Case report

Report of hereditary persistence of α-fetoprotein in a Spanish family: molecular basis and clinical concerns

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The serum level of α-fetoprotein in normal adults is lower than 10 ng/ml. High levels of α-fetoprotein in adults are linked to cirrhosis, acute or chronic hepatitis, hepatocellular carcinomas and other pathologies, as well as to foetal malformation, and this protein is therefore used as a regular clinical marker for these diseases. We report a Spanish family in which very high levels of α-fetoprotein have been detected in nine members from the screening of a total of 17 relatives. These levels of α-fetoprotein are not accompanied by a causing pathology, are inherited as an autosomal dominant genetic trait, and are associated to a G → A substitution at position −116 of the 5′-flanking region of the α-fetoprotein gene. This is an unusual benign trait of hereditary persistence of α-fetoprotein. This paper provides a detailed clinical report of the family including a study of the molecular basis of this trait. The desirability of a test to detect and/or rule out this benign trait in adults with abnormal levels of α-fetoprotein is considered.

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1. Introduction

Human α-fetoprotein (AFP) is a major foetal serum glycoprotein that is synthesized in the embryonic yolk sac and foetal liver, where it is expressed at high levels, as well as in the developing gastrointestinal tract [1]. It occurs in the plasma of foetuses more than 4 weeks old, reaches the highest levels during the 12th–16th week of gestation (1.2–4 mg/ml) [2,3], and drops to trace amounts after birth. The serum level in normal adults is <10 ng/ml [4].

High concentrations of AFP in adults have been linked to cirrhosis, acute or chronic hepatitis, hepatocellular carcinomas (AFP > 400 ng/ml) and testicular cancer [5–7]. In children, the occurrence of hepatoblastoma [8], hereditary tyrosinemia [9] and ataxia telangiectasia [10] has been reported to be associated with elevated concentrations of AFP. Also, increased values of AFP in maternal serum correlate with foetal malformation (anencephaly, open spina bifida, exomphalos, gastrochisis, threatened abortion, foetal death in uterus and multiple pregnancy) [11,12] while decreased levels have been related with chromosomal abnormalities in the foetus [13]. Indeed AFP is used as a regular clinical marker for all these pathologies.

In 1983, a case was discovered of a woman with a high expression of AFP that was shown to be due to an autosomal dominant genetic trait: Hereditary Persistence of Alpha-FetoProtein (HPAFP) [14].

Interestingly, studies carried out on affected members of another family with HPAFP showed that all of them exhibited an identical haplotype: a G → A substitution at position −116 of the 5′-flanking region of the α-fetoprotein gene, in a potential hepatocyte nuclear factor I (HNF I) binding site [15].

In this paper we report a family in the Valencian Community (Spain), which includes 17 relatives in three generations, displaying HPAFP which is also linked to a G → A substitution at position −119 of the 5′-flanking region of the AFP gene. Attention should therefore be paid to this benign
trait to prevent an erroneous diagnosis in those patients with abnormal AFP values.

2. Description of the case

A 48-year-old white woman with asthenia of 5 months’ duration and without additional symptoms presented at the outpatient unit. She had had four normal pregnancies and had had a surgical hip intervention 23 years ago, with blood transfusion. She had a history of appendectomy and tonsillectomy, did not report suffering acute hepatitis and denied alcohol consumption. Results of her physical examination were unremarkable, and chronic liver pathology stigma and hepatomegaly were ruled out.

Blood analysis indicated a mild elevation of alanine aminotransferase (70 mU/ml; N < 56) and γ-glutamyltranspeptidase (103 mU/ml; 8 < N < 73 mu/ml) values. The results of haemogram, biochemical coagulation, AST and proteinogram were normal. Anti-HCV was positive and results of haemogram, biochemical coagulation, AST and alkaline phosphatase (103 mU/ml; 8 < N < 73 mu/ml) values. The levels of HBV markers, iron, alkaline phosphatase, bilirubin and ferritin were normal.

Analysis of α-fetoprotein showed 1500 ng/ml in serum. Therefore abdominal echography and computed tomography (CT) scan were carried out as well as exploration of liver, spleen and porta. Abdominal echography revealed only cholelithiasis but other explorations were normal; hepatomegaly, splenomegaly and nodules were not detected. Abdominal CT scan ruled out hepatic tumours. The study of a hepatic biopsy showed a mild chronic hepatitis, without fibrosis (A2, F0/METAVIR). Other studies included opaque enema, gastroscopy, gynaecological exploration and echography, as well as cytological analysis. The results of this series of studies were normal.

Because elevated serum AFP levels, ranging from 1500 to 3564 ng/ml (in five sequence tests), seemed to occur in the absence of a discernible pathology, a familial study of AFP levels in serum was performed with the formal consent of all the members of the family, who were previously informed of the aim of the study.

Fig. 1 shows the family pedigree indicating the presence/absence of the trait as well as the level of serum AFP in ng/ml for her relatives. The total number of individuals analysed was 17, including three generations.

A complete hepatic biochemical screening (including AST, ALT, γ-GT, alkaline phosphatase, and bilirubin) was carried out with those relatives of the proband who showed high values of AFP. This study ruled out liver pathologies in all of them.

Since this is a clinically autosomal dominant trait, it is assumed that it was transmitted to the proband through her father (deceased), as the level of serum AFP in her mother (I-2) was normal. From a total of five siblings, three brothers (II-1, II-7, II-8) and the proband (II-4) were carriers of the trait, and the sister (II-6) was normal. From a total of four children of the proband, two sons (III-4, III-5) inherited the HPAFP trait. Three children (III-1, III-2, III-3) of her oldest brother were also carriers.

2.1. Genetic testing

Studies carried out to characterize the molecular basis underlying this trait showed the proband and all the affected relatives (eight of a total of 16 relatives) present a G → A heterozygous substitution at position −119 in the 5′-flanking region of the gene encoding AFP (Fig. 2). This mutation was absent in the non-affected relatives, whose serum levels of AFP ranged between 0 and 3 ng/ml.

3. Discussion

The first reported case of HP AFP [14] was in 1983 and the gene encoding this trait was demonstrated to be located in chromosome 4 [16]. As far as we know, only seven families with HP AFP have so far been reported [14,17–22]. However, only one of them has been substantiated by studies of its molecular basis [15], which provide evidence that correlate a G → A substitution at position −119 of the 5′-flanking region of the gene encoding AFP with overexpression of this protein in healthy adults. Such a mutation occurs in a potential ‘hepatocyte nuclear factor I’ (HNF I) binding site, thus improving the similarity of the sequence to a consensus HNF I recognition site, that is concomitant with an increase in AFP transcription.

In 1999 Cochran et al. reported a case of elevated AFP levels in a 20-month-old child, who underwent surgery for a testicular germ cell tumour. As he had persistent mild elevations of AFP, he received three rigorous trials of chemotherapy until it was realized that he had HP AFP.

Our results on the molecular basis of this case fully confirm those obtained by McVey et al. in 1993. The G → A substitution at the position −119 of the 5′-flanking region was present in all the affected members and it was absent in the members showing normal AFP levels. Such a
position for the substitution site resulted in considering the bold ‘A’ of the DNA sequence of Fig. 2 as the cap site of the AFP gene by these authors. However, the cap site in the current sequence provided by GenBank (accession number NM_001134) for the mRNA of the human AFP is located three bases 5' upstream: base +1 in Fig. 2. According to this change, the G → A substitution should now be considered as located at position −116.

We report a case of HPAFP that includes 17 relatives covering three generations. It is worth noting the high levels of AFP exhibited by the proband as compared to the levels of AFP in the affected brothers which were in a range of 364–881 ng/ml, while the range in the next generation was 240–583 ng/ml. The size of the sample of affected people is small for statistical conclusions concerning correlations between range and sex, versus concentrations of serum levels of AFP. Certainly the level of the proband is exceptionally high. However, the clinical data rule out that such a

Fig. 2. (A) The nucleotide sequence of the 5' termini of the human AFP gene. The region −196 to +64 of the human AFP gene was amplified by PCR using oligonucleotides JBp1 and JBp2. The TATAA box is underlined. The cap site is numbered as +1 and the cap site designated by McVey is bold. The HNF I binding site is boxed. Intron region bases are in lower case. (B,C) Electropherograms of two members of the HPAFP family. (B) Member not affected showing a G at the position −116 of the AFP gene. (C) Member affected showing both G and A at position −116 of the AFP gene corresponding to a heterozygous substitution. The arrows indicate the base −116 of the AFP gene.
level could be due to underlying liver disease, since such high levels might only be detected in individuals with a very active hepatic inflammation usually associated with marked increases in transaminases concentration.

It would be very interesting to follow the evolution in the future of the expression of AFP in this family through periodic testing of the affected members and their offspring in order to learn whether and how age and/or sex affect this process.

Finally, although the frequency of this benign anomaly is unknown because of the sparseness of reported cases, attention should be paid to this trait because the AFP level is considered as a marker for tumours, as well as for chromosomal abnormalities in the foetus. The occurrence of this benign trait should be included as a usual test, analysing the AFP levels in the first-degree relatives in order to prevent inappropriate treatment decisions. Additional analysis to detect the mentioned G → A substitution would also be of interest from both diagnostic and genetic points of view.

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References


