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REVIEW

Hereditary persistence of alpha-fetoprotein (HPAFP): review of the literature

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ABSTRACT

Alpha-fetoprotein (AFP) serum levels are raised in several clinical conditions, ranging from non-pathological conditions to malignancies. Hereditary persistence of alpha-fetoprotein (HPAFP) is a rare benign disorder with elevated AFP levels. HPAFP is described as a benign autosomal dominantly inherited condition which is not associated with any clinical disability or additional symptoms. In the past 28 years, only 19 families have been described; due to this unfamiliarity with HPAFP, elevated AFP levels are never attributed to HPAFP. However, undiagnosed HPAFP can result in inappropriate and unnecessary treatment decisions. Therefore, HPAFP should be taken into consideration in patients with unexplained elevated AFP levels, and especially in patients with urological disorders.

KEYWORDS

Alpha-fetoprotein (AFP), gene transcription, hereditary persistence of alpha fetoprotein (HPAFP), tumour marker

INTRODUCTION

The serum protein alpha-fetoprotein (AFP) was first detected in 1956.[1,2] It is produced in the foetus by the yolk sac and the foetal liver, and is, to a lesser extent, also produced in the gastrointestinal tract.[3]

Foetal serum shows measurable AFP levels 29 days post conception; production of the foetal serum AFP increases until week 30 to 32, and subsequently levels fall. This decrease in the foetal serum concentration is due to both foetal growth and volume expansion. These aspects are discussed in detail in the review by Thomas *et al.*[4] Infants reach the same AFP levels as adults at approximately eight months of age.[5] These adult levels vary from 1 to 5 ng/ml; 99% of normal adults have levels lower than 10 ng/ml.[6] The main properties of AFP are: drug conjugation, cytotoxicity induction, growth control, ligand binding and ligand transport.[7]

Elevated AFP levels may result from a variety of clinical conditions: from normal conditions such as pregnancy to disorders such as liver cirrhosis and malignancies.[8] AFP's role as an important tumour marker has been well established.[9] In addition, AFP can also be falsely increased due to heterophilic antibodies. Heterophilic antibodies are antibodies in serum that can interfere in two-site immunoassays and which can be responsible for falsely high AFP levels.[10,11]

Another cause of elevated AFP is hereditary persistence of alpha-fetoprotein (HPAFP). In 1983 the first case of HPAFP was described; it was identified in an antenatal screening programme for spina bifida. HPAFP is a rare benign disorder in which serum AFP levels are persistently elevated without any clinical disability or additional symptoms. When family members of the patient described were tested, they were also found to have elevated levels of serum AFP. The trait was described as autosomal dominantly inherited and as not associated with any clinical disability or symptoms.[12]

The objective of the present review is to give an overview of all the described cases of HPAFP, to describe the genetics and pathophysiology of HPAFP and to describe the clinical conditions causing elevated AFP levels.

LITERATURE SEARCH

On 12 April 2010 a systematic search was conducted in the bibliographic databases PubMed, EMBASE, Cochrane and the Cumulative Index to Nursing and Allied Health Literature

(CINAHL). *Table 1* presents the search strategy used. The search term yielded 17 articles in PubMed and six articles in EMBASE. No articles were retrieved from the Cochrane and CINAHL databases. Twelve articles were excluded because they failed to report on any new cases of HPAFP. The reference lists and related articles of the studies yielded by this search were checked for additional relevant articles, and this resulted in five additional articles. In the end, the search revealed 16 articles describing 19 new cases of HPAFP.

RESULTS

Since the first family with HPAFP was described in 1983, 18 additional families have been reported (*table 2*). The diagnosis HPAFP was based on family studies which showed elevated AFP levels in family members. The families described were from all over the world, from Scotland to Japan.

Of the 19 families with HPAFP, eight index patients showed higher AFP levels after they had presented with urological disorders: four patients with a seminoma testis, one patient with a non-seminoma testis, one patient with a benign testicular cyst, one patient with a testicular nodule and one patient with testicular pain.[13-19] Index patients had serum AFP levels varying between 15 and 3564 ng/ml after treatment of the initial diagnosis (*tables 2* and *3*). Serum AFP levels of family members varied from 9 to 1260 ng/ml. Patients presenting with urological disorders revealed serum AFP levels ranging from about 9 to 65 ng/ml, with peaks of up to a maximum of 159 ng/ml.[13-19] To date, in six of the 19 families a point mutation has been reported; five families showed a -119 G > A substitution and one family showed a -55 C > A substitution.[20-23] In two families DNA sequencing was performed; however, the results failed

Table 1. *Search strategy (12 April 2010)*

No.	Synonyms
#1	hereditary AND persistence
#2	alpha OR alfa
#3	fetoprotein OR foetoprotein OR fetoproteine OR foetoproteine
#4	#2 AND #3
#5	(#4 AND #1) [Title/Abstract]

Table 3. *Conversion table for alpha-fetoprotein* [41]

Amount	Unit
1.0000	µg/l
1.0000	ng/ml
1.2100	kU/l

Table 2. *Described families*

Year	Author	Primary condition	Range serum AFP index patient	Range serum AFP family	Mutation	Unnecessary treatment
1983	Ferguson Smith[12]	Pregnancy	'Grossly elevated'	'High serum levels AFP'	-119 G>A	None
1986	Staples[13]	Hereditary spherocytosisand seminoma	14-21 kU/l	'Elevated'	-	None
1990	Greenberg[14]	Testicular cyst	30-46 ng/ml	17-64 ng/ml	-	None
1993	Tokoro[25]	Idiopathic familial basal ganglia calcification and ganglioglioma	290 ng/ml	245 ng/ml	-	Chemotherapy
1994	Feng[39]	Check up	21-129 ng/ml	46-198 ng/ml	-	None
1997	Mal[40]	Tuberculosis	200-800 ng/ml	637-1080 ng/ml	-	None
1998	Schefer[15]	Testicular nodule	20-24 ug/ml♦	22-51 ug/ml♦	-	Surgery
1999	Cochran[16]	Testicular germ cell tumour	61.3-152.9 ng/ml	21.4-27.7 ng/ml	*	Chemotherapy
2001	Flechon[17]	Seminoma testis	31.9-42.5 ng/ml	9-65 ng/ml	-	None
2001	Flechon[17]	Testicular pain	15 ng/ml	12.5 ng/ml	-	None
2002	Platini[18]	Seminoma testis	35-43 ng/ml	21-159 ng/ml	-	Chemotherapy
2003	Blesa[21]	Asthenia	1500-3564 ng/ml	240-881 ng/ml	-119 G>A	None
2004	Alj[22]	Pleurisy	900 U/ml	500-880 U/ml	-119 G>A	None
2004	Alj[22]	Dorsal pain	180 U/ml	420-580 U/ml	-55 C>A	None
2004	Yeh[24]	Check up	143 ng/ml	66-322 ng/ml	*	None
2004	Klümpen[19]	Seminoma testis	20-51 ug/l	26 ug/l	-	Surgery
2005	Nagata[23]	Check up	516 ng/ml	292-465 ng/ml	-119 G >A	None
2005	Nagata[23]	Check up	1200 ng/ml	1260 ng/ml	-119 G >A	None
2008	Xiaxin Li[8]	Endocrine evaluation	55-88 ng/ml	19-39 ng/ml	-	None

- = not known; ♦ = the unit is expressed in ug/ml; we assume this is not well reported; * = not found.

to reveal the previously described mutations associated with HPAFP.[16,24] In 26% of the index patients (5/19), unnecessary treatment was administered, namely surgery (two patients) and chemotherapy (three patients).[15,16,18,19,25] Of these five patients who underwent unnecessary treatment, 80% (four patients) had originally presented with urological disorders.[15,16,18,19]

DISCUSSION

Our literature review revealed that little is known about HPAFP. Therefore, it is necessary to describe the genetics and pathophysiology of HPAFP and other disorders that may lead to elevated AFP levels (*table 4*). Subsequently, an overview of our findings on HPAFP will be presented.

Genetics and pathophysiology of HPAFP

The AFP gene has been localised on chromosome 4 within the q11-13 region.[26,27] The expression of a gene is regulated by three elements: enhancers, promoters and silencers. These elements are characteristic DNA sequences usually located in the proximal part of the gene, the 5'-end. Concerning AFP, the 5'-end of the AFP region is exceedingly important in regulating the gene transcription because it contains all the three elements that provide a precisely regulated AFP gene transcription. These elements contain sequences that are specific to the binding of transcriptional factors. These transcriptional factors determine whether the rate of transcription will be increased or decreased. The transcriptional factors participating in the AFP gene regulation are a hepatocyte nuclear factor (HNF-1), which can bind both proximally and distally on the 5'-end region, and a non-tissue-specific factor (NF-1).[9]

HNF-1 stimulates the AFP gene activation. By contrast, NF-1 suppresses the activity in a high concentration, whereas in a low concentration it weakly stimulates AFP gene activation.[28,29] So far, two specific point mutations have been identified in the HNF-1 binding sites of the AFP gene promoter, which are associated with an increased gene transcription causing HPAFP. These point mutations are a -55 C> A substitution in the proximal HNF-1 binding site and a -119 G > A substitution in the distal HNF-1 binding site.[20,22] These point mutations lead to increased binding of HNF-1; as a result, AFP gene transcription is increased, which results in elevated AFP levels. Interestingly, the HNF-1 binding site partially overlaps the recognition site for NF-1; therefore, an increase in HNF-1 will cause a decrease in NF-1 binding, and will also result in elevated AFP levels. In a low concentration, NF-1 weakly stimulates AFP gene activation. In short, these two point mutations lead to an increase in AFP gene transcription, resulting in elevated AFP levels.[9]

Table 4. *Clinical conditions with elevated alpha-fetoprotein*

Condition		Serum AFP ng/ml	References
HPAFP		9-3564	*Table 2*
	Urological disorders	9-159	*Table 2*
Normal conditions		1-5	6
	Pregnancy:		42
	• 1st trimester	9-18	
	• 2nd trimester	53-79	
	• 3rd trimester (first half)	142-283	
	• 3rd trimester (second half)	99-192	
Congenital disorders	MSAFP	100-500	31
	Neural tube defects • MSAFP between 9-28 weeks of gestation	20-655	30
Non-malignant conditions	Non-hepatic diseases	<40	32,33
	Liver cirrhosis	30-460	35
		40-500	32
		<500	34
	Drug-induced liver damage	<500	33
	Acute and chronic hepatitis	40-500	32,33
		<500	34
Malignancies	Hepatoblastoma	500-10,000	34
	Testicular carcinoma	40-3000	32
		<50	34
	Germ cell tumours	<1,000	34
	Cancers in biliary tract and pancreas	20-557	38
		40-3000	32
	Other cancers: • gastric • cancer – colonic • cancer – lung cancer	40-3000	32
	Hepatocellular carcinoma	44-5,000,000	32
		30-7080	35
		20-9961	38

HPAFP = hereditary persistence of alpha-fetoprotein; MSAFP = maternal serum alpha-fetoprotein.

Elevated serum AFP

There are several causes of an elevated serum AFP: congenital disorders, non-malignant conditions and malignancies (*table 4*).

Congenital disorders

In 1974 Brock *et al.* described 13 cases of anencephaly and spina bifida. They measured the maternal serum AFP (MSAFP) between nine and 28 weeks of gestation and concluded that a form of prenatal diagnosis would be useful for both neural tube defects.[30] Mizejewski *et al.* stated in their review that the MSAFP levels associated with foetal defects are abnormally high: between 100 to 500 ng/ml. Their review also includes a clear overview

of all the congenital disorders causing elevated AFP levels.[31]

Non-malignant conditions

Non-malignant conditions causing elevated AFP levels can be divided into non-hepatic disorders and hepatic disorders. In non-hepatic disorders such as benign breast disease, ulcerative diseases and chronic lung diseases, serum AFP levels do not exceed 40 ng/ml; the same is true for blood bank donors. In liver cirrhosis, acute and chronic hepatitis and drug-induced liver damage, AFP levels varied between 40 and 500 ng/ml.[32-35] Serum AFP levels can also be elevated due to hepatic regeneration, since AFP is synthesised by the developing foetal liver.[33,36]

Malignancies

AFP has been associated with malignancy since Abelev *et al*. demonstrated in 1963 that AFP was detectable in transplantable hepatomas in mice.[37] In hepatoblastoma, serum AFP levels range from 500 to 10,000 ng/ml.[34] Testicular carcinoma, including testicular teratocarcinoma or germ cell tumours of the testis, showed AFP concentrations of over 40 ng/ml but less than 3000 ng/ml, with peaks of up to 8438 ng/ml.[32,34] Patients with germ cell tumours showed serum AFP levels of less than 1000 ng/ml.[34] Non-hepatic derived tumours, such as pancreatic cancer, gastric cancer, colonic cancer and lung cancer, had positive AFP levels with values between 40 and 3000 ng/ml.[32,38] Patients with hepatocellular carcinoma (HCC) had elevated AFP levels with a range in serum concentration of 44 to 5,000,000 ng/ml.[32,38] In 1993 Sato *et al*. described 33 patients with HCC and liver cirrhosis. Their patients had serum AFP levels of 30 to 7080 ng/ml at the time of tumour detection.[35]

Overview

Our literature search has revealed that little is known about HPAFP: in all, only 19 families have been described. In eight out of 19 patients, HPAFP was diagnosed because of urological disorders. In these patients, the high serum AFP levels were initially linked to the urological disorder and ultimately to HPAFP. These cases show that HPAFP is a disorder which mostly remains unrecognised, and this results in unnecessary diagnostic evaluation and inappropriate treatment decisions (e.g. radiation, chemotherapy and surgery).

We found that in non-hepatic disorders serum AFP levels do not exceed levels of 40 ng/ml, in benign hepatic disorders they do not exceed 500 ng/ml, and in malignancies serum AFP levels can be as high as thousands of ng/ml (*table 4*). Although there is a clear line of demarcation between the non-malignant conditions and malignancies, serum AFP levels can vary greatly. Malignancies cannot be ruled out if AFP is within normal levels. It remains unclear why there is such a wide variation in serum AFP levels.

In patients with elevated AFP levels, HPAFP can be a confounding factor, especially in HPAFP patients with a urological disorder. These patients can present with serum AFP levels ranging from 9 to 65 ng/ml, with peaks of up to a maximum of 159 ng/ml.[13-19] Consequently, it is difficult to differentiate between a urological malignancy or a recurrence of such a malignancy and the benign condition HPAFP.

However, not all elevated levels of serum AFP are linked to a clinical condition. In the Netherlands, several different methods are used to measure AFP. These methods show a great inter-method variability, due to the binding of the antibodies to different epitopes on the AFP molecule. This may have consequences for patients with values just above the reference range. Moreover, the number of check-ups has grown substantially. As a result, increased AFP levels are found more frequently.

CONCLUSIONS

The hereditary condition HPAFP should be taken into consideration in patients with an unexplained persistent elevation of AFP levels, and especially in patients with malignant or non-malignant urological disorders. Persistent high serum AFP levels may lead to inappropriate diagnostic evaluations and inappropriate treatment decisions, which may easily result in unnecessary treatment such as radiation, chemotherapy and surgery.

RECOMMENDATIONS

From this review it has become evident that HPAFP should be taken into consideration in patients with unexplained elevated AFP levels. Kashyap *et al*. recommend that all patients with AFP levels higher than 20 ng/ml should undergo a thorough examination so as to eliminate malignancies.[38] However, consensus has not been reached on the AFP level that would rule out a malignancy. Therefore our advice for patients with an unexplained persistent AFP elevation is a complete physical examination and a biochemical screening, including blood cell counts, renal function (creatinine), liver enzymes, coagulation status, hepatitis B surface antigen (HBsAG), antibody to hepatitis B surface antigen (anti-HBs), hepatitis C virus antibody (anti-HCV), and an ultrasonographic examination of the liver. All these tests are necessary to exclude a liver disorder as the cause of the elevated AFP. If all these tests are negative, it is useful to take HPAFP into consideration and to perform a family study in which AFP levels are determined in first-degree relatives. Alternatively

HPAFP could be confirmed by identifying a mutation in the 5'- regulatory region of the AFP gene in the index patient and possibly in other family members as well.

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