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REFERÊNCIA

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Aggressive prolactinoma in a child related to germline mutation in the ARYL hydrocarbon receptor interacting protein (AIP) gene

Prolactinoma agressivo na infância relacionado à mutação no gene da proteína ARYL hidrocarbono (AIP)

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SUMMARY

The objective of this study was to describe a familial screening for *AIP* mutations in the context of aggressive prolactinoma in childhood. A 12-year-old boy, presented headaches and bilateral hemianopsia. He had adequate height and weight for his age (50th percentile), Tanner stage G1 P1. His bone age was 10 years. Prolactin was 10.560 ng/mL (3-25), FSH and LH were undetectable, IGF-1, TSH, FreeT4, ACTH, and cortisol were within normal ranges. MRI showed a pituitary macroadenoma, 5.3 X 4.0 X 3.5 cm with compression of the optic chiasm, bilateral cavernous sinus invasion, encasement of carotids, and extension to clivus. Surgical debulking was performed. Resistance to cabergoline was characterized and he was submitted to two surgeries and radiotherapy. Immunohistochemical evaluation included prolactin, ACTH, GH, FSH, LH, AIP, c-erb B2, Ki-67, and p53. Genomic DNA was isolated from the index case and 48 relatives, PCR and sequencing were performed. A germline A195V mutation in *AIP* was identified in the index case and in five asymptomatic relatives. Germline mutations in the *AIP* gene may be involved in the predisposition to pituitary adenoma formation, as cause or co-factor in pathogenesis of aggressive tumors in young patients. Arq Bras Endocrinol Metab. 2010;54(8):761-7

SUMÁRIO

O objetivo deste estudo foi descrever o rastreamento familiar para mutações AIP em paciente portador de prolactinoma agressivo e resistente na infância. Um menino de 12 anos foi avaliado com queixa de cefaleia e hemianopsia bitemporal. Apresentava peso e altura adequados para a idade (percentil 50), estágio puberal Tanner G1 P1 e idade óssea de 10 anos. Prolactina 10.560 ng/mL (3-25), FSH e LH indetectáveis, IGF-1, TSH, T4 livre, ACTH, e cortisol normais. A ressonância magnética de sela evidenciou macroadenoma hipofisário, 53 X 40 X 35 mm com compressão de quiasma óptico, invasão de seios cavernosos, envolvimento de carótidas internas e extensão para o *clivus*. Foi realizada descompressão cirúrgica por via transesfenoidal e caracterizada resistência a doses máximas de cabergolina, sendo o paciente operado por mais duas vezes e submetido à radioterapia. Realizou-se imuno-histoquímica para prolactina, ACTH, GH, FSH, LH, AIP, c-erb B2, Ki-67 e p53. O DNA genômico foi extraído do caso índice e de 48 familiares, e PCR e sequenciamento. Uma mutação A195V na *AIP* foi detectada no paciente e em cinco parentes assintomáticos. As mutações no gene da AIP podem estar envolvidas na predisposição à formação de adenomas, como causa ou cofator na patogênese de tumores agressivos em jovens. Arq Bras Endocrinol Metab. 2010;54(8):761-7

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INTRODUCTION

Clinically relevant pituitary adenomas have a prevalence of 1 case per 1064-1289 of the population and prolactinomas are the most common comprising 57%-66% of the total (1,2). As with all pituitary adenomas, prolactinomas are unfrequent in childhood, only about 3.5%-8.5% of pituitary adenomas are diagnosed before the age of 20 years and an indolent course may mean that tumors occurring in adolescents are not actually diagnosed until early adulthood (3,4).

Clinical presentation in childhood is variable and symptoms related to tumor growth are the most prevalent. In young children, decrease in growth velocity is a rare symptom, what could contribute to subclinical disease evolution and the delay in diagnosis. Impairment of gonadal axis is the most frequent endocrine disorder in late childhood and adolescence, leading to delayed puberty (4-6).

First-line treatment of prolactinomas relies on dopamine agonists, such as, cabergoline, and relative or complete resistance is very uncommon. Clinical factors associated with tumor aggressiveness and resistance to dopamine agonists include young age at onset, male gender, large tumor size or cavernous sinus invasion at diagnosis (7-10).

Despite many genetic abnormalities being described, the molecular pathophysiology of prolactinomas, particularly those with an aggressive clinical course, remains largely obscure. Recently, germline mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene, were reported to be involved in the predisposition to pituitary adenoma formation (11,12).

Patients with *AIP* mutations have pituitary adenomas at a younger age, which are often large at diagnosis, suggesting an aggressive phenotype. These tumors usually occur in the familial isolated pituitary adenomas (FIPA) setting (13,14) and sporadic pituitary tumors firstly appeared to be very rare (15-16). Recently, *AIP* mutations related to sporadic tumors have been increasingly reported in young patients (17,18). In a recently published international collaborative study in 96 patients with pituitary adenomas and *AIP* mutations, 10.4% had a familial *AIP* mutation but no known relatives with pituitary adenomas, and 30.2% were apparently sporadic cases. Most are somatotropinomas with characteristics that have now been well documented, followed by prolactinomas, and rare non-secreting adenomas (17).

We report here the clinical and pathological features of a young patient with a highly aggressive and invasive

prolactinoma that was resistant to dopamine agonists, in whom a germline *AIP* mutation was identified, and extensive familial screening was performed.

SUBJECTS AND METHODS

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and genetic analysis was approved by the Ethics Committee of the University of Brasilia. The subjects and guardians provided written informed consent for the genetic and other investigations performed.

Histology and immunohistochemistry

The tumor specimen was fixed in 10% formalin and paraffin-embedded. Hematoxylin and eosin staining was performed in all sections. Immunohistochemical evaluation using the Streptavidin-Biotin system (Dako Corporation, polyclonal antibodies) included prolactin (dilution 1:2000), FSH (clone C10-1:50), LH (clone C93-1:50), TSH (clone 42-1:50), GH (1:2000), ACTH (clone O2A3-1:100), c-erb B2 (oncoprotein C, 1:400), and monoclonal antibodies (Dako Corporation) were used for Ki-67 (Mib-1, 1:100) and p53 (DO7, 1:50). Mouse monoclonal antibodies directed against *AIP* (clone 35-2) and *AHR* (clone RPT9, referred to as "N-mAb") were performed as previously described (18).

Genetic screening

Genomic DNA was isolated from peripheral blood of the participating subjects. Primers used for the analysis of the *AIP* exonic and flanking intronic sequences are as reported by Vierimaa and cols. and the PCR reaction/sequencing were performed as reported previously (11-13).

CASE REPORT

A male patient was firstly evaluated at the age of 12 years, complaining of headaches and visual loss. There was no family history of pituitary adenomas or other endocrine diseases. Physical examination demonstrated adequate height and weight for chronological age (50th percentile), Tanner stage G1 P1. Bone age was 10 years. Bilateral hemianopsia was confirmed by computed visual field. MRI showed a pituitary macroadenoma, 5.3 X 4.0 X 3.5 cm with compression of the optic chiasm, cystic degeneration of the suprasellar portion, and bilateral

cavernous sinus invasion with total (left) or near-total (right) encasement of internal carotids, and extension to pontine cistern and clivus (Figure 1). The first prolactin obtained was 226 ng/mL and after a 1:100 dilution, the hook effect was confirmed and prolactin was 10.560 ng/mL (normal range 3-25 ng/mL), FSH and LH were undetectable, IGF-1, TSH, Free T4, ACTH, and cortisol were within normal ranges for gender and age (Table 1). Due to imminent threat to the patient's vision, surgical debulking via transsphenoidal approach was performed, and tumor volume reduced to 4.3 X 3.5 X 2.0 cm (Figure 2). The patient was treated with cabergoline after surgery, starting at a dose of 2 mg/week for two months, 3 mg/week for a further three months and then 3.5 mg/week for two years. However, the lowest prolactin level achieved was 3.792 ng/mL. Tumor size decreased by only a further 20% after two years of medical treatment (Table 1). The patient was reoperated on

via the transcranial route, followed by a second transsphenoidal approach one month later, achieving significant debulking, but intracavernous remnants persisted. Fractionated stereotaxic radiotherapy was performed and the linear accelerator-delivered dose of 50.4 Gy (5 × 1.8 Gy weekly), with a 2-mm safety margin was administered. After 10 months of radiation follow-up, at patient's chronological age of 15 years and 10 months, no spontaneous signs of puberty were observed (Tanner G1 P1), his height was 165.5 cm (Target Height = 171,5 cm), Bone age was 11 years of age. A thyrotrophic deficiency was detected and levothyroxin 75 µg was prescribed. The prolactin nadir after multiple treatments was of 2,198 ng/mL, FSH 1.9 mUI/mL (pre-pubertal levels < 6), LH 0.5 mUI/mL (pre-pubertal levels < 5), Testosterone 37 ng/dL (30-580). Cabergoline treatment was maintained at a dose of 3.5 mg/week, and no growth hormone replacement was prescribed.

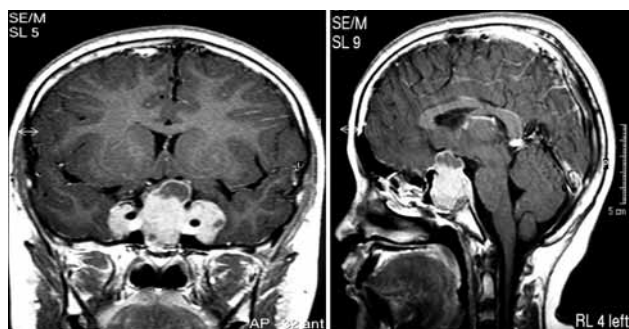


Figure 1. Pre-operative MRI showed a pituitary macroadenoma, 5.3 X 4.0 X 3.5 cm with compression of optic chiasm, cystic degeneration of the suprasellar portion, and bilateral cavernous sinus invasion with total (left) or near-total (right) encasement of internal carotids, and extension to pontine cistern and clivus.

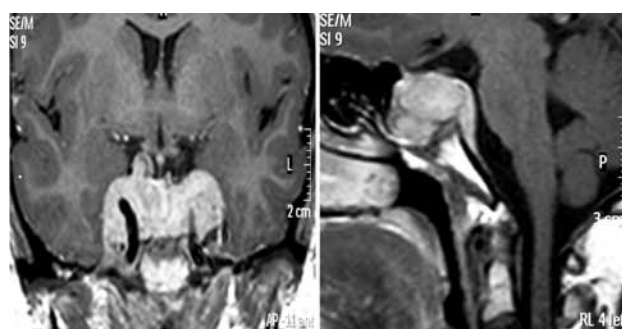


Figure 2. Post-operative MRI showed a pituitary macroadenoma, 4.3 X 3.5 X 2.0 cm with bilateral cavernous sinus invasion with total (left) or near-total (right) encasement of internal carotids, and extension to pontine cistern and clivus.

Table 1. Hormone levels and tumor volume throughout treatment

	Diagnosis	First surgery (TSS)	Cabergoline 3.5 mg/wk 2 years	Second approach (TC + TSS)	Stereotaxic radiotherapy
Chronological Age	12 y	12 y,3 mo	13 y,10 mo	14 y, 5 mo	15 y,10 mo
Prolactin (2-21 ng/mL)	Pre-dilution: 226 Post-dilution: 10,560	6,589	3,792	3,130	2,198
FSH(< 6 mUI/mL)	1.8	3.3	2.1	1.3	1.9
LH (< 6 mUI/mL)	0.1	2.2	1.5	0.5	0.5
Testosterone (15-305 ng/dL)	22.5	13.2	84.7	67.3	37
TSH(0,5-5 uIU/mL)	1.05	0.55	0.7	0.3	0.4
FT4 (0.7-1.6 ng/mL)	1.2	1.1	1.0	0.9	1.0
Cortisol (8-25 ng/mL)	14.0	12.9	13.8	10	11.9
ACTH (10-60 pg/mL)	16.8	19.0	14.1	15.1	14.5
IGF-1 (143-693 ng/mL)	142	98.1	112	141	130
Tumor diameter*	5.3 X 4.0 X 3.5 (38.76 cm ³)	4.3 X 3.5 X 2.0 (15.72 cm ³)	4.0 X 3.0 X 2.0 (12.54 cm ³)	3.5 X 3.0 X 1.8 (9.87 cm ³)	3.0 X 3.0 X 1.6 (7.54 cm ³)

* Tumor volume was calculated using the Cavalieri principle $4/3 \times \pi \times r^1 \times r^2 \times r^3$.

Histopathology

Immunohistochemistry studies have confirmed strong (++++) staining of the tumor for prolactin, and negative staining for FSH, LH, GH, TSH, and ACTH. Ki-67 and p53 labeling indexes were 25% and 10% of

tumor cells, respectively, no membrane immunoreactivity for c-erbB2 was observed (Figure 3). The tumor sample was weakly positive for AIP immunostaining and negative for AHR immunostaining, respectively (Figure 4).

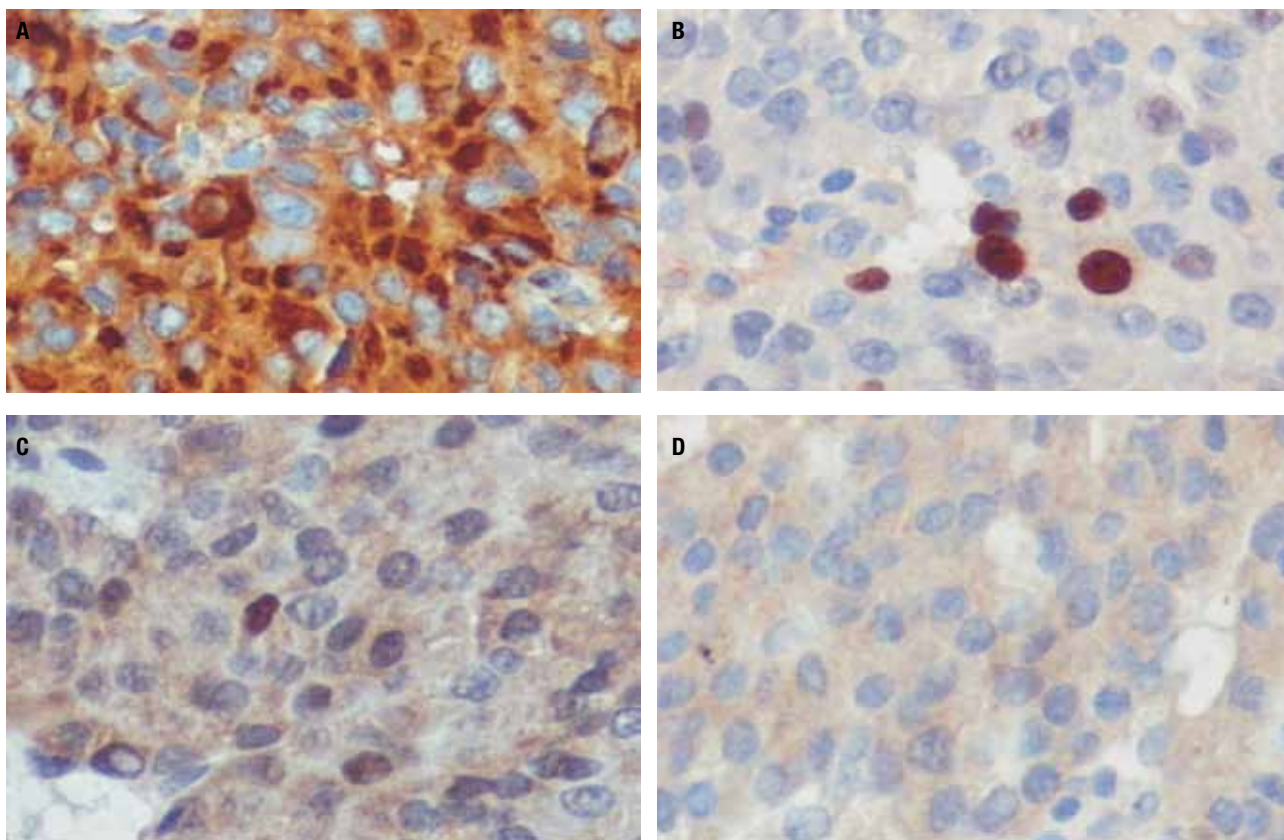


Figure 3. Semiquantitative immunostaining for (a) prolactin (+++/4), (b) Ki-67 (++/4), p53-clone DO-7 (+/4) and c-erb B2 (negative). Staining was classified according to the guidelines of Brazilian Society of Pathology: +, 10% cells positive; ++, 10%-25% cells positive; +++, 21%-50% cells positive; +++++, > 50% cells positive.

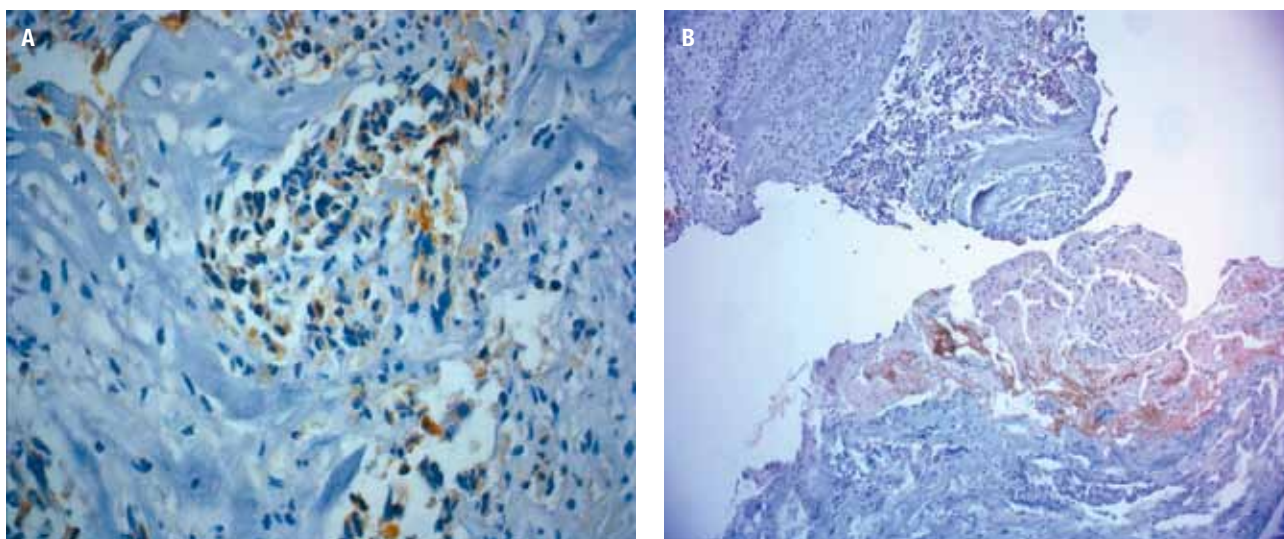


Figure 4. Semiquantitative immunostaining for (A) AIP (X40) and (B) AHR (X10). The AIP staining was 10% in adenomatous cells (A) and AHR was negative (B).

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Genetic analyses and familial screening

In the affected patient a germline A195V mutation in the *AIP* was identified. Thereafter, comprehensive genealogical data were collected from the family and screening for the mutation was performed in all consenting subjects. The genealogical tree for the family was constructed using Genopro-Beta® program, and comprised 48 individuals in 15 sub-families. Screening identified five additional asymptomatic carriers of the A195V mutation across three generations; the mutation was traced to the maternal grandmother of the index case. In the five asymptomatic A195V mutation carriers, clinical, hormonal (basal prolactin, FSH, LH, cortisol, ACTH, GH, and IGF-1), and radiological (pituitary MRI) screening was performed. No pituitary adenomas have been diagnosed in these five individuals until the present moment.

Study of the frequency of A195V nucleotide changes control individuals in Brazilian population

We studied 177 control subjects in Brasilia, with no diagnosis of endocrine diseases. These subjects were assessed for the presence of *AIP* polymorphisms. The A-V amino acid substitution at position 195 was not observed in control subjects. These results were compared to 298 non-MEN1, non-CNC acromegalic patients, in order to compose the control group database recently published in the context of an international collaborative study (17). Neither in non-AIP mutated acromegalic patients nor in the control subjects, was this A-V substitution observed, therefore the polymorphism at this position was excluded.

Study of the frequency of A195V nucleotide changes in other species

Genbank was consulted and reported sequences of the AIP protein in other species indicate that it belongs to a highly conserved region. In a minority of aquatic species (*Dario Rerio* and *Xenopus*), but not in others (*Salmo Salar*), the V195 residue is lost together with significant differences in the whole region, strongly suggesting interaction of AIP with different proteins. AIP protein length varies between 328 and 356 amino acids. Of note, the V195A change was not observed in any species (Table 2).

DISCUSSION

Pituitary adenomas in children, although rare, can pose particularly difficult clinical problems when they are invasive or require multi-modal therapy as they can interfere with growth and pubertal development. The search for predictors and prognostic factors is an open field, despite the large number of molecular abnormalities described to date in the pituitary tumor tissue. The current case illustrates many of the existing clinical and pathological challenges in the pediatric pituitary tumor setting. Our patient maintained the growth velocity and adequate height for familial pattern, despite subnormal IGF-1 levels, confirming previous reports that a clinically evident growth deficit is not a common finding in young patients with prolactinoma (19). Delayed puberty related to hyperprolactinemia and gonadotropic deficiency after multiple pituitary interventions was observed and is in accordance with previous case reports. The resistance to treatment with dopamine

Table 2. Comparison between AIP protein sequences among species

Species	Genbank	AIP	Sequence Homology around Valine 195 (human)
<i>Homo sapiens</i>	NF_003968	330 aa	..mtdeekakavplihgegnrlyreghv ke aaakydaiaiclknlgmkeqpgs..
<i>Macaca mulata</i>	NF_001181242	330 aa	..mtdeekakavplihgegnrlyreghv ke aaakydaiaiclknlgmkeqpgs..
<i>Mus musculus</i>	NF_057875	330 aa	..mtdeekakavpvihgegnrlyreggv ke aaakydaiaiclknlgmkeqpgs..
<i>Rattus norvegicus</i>	NF_758830	330 aa	..mtdeekakavplihgegnrlyreggv ke aaakydaiaiclknlgmkeqpgs..
<i>Bos taurus</i>	NF_898905	330 aa	..mtdeekakavpvihgegnrlyreghv ke aaakydaiaiclknlgmkeqpgs..
<i>Equus caballus</i>	NF_001075406	356 aa	..mtdaekakavpvihgegnrlyreghv ke aaakydaiaiclknlgmkeqpgs..
<i>Gallus gallus</i>	NF_989800	327 aa	..mtdeeklqavplihgegnelyrqqk v reaatkydaiaiclkn1gmkeqpgs..
<i>Salmo salar</i>	NF_001133532	342 aa	..mtddeklvvpqihvegnalykkgd v keaaekyhnaiaiclknlgmkerpgd.
<i>Dario rerio</i>	NF_999877	342 aa	..mtddeklgaipqihgegnalfksgdisgaekyynaiaiclkslqmkerpgd...
<i>Xenopus</i>	NF_001096219	328 aa	..mtdgekmeavpvihgegnlykkgktn daa akyyeiaiclkslqmkeqpgs..

The human V195 residue in the AIP protein sequence is considered to be one of the 10 amino-acids involved in the binding surface of the TPR region (see NP_003968). Reported sequences of the AIP protein in other species indicate that it belongs to a highly conserved region, with polymorphisms being recognized around the V195 residue (indicated in bold red), the V195 residue itself being conserved (highlighted in green). In a minority of aquatic species (*Dario Rerio* and *Xenopus*), but not in others (*Salmo Salar*), the V195 residue is lost together with significant differences in the whole region, strongly suggesting interaction of AIP with different proteins. The AIP protein length varies between 328 and 356 amino-acids. Of note, the V195A change was not observed in any species.

agonists, specially cabergoline, may be related to dopamine-receptor expression in the adenomatous tissue (7-10), although tumor aggressiveness may be related to *AIP* mutations in young patients (12,13).

Mutations on *AIP* may be involved in cell proliferation in several ways: multiple protein-protein interactions may lead in particular to AHR stabilization in the cytoplasm, thereby enhancing its ligand-induced nuclear translocation, and modulation of specific phosphodiesterases in some pituitary cells (16,20,21). The role of endocrine disrupters is a field of interest, and a recent Italian study evaluated the incidence of pituitary tumors in the Seveso population exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin following an industrial accident in 1976, and no statistically significant increase of incident pituitary tumors was shown in this area (22).

In an unselected series of sporadic pituitary adenoma patients, mutations in *AIP* are rarely found, (15,16,23). However, as most patients with *AIP* mutation-related pituitary adenomas present with early onset tumors, screening for germline *AIP* mutations should be limited to selected groups of sporadic patients, particularly young patients with somatotropinomas or macroadenomas (17,24). In our patient, a V195A missense mutation was observed in the index case. Although no functional studies are available, elements arguing for a pathogenetic mutation include: 1) the lack of V195A alleles among 298 acromegalic patients (17) and 177 Brazilian controls, respectively 2) Valine is highly conserved at 195 position during the evolution, as shown in table 2; 3) its identification as one out of the few amino acids involved in the binding surface of the TPR region, which mediates most of the protein-protein interactions of *AIP* (25).

The same mutation was also identified in 5 asymptomatic relatives. This suggests a low penetrance of the mutation, as already described in most sporadic cases (16,17). Noteworthy, modifier genes have been proposed to influence the penetrance of *AIP* mutations in familial and also in sporadic settings (23). In this patient we studied some proliferative markers that are used to define prognosis in several oncologic conditions. The *AIP* immunostaining was weakly positive in tumor tissue, in accordance with previous reports in non-truncating mutations. However *AIP* immunostaining does not appear to have any prognostic value in prolactinomas (18,26).

The Ki-67 protein is present in the nucleus of a dividing cell (G1, S, G2/M phase) but is absent from

the resting cells (G0 phase). Thus, it can provide some information concerning proliferative potential of cancer cells and about the prediction of response to a certain therapy. Ki-67 labelling in more than 3% of the cells is commonly associated with tumor invasiveness (27). In GH and PRL secreting adenomas, Ki-67 is generally low in the presence of pre-operative pharmacological treatment (27). In our study we observed positive immunostaining for Ki-67 in about 25% of tumoral cells, in samples from the first and confirmed in tumor tissue from third surgery. Thus, Ki-67 labelling was conserved after dopamine agonist treatment, and can be considered an additional marker of aggressiveness and pharmacological resistance in our patient.

The tumor suppressor gene p53 controls entry of the cells into the cell cycle, on phase G1, and mutations on this gene could permit progression of tumor cells. The presence of p53 mutations in pituitary tumors is rarely described (28), but some authors found a relationship with proliferative states (29,30). In our patient we detected positivity in 10% of the tumoral cells. This finding suggests that p53 would not have an important role in our patient tumor evolution.

The proto-oncogene *c-erbB2* encodes a transmembrane receptor protein with tyrosine kinase activity belonging to the epidermal growth factor receptor (EGFR) family. *C-erb B2* expression is a marker of tumor aggressiveness in breast cancer (31), but few studies have assessed *c-erbB2* in the pituitary. Our group previously reported variable *c-erbB2* immunoreactivity in somatotropic and lactotrophic tumors and it might have some influence on their evolution, considering the intimate relationship between *c-erb B2* and the epidermal growth factor (EGF) (28,30). We recently described a strong *c-erb* staining in aggressive somatotropic adenoma in the context of Familial Isolated Pituitary Adenomas (FIPA) with a 174 frameshift *AIP* mutation (13). In this case, *c-erb B2* was negative and had no relation to tumor aggressiveness.

In conclusions, the spectrum of *AIP* mutation-associated pituitary tumors includes all clinical subtypes. *AIP* mutations confer an aggressive pituitary tumor phenotype with at an early age onset, and may be screened in childhood-adolescence. *AIP* mutations are likely to represent co-factors in the pathogenesis rather than the causative abnormality, confer an aggressive pituitary tumor phenotype with early age onset, and may be screened in childhood-adolescence.

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