



Case Report

13q interstitial deletion in a moroccan child with hereditary retinoblastoma and intellectual disability: A case report

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ABSTRACT

Retinoblastoma is the most common malignant tumor of the eye in children (incidence: 1/15,000 to 1/20,000 births), with a sex ratio of 1,5/1. Retinoblastoma, in its inherited form, is a disease caused by a syndrome of genetic predisposition to cancer. The RB1 gene, a tumor suppressor gene, is localized at 13q14. This case report shows the indication of the cytogenetic analysis in the management of patients with retinoblastoma, and the interest of a genetic counseling.

We report the medical observation of a five and a half years old patient who was followed in the medical genetic's department for intellectual disability: associated with facial dysmorphism. The cytogenetic study objectified the presence of an interstitial deletion of the long arm of chromosome 13: 46, XX, del (13) (q14q22). A genetic counseling, with study of the karyotype of the parents is planned, specially to search for a balanced insertion: 13q14 insertion and deletion. In addition, the patient has been followed since the age of 9 months at the pediatric ophthalmology department for a bilateral retinoblastoma, in remission.

A subject carry in constitutional mutation of the RB1 gene has a greater than 90% risk of developing retinoblastoma, and moreover has a genetic predisposition to secondary tumors.

This medical observation shows the benefit of the constitutional cytogenetic study for patients with retinoblastoma, in particular in the event of bilateral retinoblastoma.

The monitoring of psychomotor development must supplement the ophthalmological monitoring of these patients, with a systematic genetic counseling.

1. Introduction

Hereditary retinoblastoma is a disease due to a syndrome of genetic predisposition to cancer [1]. The RB1 gene, which is a tumor suppressor gene, is located in the long arm of chromosome 13 (13q14). Retinoblastoma is the most common malignant intraocular tumor in childhood. Its incidence is 1/15,000 to 1/20,000 births, with a sex ratio of 1,5/1 [2].

2. Interests of the study

- Interest of the cytogenetic analysis in the management of patients with retinoblastoma.

- Benefit of a family investigation with genetic counseling in the event of discovery of retinoblastoma.

3. Patient and method

This is a case report about a patient followed at the Ibn Rochd university hospital in Casablanca since 2015, for a 13q deletion syndrome, associated with bilateral retinoblastoma.

4. Observation

We report the case of a little girl T.S, aged of 5 years old and half. She is the eldest of two siblings. This patient is followed in the medical genetic department of the Ibn Rochd University Hospital for an intellectual

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disability: associated with facial dysmorphism.

There is a notion of first-degree consanguinity in the family (Fig. 1). The delivery was made by cesarean section with the notion of neonatal suffering and prematurity (gestational age estimated at 30 weeks of amenorrhea), requiring hospitalization in the neonatal department for one month. The patient has a brother who died at the age of 1 year and a half in a table of acute dehydration but the etiology was not specified.

The patient was also followed by the pediatric ophthalmology department, pediatric oncology and hematology departments for a bilateral retinoblastoma, currently in remission for three years. The retinoblastoma was revealed at the age of 9 months by leukocoria and pseudo-cellulitis of the left eye with strabismus of the right eye. Retinoblastoma is classified according to the Reese or ABC classifications, respectively: stage Ia/A (right eye) and stage V/E (left eye).

The patient was treated by neo-adjuvant chemotherapy and received a preoperative chemotherapy, based on carboplatin, etoposide and vincristine. Then the left eye has been enucleated. The right eye has been treated by cryotherapy.

The clinical examination found a conscious patient, in good general condition with normo-colored conjunctiva. The clinical assessment found a dysmorphic face, an epicanthus, a broad root of the nose, a large mouth, a broad philtrum, and low implanted ears. We also notice the presence of an external left ocular prosthesis, without other clinical signs, in particular no walking or behavior disorders or failure to thrive.

The anatomopathological analysis of the enucleation confirmed the diagnosis of moderately differentiated retinoblastoma. The limits of the optic nerve resection were healthy without invasion of the riddled blade.

Cerebral magnetic resonance imaging found a diffuse cortico-subcortical atrophy, associated to a passive dilation of the ventricular system, without the presence of an endocranial tumor extension, or a mass in the pineal region. Therefore it was not a trilateral retinoblastoma (bilateral retinoblastoma associated to a primary neuroectodermal tumor of pineal or suprasellar location).

The constitutional cytogenetic study carried out using a heparinized tube sample of peripheral venous blood, was performed in Reverse band with a 400 bands resolution. We found a female karyotype and the presence of an interstitial deletion of the long arm of chromosome 13 (Fig. 2): 46, XX, del (13) (q14q22).

The family survey (Fig. 1) did not find in the family any case of retinoblastoma, of facial dysmorphism, or psychomotor retardation. The mother is currently pregnant at 20 weeks of amenorrhea. Genetic counseling, with a study of the karyotype of the parents is planned, in particular to search for a balanced insertion (13q14 insertion and deletion). The ophthalmological examination of the parents did not find retinomas (spontaneously involuting retinoblastomas).

5. Discussion

Retinoblastoma is a model of tumor development based on a default of an anti-oncogene [2]. A subject carrying the constitutional mutation of the RB1 gene has a greater than 90% risk of developing retinoblastoma, and moreover has a genetic predisposition to secondary tumors

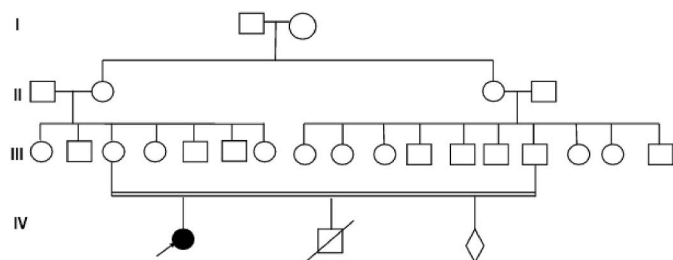


Fig. 1. Genealogical tree of the family showing first degree inbreeding and the absence of similar cases in the family.



Fig. 2. The Reverse band cytogenetic study (with a 400 band resolution) demonstrates a female karyotype, and the presence of an interstitial deletion of the long arm of chromosome 13: 46, XX, del (13) (q14q22).

[1], hence the importance of regular monitoring of patients on a long-term basis.

The RB1 gene responsible for retinoblastoma is located on chromosome 13, at band q14 [3]. It comprises 27 exons and is expressed in the tissues analyzed. This gene codes for a phosphoprotein of 928 amino acids: the p110RB protein [4]. It is involved in the regulation of the cell cycle.

5.1. The hypothesis of the two mutations

According to Knudson's theory [5,6], the occurrence of retinoblastoma, hereditary or non-hereditary, requires 2 mutations of the gene RB1 with inactivation of the 2 alleles of the gene. Two forms are possible:

The hereditary form, which is often bilateral and multifocal, the first mutation is germinal, transmissible to descendants in an autosomal dominant manner, with a high penetrance of 90% (risk of transmission to descendants of 45%). The 2nd mutation is somatic in the retinoblast, acquired during fetal life or in the first months of life.

The sporadic form is always unilateral and unifocal: the two mutations are somatic and occur in the same retinal cell. This form is not transmissible to descendent.

A constitutional partial deletion of chromosome 13, del (13q14) is in fact present in certain families with hereditary retinoblastoma, like this case report, but a second event, somatic, leading to the physical or functional loss of the homologous gene on the other chromosome 13, must occur, before the development of the tumor [7]. The mutated RB1 gene is recessive at the cellular level; the first mutation only predisposes the retinal cell to developing a tumor.

5.2. The balanced insertion hypothesis

Cytogeneticists have provided one of the possible explanations for the transmission of retinoblastoma from unaffected individuals. Several observations of balanced insertions have been published, including the study by Strong et al. [8]. These balanced insertions can produce in the descendance partial monosomia 13q14 with retinoblastoma, or balanced insertions with risk of retinoblastoma transmission and low probability of retinoblastoma (Fig. 3).

5.3. Genetic counseling

With the improvement in survival, the number of children treated

The geneticist relies on molecular tests, oriented by the analysis of the personal and family history of the affected child, without omitting the examination of the fundus of the parents and siblings for retinomas (Table 1). [10].

Multifocal forms of retinoblastoma without a family history are linked, in the majority of cases, to a neomutation that has appeared in the gametes of one of the two parents [11].

Molecular diagnosis, when it identifies the mutation, makes it possible to predict recurrence in siblings or transmission in the descendance by prenatal or neonatal diagnosis of carrier subjects [2].

6. Conclusion

This medical observation shows the benefit of the constitutional cytogenetic study for patients with retinoblastoma, in particular in the event of bilateral retinoblastoma, or associated with mental retardation or a dysmorphic syndrome.

Patient's parents consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient's parents.

Provenance and peer review

Not commissioned, externally peer reviewed.

Ethical approval

Ethical approval has been exempted by our institution.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient's parent.

Author contribution

L.Kora: writing the paper. G. Jabrane: correction of the paper. N.

Serbati: correction of the paper. L. El Maaloum: correction of the paper. B. Allali: correction of the paper. A. El Kettani: correction of the paper. H. Dehbi: correction of the paper.

Declaration of competing interest

The authors declare having no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.amsu.2020.10.063>.

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