

Alpha-fetoprotein as a biomarker for recessive ataxias

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Alpha-fetoprotein (AFP) is a fetal protein produced in the yolk sac and in the fetal liver. AFP has been implicated in both ontogenic and oncogenic growth disorders¹. Although the main biologic role of AFP during pregnancy remains controversial to this day, AFP has been related to fetal birth defects and tumors¹. AFP is recognized as one of the first tumor markers. It was first associated with hepatocellular carcinomas and later to germ cell tumors².

The autosomal recessive ataxias, including ataxia-telangiectasia (AT) and ataxia with oculomotor apraxia type 2 (AOA2), belong to a special group of hereditary ataxias with heterogeneous presentation. Simple laboratory studies, like AFP measurement, have been reported to be helpful in the differential diagnosis of ataxias.

The purpose of this review is to describe the association of serum AFP with recessive ataxias. We report the clinical and laboratory findings of three patients with a recessive ataxia profile.

CASES

We identified two patients with clinical and laboratory features of AOA2 and one patient with AT. Informed and written consent were obtained from all participants.

Patient 1

A 28-year-old man was seen at the neurology department with a twelve-year history of progressively worsening balance. He had been a normal full-term delivery from consanguineous parents. His intelligence was normal. Over the years, he de-

veloped difficulties in writing and speaking. The symptoms progressed slowly over the following years.

His neurological examination showed muscle strength 5/5, with absent reflexes. An ataxic gait with mild enlargement of lower-limb basis, considerable staggering and difficulties with half turn were observed. He was unable to perform tandem walk (heel-to-toe). Finger-nose and heel-shin ataxia were evident. He presented clumsiness of fine finger movements. Gaze-evoked horizontal nystagmus, ocular saccadic overshoot, ocular apraxia and cerebellar dysarthria were also present. Vibration and position senses were also impaired. Fundoscopy and visual acuity were normal, and there were no telangiectasia.

In order to score the cerebellar dysfunction, we used the International Cooperative Ataxia Rating Scale (ICARS). It consists of four parts: postural and stance disorders (7 items; 34 points), limb ataxia (7 items; 8 points), dysarthria (2 items; 8 points), and oculomotor disorders (3 items; 6 points), with a total of 100 points³. The patient reached a score of 47.

Specific laboratory studies were as follows: albumin: 4.2 g/dl (3.2-5.6 g/dl); total cholesterol: 200 mg/dl (<200 mg/dl); AFP: 9.2 IU/ml (<5.5 IU/ml); vitamin E: 0.5 mg/dl (0.5-1.8 mg/dl). Routine blood and urine testing, echocardiogram and electrocardiogram (EKG) were all normal. The audiogram showed normal hearing. A genetic study for Friedreich ataxia was negative.

Brain magnetic resonance imaging (MRI) revealed atrophy of the cerebellar hemispheres and vermis, with relative preservation of the brainstem and no ab-

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ALFA-FETOPROTEÍNA COMO BIOMARCADOR DE ATAXIAS RECESSIVAS

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normality in the cerebral hemispheres. Electromyography showed severe axonal sensory-motor neuropathy. The absence of telangiectasias, immunodeficiency or neoplasia, an increased AFP levels and the later age of disease onset pointed towards the diagnosis of AOA2. This patient will be screened for senataxin (SETX) and ataxia telangiectasia mutated (ATM) gene mutation.

Patient 2

Patient 2 was a 20-year-old female. Her conditions of birth and early motor and language development were normal. Her parents were consanguineous. From the age of seventeen years, she began to trip and fall and, by 18 years, her walking was unsteady, her writing had deteriorated and she developed speech slurring. She had normal intelligence. Neurological examination showed normal visual acuity, normal optic fundi and no telangiectasia. Her eye movements revealed oculomotor apraxia and square wave jerks on pursuit movements with horizontal and vertical nystagmus on lateral and vertical gaze respectively. Her speech was characteristic of a mild cerebellar dysarthria. Strength was normal and reflexes were absent. Pain, light touch, vibration and position sense sensitivity were all normal. Tests of coordination revealed moderate appendicular and gait ataxia. Her ICARS score was 34.

EKG and echocardiogram examinations were normal. Brain MRI demonstrated marked atrophy of the cerebellar hemispheres and vermis, with relative preservation of the brainstem and no abnormality in the cerebral hemispheres.

Laboratory investigations revealed total cholesterol: 180 mg/dl (<200 mg/dl); albumin: 3.6 g/dl (3.5-4.8 g/dl); AFP: 56.25 ng/ml (<10 ng/ml); vitamin E: 1.2 mg/dl (0.5-1.8 mg/dl). A genetic study for Friedreich ataxia was negative. Like the first patient, the absence of telangiectasias, immunodeficiency or neoplasia, the increased AFP levels and the later age at onset of disease all pointed towards the diagnosis of AOA2. This patient will also be screened for SETX and ATM mutations.

Patient 3

Patient 3 was a nine-year-old boy. His birth and early motor and language development were normal. From the age of 18 months, he experienced unsteadiness in walking with frequent falls. His speech became slurred from the age of 7 years, and he developed difficulties in writing. His ataxia worsened progressively, but he did not need support to walk. No cognitive deficits were detected. During the next few years, he presented frequent respiratory infections.

Physical examination showed his head tilted to the right side. Telangiectasia over the bilateral conjunctivae was found (Figure). Neurological examination revealed



Figure. Characteristic conjunctival telangiectasia observed in patient 3.

oculomotor apraxia. His speech was characteristic of mild cerebellar dysarthria. Strength was normal, and reflexes were absent. Cervical and limb dystonia were also observed. Tests of coordination revealed moderate appendicular and gait ataxia. His ICARS score was 58.

On laboratory investigation AFP was elevated to 190.2 ng/ml (<10 ng/ml), immunoglobulin levels were in the normal limits. ATM was detected and the AT diagnosis was confirmed.

DISCUSSION

AT is a rare autosomal recessive disorder characterized by ataxia in early childhood, presence of telangiectasias, chromosomal abnormalities, with an increased sensitivity to ionizing radiation, immunodeficiency and malignancies. Additional findings are oculomotor apraxia, dysarthria, peripheral neuropathy and increased AFP level. AT is caused by mutations in the ataxia telangiectasia mutated (ATM) gene⁴. Recently, Verhagen et al described 13 adults with variant AT, without ataxia or telangiectasia, but some with hyperkinetic disorders and sensory-motor neuropathy⁵. The alpha-fetoprotein levels were elevated in all variant cases. Therefore, the diagnosis of AT must be considered not only in the classic presentation of the disease, but also in chorea, rest tremor and dystonia of unknown etiology, even when neuroimaging is normal. Our cases may be included in this variant AT group.

Ataxia with oculomotor apraxia type 2 (AOA2) is considered one of the most frequent (8%) non-Friedreich autosomal recessive cerebellar ataxias⁶. It is defined genetically by mutations in SETX at 9q34. Features include onset between ages of 10 and 22 years (age \leq 25 years), elevated serum AFP levels, peripheral neuropathy, occasional oculomotor apraxia and progressive cerebellar ataxia^{7,8}. On the other hand, ataxia with oculomo-

tor apraxia type 1 (AOA1) has different features such as early age at onset, normal serum AFP levels, and hypercholesterolemia and hypoalbuminemia⁸. In AOA2, oculomotor apraxia is an occasional and inconstant finding, while AFP is elevated in almost all patients (even if sometimes it is only in the upper range of normal values). A recent cohort of 90 patients with AOA2 diagnosis showed the usefulness of AFP as a good cutoff parameter for selecting patients who should go for sequencing of SETX. The same study showed that the likelihood of missing a case using this cutoff was 0.23%, while the likelihood that a non-Friedreich ataxia, non-ataxia-telangiectasia ataxic patient might be affected with AOA2 was 46%⁹. Other mutations of SETX have been associated with the autosomal dominant form of juvenile amyotrophic lateral sclerosis (ALS4)^{7,8}.

Beyond the AFP level, when considering neuroimaging findings, both AT and AOA2 present cerebellar atrophy. This finding is an important clue for the differential diagnosis with Friedreich ataxia¹⁰. AFP levels are normal in other recessive ataxias like Friedreich ataxia, ataxia with vitamin E deficiency, Abetalipoproteinemia, Charlevoix-Saguenay spastic ataxia, Refsum disease, Marinesco-Sjogren ataxia and cerebrotendinous xanthomatosis. The laboratory investigative tests on recessive ataxias should include: vitamin E, cholesterol, alpha-fetoprotein levels, albumin, acanthocytes, phytanic acid, cholestanol and lysosomal enzymes¹¹. Numerous autosomal recessive cerebellar ataxias remain without clarification of their etiology.

While no treatment for these progressive degenerative ataxias is available, the correct diagnosis is extremely

important, especially among AT patients, due to the risk of cancer and adverse reaction to radiation. High levels of alpha-fetoprotein are good markers for suggesting that molecular studies on the SETX or ATM gene should be carried out. AFP levels should be included in all investigations of recessive ataxias or early adulthood hyperkinetic movement disorders of unknown etiology.

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