in the central Cape had high stillbirth, ENND and LBW rates, which suggest both poor living conditions and inadequate perinatal care. Of interest are the eastern Cape regions where the stillbirth rate is high in spite of relatively few LBW infants. The reasons for this are uncertain, but intrapartum deaths due to hypoxia in well-grown infants may be common.

The two regions with the highest PMRs were Lower Orange River and Port Elizabeth-Uitenhage. The Lower Orange River region is an area that stretches over a great distance with a low population density and only 6 889 deliveries. A probable explanation for the high PMR is the inaccessibility of health services in this region. In contrast Port Elizabeth-Uitenhage, which is a densely populated region, has a large, unemployed community and many migrants seeking care from limited services.

Having identified regions with many LBW infants and high PMRs, further studies are needed to address the causes and plan appropriate intervention policies. A shortcoming of the present study was that data were collected according to the place of birth and not the place of residence. The results could therefore be influenced by patterns of migration and referral. Coding data according to home addresses would be of greater value but more difficult to collect. All infants weighing between 500 and 1 000 g should also be included in future surveys. These additional data would increase the mortality rates, especially the stillbirth rate.

In conclusion, a survey of perinatal mortality within the planning regions of the Cape Province reveals wide geographical differences and a pattern expected in a developing country. In addition, the survey identifies regions where particular attention must be paid to living conditions and perinatal health services.

We would like to thank the staff of all the hospitals and clinics in the Cape Province who helped with the collection of the data presented in this study.

REFERENCES

Familial defective apolipoprotein-B is rare in hypercholesterolaemic South African Afrikaners, coloureds and Indians

David C. Rubinsztei, Gerhard A. Coetzee, Deneys R. van der Westhuysen, Elzet Langenhoven, Maritha J. Kotze

The frequency of familial defective apolipoprotein B-100 (FDB) was assessed among hypercholesterolaemic Afrikaners, coloureds and Indians. Patients selected for screening did not carry any of the founder or common LDL-receptor mutations known to be associated with these groups. No FDB was detected and the mutation is therefore a rare cause of hypercholesterolaemia in these South African populations.


Familial defective apolipoprotein B-100 (FDB) is characterised by the presence of LDL particles that carry apolipoprotein B-100 with the arg<sup>apo B</sup><sub>glu</sub> mutation; these have a markedly lower affinity for the LDL receptor and are cleared abnormally slowly from the circulation. The heterozygotes for this disorder present with hypercholesterolaemia and clinical sequelae such as xanthomata with a frequency and severity similar to that found in heterozygotes with familial hypercholesterolaemia (FH), a disorder caused by LDL-receptor mutations. Some individual cases, however, have been reported in which FDB heterozygotes and one homozygote had relatively moderate hypercholesterolaemia. The incidence of FDB is about 1/500 - 1/700 in North America and Europe. Detailed haplotype analysis of mutant apo B alleles from many FDB individuals suggests that this is a founder-type mutation that occurred only once on an ancestral chromosome. The frequency of such a mutation in different populations is likely to be governed by founder effects and random genetic drift and should vary greatly. Indeed this mutation has not been

Medical Research Council/UCT Research Unit for the Cell Biology of Atherosclerosis, Department of Medical Biochemistry, University of Cape Town

David C. Rubinsztei, M.B. CH.B., PH.D.
Gerhard A. Coetzee, Ph.D.
Deneys R. van der Westhuysen, Ph.D.

Department of Human Genetics, University of Stellenbosch, Tygerberg, W. Cape

Elzet Langenhoven, M.SC.
Maritha J. Kotze, PH.D.
detected in Finns, Japanese or Israelis. Consequently, in order to determine the impact of this mutation in South Africa, its frequency was determined in hypercholesterolaemic Afrikaners, coloureds and Indians with or without xanthomata.

Methods

All patients were unrelated and attended lipid clinics in Cape Town, Durban and Johannesburg. Individuals were considered Afrikaner, coloured or Indian only if both parents belonged to that population group. The so-called coloured population of South Africa are of mixed racial descent and have genes of indigenous Africans and of European and Indonesian settlers. The Indian population is descended from Indian immigrants who arrived in South Africa between 1860 and 1911. Blood was taken after informed consent had been obtained, and with ethical approval by the appropriate institution.

DNA isolation from blood was carried out as described by Talmud et al. FDB was screened for as described by Hansen et al. and Tybjærg-Hansen et al. The FH Afrikaner-1, FH Afrikaner-3 and FH Cape Town-2 mutations were assayed as described previously. The FH Afrikaner-2 mutation was detected by means of an amplification refractory mutation system (ARMS) polymerase chain reaction assay. All Indian patients were screened for the FH Zambia mutation, as described by Rubinsztein et al.

Results and discussion

Hypercholesterolaemic South African Afrikaner, coloured and Indian patients were selected for screening for FDB after individuals who had any one of the common or founder LDL-receptor mutations known to be associated with these groups had been eliminated (Table I). These individuals were classified as having either definite monogenic hypercholesterolaemia or type 2A hyperlipidaemia. Individuals were considered to have definite monogenic hypercholesterolaemia, i.e. either FH or FDB, if they had total cholesterol concentrations greater than 7.5 mmol/l or LDL-cholesterol concentrations greater than 5.2 mmol/l, together with xanthomata or thickened tendons in themselves or in a first-degree relative. Cholesterol concentrations above these limits are compatible with FH. Three founder LDL-receptor mutations, FH Afrikaner-1, -2 and -3, account for approximately 90% of the FH in Afrikaners. These three mutations and the FH Cape Town-2 mutation have been found in the coloured population (D. J. van der Westhuizen and M. J. Kotze — unpublished data). Therefore, all patients with these mutations were eliminated from the study. The only mutation detected so far in more than one South African Indian family is FH-Zambia. Similarly, all Indian patients with this mutation were not considered. None of the patients listed in Table I was found to have FDB. Therefore, all patients with definite monogenic hypercholesterolaemia are likely to have rare sporadic LDL-receptor mutations. FDB has been detected in two unrelated families in South Africa of mixed English and Afrikaner descent. It was impossible to determine the geographical or genetic origin of the mutation in these two cases.

Table I. Summary of South African lipid clinic patients screened for FDB

<table>
<thead>
<tr>
<th></th>
<th>Definite MH</th>
<th>'Type 2a'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrikaners</td>
<td>20†</td>
<td>23</td>
</tr>
<tr>
<td>Coloureds</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Indians</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

† All patients listed in this table were negative for FDB.

The frequencies of FDB and FH in North America and Europe are both about 1/500, and the two diseases are clinically almost indistinguishable in terms of the presence of xanthomata. In such populations, one would expect to find equal numbers of FDB and FH alleles in hypercholesterolaemic individuals with xanthomata from which FH patients with common or founder LDL-receptor mutations were excluded. Since we detected no such patients with FDB, this disorder is probably not as common in Afrikaners, coloureds and Indians as sporadic FH. Also, because no FDB was detected in patients with type 2A hyperlipidaemia without xanthomata, it is likely that the frequency of FDB in these populations is less than 1/500. The possibility exists that FDB does occur with a higher frequency in these groups, but does not cause hypercholesterolaemia or xanthomatisis uniquely. We consider this possibility unlikely.

Since FDB is a founder-type mutation, its frequency is likely to vary between different populations. To our knowledge, FDB has not been detected yet among Finns, Japanese or Israelis and no studies have been reported for Indians or black Africans. It is possible that this mutation might have occurred after the events that gave rise to the different racial groups. The absence of FDB in the Afrikaners and coloureds could have arisen from a 'negative' founder-effect that diluted the frequency of this gene in the settlers relative to their parent European populations. We conclude that FDB is a rare cause of hypercholesterolaemia in these South African populations.

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Recurrent LDL-receptor mutation causes familial hypercholesterolaemia in South African coloureds and Afrikaners

M. J. Kotze, E. Langenhoven, L. Theart, O. Loubser, A. Micklem, C. J. J. Oosthuizen

Three low-density lipoprotein receptor (LDLR) gene mutations were previously shown to cause familial hypercholesterolaemia (FH) in up to 90% of affected Afrikaners. Association of each mutation with a single chromosomal background provided molecular genetic evidence that the proposed 'founder gene effect' was responsible for the high prevalence of FH among white Afrikaners. In this study we report the identification of the FH Afrikaner-2 (FH2) mutation, Val1590Met, in the so-called coloured population of South Africa, a people of mixed ancestry, with rapid non-radioactive methods for mutation detection. Haplotype analysis with polymorphisms on both sides of the FH2 mutation indicated that the identical LDLR gene mutations found in two different South African population groups were caused by independent events at a potential CpG mutational 'hot spot'. The allelic variation giving rise to the different chromosomal backgrounds of the FH2 mutation does not affect the properties of the abnormal LDLR protein which causes FH in these subjects. This mutation is thus expected to cause the same severe form of FH in affected coloureds as was previously demonstrated in Afrikaners. Detection of mutant LDLR gene alleles in polymerase chain reaction products, directly after gel electrophoresis, now allows accurate presymptomatic diagnosis of the FH2 mutation in FH patients from two different South African population groups.