Compound heterozygosity for abetalipoproteinaemia and familial hypobetalipoproteinaemia

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Abstract
A 10 year old boy with abetalipoproteinaemia is reported. His mother and grandfather suffered from familial hypobetalipoproteinaemia, but his father had a normal lipoprotein profile. This is the first report of abetalipoproteinaemia resulting from compound heterozygosity for abetalipoproteinaemia and familial hypobetalipoproteinaemia.

Abetalipoproteinaemia (ABL) is a rare disorder of lipid metabolism characterised by the absence of apoprotein B containing lipoprotein in plasma. This genetically determined disorder was first described in 1950 by Bassen and Kornzweig.1 Of all known affected subjects, 25% have been Ashkenazi Jews. Available data are consistent with an autosomal recessive mode of inheritance. Obligate heterozygotes for classical ABL cannot be identified in the absence of an affected child at present, as their lipid and apoprotein B levels are normal.

The syndrome of familial hypobetalipoproteinaemia (FHBL) was recognised in 1960 by Salt et al2 and was eventually described in several more families. As a clinical entity FHBL may go unrecognised, yet the consistent laboratory findings of reduced serum cholesterol and betalipoprotein define it as a distinct syndrome. FHBL is known to be transmitted in an autosomal dominant manner; however, it should be noted that the possibility of an autosomal recessive condition with limited expression in the heterozygous state cannot be ruled out.

Since 1973, families have been described where ABL has been inherited in a different manner from classical ABL, in that children with ABL have been born to parents with FHBL. These cases were referred to as 'familial homozygous hypobetalipoproteinaemia', a new form of ABL.

This report documents the first case of ABL resulting from compound heterozygosity for ABL and FHBL.

Case report
The proband was a 10 year old Ashkenazi Jew who suffered from mild gastrointestinal disturbances. There was no neurological dysfunction and no retinitis pigmentosa was seen. All other family members were healthy. The family pedigree is shown in the figure.

Plasma lipoproteins were separated by discontinuous density ultracentrifugation and their profiles were measured as described before.3 Plasma levels of apo AI and apo B were determined by rocket electrophorimunoassay.4 As can be seen in the table, the proband had no apo B and total cholesterol was very low. His mother and grandfather had low levels of these, which is consistent with FHBL. The father, sister, and grandmother had normal lipoprotein profiles and apo B levels. Vitamin E levels were between 0·1 and 0·17 mol/l (normal 1·2 to 3·8) and marked acanthocytosis was seen in the blood smear.

Discussion
While ABL and FHBL are known to exhibit a number of clinical and laboratory similarities, their genetic basis is regarded as different. The ABL mutation is thought to show autosomal recessive...
transmission. Apparently heterozygous relatives have no laboratory or clinical manifestation which might allow their detection. However, FHBL is thought to be caused by heterozygous inheritance of an autosomal dominant gene. It was concluded, therefore, that ABL and FHBL were genetically distinct diseases and that the gene loci for ABL and FHBL were not the same.

Biemer and McCammon described a family where a form of ABL owing to homozygous FHBL had occurred. They pointed out that homozygous FHBL could be distinguished from classical ABL only by the finding of heterozygous FHBL first degree relatives. Consanguinity was noted in this family in that the parents of the proband were first cousins. The mother was found to have FHBL and the father, who was not evaluated, was presumed to have FHBL. Berger et al. described a similar family where the mother had FHBL, the father was not evaluated, and the patient was described as homogygous for FHBL.

In a few other families both parents had FHBL and the children homozygous for FHBL were reported to have ABL.6

Our present report is unique as it is the first reported family where all possible affected subjects had their blood lipoprotein levels examined. The trait for hypobetalipoproteinaemia in this kindred is vertically transmitted through two generations. All family members examined apart from the proband were in good health and acquired dyslipoproteinaemia could be excluded. As the mother was noted to have FHBL, while the father was found to have normal levels of blood lipoproteins, two possibilities regarding the mode of inheritance can be considered.

The first possibility is that FHBL is an autosomal dominant trait with variable expression up to ABL. As this has never been reported, we do not believe that this explains our case. Rather, we favour the possibility that the father is heterozygous for ABL. Such persons have normal lipoproteins and are recognised only by having a child affected with ABL. If this is the case in our family, the proband is a compound heterozygote for ABL and FHBL. This possibility was not excluded by Berger et al. when discussing the occurrence of ABL in a family with FHBL. This would involve heterogeneity of the mutations contributing to the ABL and FHBL phenotype with compound heterozygosity a distinct possibility.

McKusick, in his catalogue, comments on the possibility that ABL and FHBL may be determined by two different mutant alleles at the same locus, implying the possibility of a genetic compound ABL/FHBL. Such inheritance has been recognised in different disorders such as cystinuria and Hurler-Scheie compound syndrome, where the phenotype is an intermediate compound of the effects of these two allelic mutant genes. This possibility is quite likely in our case in view of the benign course of the disorder in the proband. We can conclude that classical ABL is transmitted as an autosomal recessive disease.

### Lipoprotein profile and apo A–I and apoB levels in patient, family, and control.

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<thead>
<tr>
<th></th>
<th>Plasma Cholesterol (mmol/l)</th>
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<tbody>
<tr>
<td></td>
<td>Total cholesterol (mmol/l)</td>
</tr>
<tr>
<td></td>
<td>HDL (g/l)</td>
</tr>
<tr>
<td>Proband (4 y)</td>
<td>0-84</td>
</tr>
<tr>
<td>Mother (30 y)</td>
<td>4:87</td>
</tr>
<tr>
<td>Father (35 y)</td>
<td>6:05</td>
</tr>
<tr>
<td>Grandmother (70 y)</td>
<td>7-28</td>
</tr>
<tr>
<td>Grandfather (70 y)</td>
<td>4:10</td>
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<tr>
<td>Normal controls (n=5)</td>
<td>5-64±0:92</td>
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