Total cholesterol level was expressed as a multiple of the median (MoM).6 A cutoff of >2.0 MoM was used to define a screen-positive result. Parents were telephoned several days after immunization with the result and costs of screening were recorded. The study was approved by the Central London Research Ethics Committee. Cholesterol assay accuracy was assessed in 100 consecutive children by using paired samples for total cholesterol measurement with the Cholestech and a standard laboratory method. Quality control was undertaken monthly. For all analyses, total cholesterol concentrations were transformed into logarithms to allow for positive skew in the data. STATA software was used (Stata Corp, College Station, Texas).

Results

Of 214 parents asked, 200 (94%) agreed to FH screening. Concurrent heel prick and immunization was successful in all children, yielding approximately 200 µL of blood and adding approximately 2 minutes to the immunization procedure.

Figure 1 shows the total cholesterol distribution in 198 children (two Cholestech measurements failed); the median cholesterol level was 3.8 mmol/L (147 mg/dL; log SD, 0.078). No child had a cholesterol level >2.0 MoM (7.6 mmol/L or 297 mg/dL). The Cholestech results were similar to those from the laboratory analysis (Figure 2). A small (5%) negative bias (P < .001) was independent of cholesterol level and, therefore, allowed for by the use of MoMs.

Of the 200 parents of screened children, 184 were subsequently reached via phone (92%), and 181 (98%) said the screening was acceptable; 173 parents (94%) said they would have a second child screened if they had one and if screening were offered. All 7 practice staff members said screening was acceptable and would adopt child-parent screening into immunization practice if screening were routinely offered.

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FH Familial hypercholesterolemia
MoM Multiple of the median

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Funded by a grant from the British Medical Association. Alere Ltd provided the Cholestech analyzer for cholesterol measurement, and Elitech UK Ltd provided the Tenderfoot lancets. Neither the funder nor industry had any role in the design, conduct, or writing up of the study. D.W. has a patent (GB2414186A) for a medical device that combines medical injection and blood sampling. The remaining authors declare no conflicts of interest.
The cost of screening was £14 per child ($20), including the analyzer and consumables. The average staff time required was 14 minutes per child.

Discussion

Our results show that child-parent screening for FH is feasible and acceptable in clinical practice. Screening can be done at the same time as childhood immunization and requires no new clinical facilities; immunization clinics and arrangements for systematically seeing children aged 1 to 2 years already exist. There was no indication that screening adversely affected immunization rates, which were, for Haemophilus Influenza B/Meningitis-C, 71% in the year preceding the study and 84% during the study.

Neither neonatal nor adult screening for FH is satisfactory because the overlap in the cholesterol distributions in affected and unaffected newborn babies and adults is larger than at 1 to 2 years of age, yielding a detection rate of approximately 30% for a 0.1% false-positive rate instead of approximately 90%.4 Linking immunization with FH screening therefore maximizes screening performance and is also convenient.

The American Academy of Pediatrics recommends that children ≥2 years of age be screened when a family history of premature cardiovascular disease or a dyslipidemia is known.5 Limiting cholesterol testing to these groups is likely to miss many affected children because most are born to parents without such a history, and there is no reason to postpone screening until 2 years of age, provided it is performed after the child is 1 year of age.4

The cholesterol cutoff of 2.0 MoM used to define a screen-positive result was set higher than the suggested published cutoff point of 1.53 MoM (predicted to yield a positive rate of approximately 0.3%—true-positive rate of 2/1000 plus false-positive rate of 1/1000)4 as a precaution to avoid a higher than expected false-positive rate. The policy resulted in no child being classified as having a positive result for FH or any parent being screened. Had we adopted a cutoff point of 1.53 MoM, 5 of 198 children would have had positive results for FH—a rate of 2.5% (95% CI, 0.8%-5.8%), which is higher than expected, justifying a larger study to determine the precise cholesterol cutoff point that would apply in practice. The results of this pilot study show that this is now the next step.

Based on an FH prevalence of 1 in 500 (1 in 250 for each child-parent pair)4 the estimated cost per FH case detected (parent and child) is approximately £3500 (14 × 250) or $5600, and the screening would provide an opportunity to detect other affected relatives within the identified family. This compares favorably with screening for disorders such as Down syndrome (approximately £30 000 or $48 000 per case detected antenatally) and cystic fibrosis (approximately £45 000 or $72 000 per case detected).6,7

Child-parent screening for FH is feasible, simple to administer, and acceptable. Immunization clinics offer an ideal opportunity for screening. They provide a natural setting when screening for FH and immunization can be done together. If the feasibility and efficacy of the method can be demonstrated on a larger scale, it could be adopted generally. It would help prevent death and disability from one of the most common and serious inherited medical disorders.

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Figure 1. Distribution of total cholesterol (mmol/L and MoM) in 1- to 2-year-old children. (To convert mmol/L to mg/dL, multiply by 38.67.)

Figure 2. Plot of the ratio of 100 pairs of total cholesterol measurements with the Cholestech (point-of-care) and the Beckman (laboratory) assays against the geometric mean of the two results.
References