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Chemoreduction combined with partial exenteration for orbital retinoblastoma

--Manuscript Draft--

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Full Title:	Chemoreduction combined with partial exenteration for orbital retinoblastoma
Article Type:	Research article
Abstract:	Aim: To evaluate the role of chemotherapy combined with partial exenteration on orbital retinoblastoma patients. Methods: Six orbital retinoblastoma patients were enrolled in the study after ethics committee approval and written informed consent. They were treated by chemotherapy using carboplatin, vincristine and etoposide, then partial exenteration surgery (enucleating the eye and tumor mass in the orbit) was conducted according to the response of the lesion. All patients were asked to visit the doctor on time. The survival rate and growing development were evaluated. Results: Good tumor response was observed in all of patients. Among the 6 patients , 4 patients with no signs of progression received operations after 6 courses of chemotherapy and were still alive after 5 years follow-up. Unfortunately, one patient died of brain metastases after five courses of chemotherapy and the other patient died of abandoning treatment. Postoperative histological examination of the enucleation specimens showed largely fibrosis tissue and a small amount of calcification tissue in the orbit, while retinoblastoma in eyeball. Optic nerve resection margins were healthy in three cases. Only one patient received postoperative chemotherapy because of the involvement of microscopically optic nerve section. Conclusion: Chemoreduction combined with partial exenteration can be useful in orbital retinoblastoma. Trial registration: Registration number:chiCTR-ORC-17013231 ; registration time: 3 /11/2017. Retrospectively registered.
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Title page

Title: Chemoreduction combined with partial exenteration for orbital retinoblastoma

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Abstract

Aim: To evaluate the role of chemotherapy combined with partial exenteration on orbital retinoblastoma patients.

Methods: Six orbital retinoblastoma patients were enrolled in the study after ethics committee approval and written informed consent. They were treated by chemotherapy using carboplatin, vincristine and etoposide, then partial exenteration surgery (enucleating the eye and tumor mass in the orbit) was conducted according to the response of the lesion. All patients were asked to visit the doctor on time. The survival rate and growing development were evaluated.

Results: Good tumor response was observed in all of patients. Among the 6 patients , 4 patients with no signs of progression received operations after 6 courses of chemotherapy and were still alive after 5 years follow-up. Unfortunately, one patient died of brain metastases after five courses of chemotherapy and the other patient died of abandoning treatment. Postoperative histological examination of the enucleation specimens showed largely fibrosis tissue and a small amount of calcification tissue in the orbit, while retinoblastoma in eyeball. Optic nerve resection margins were healthy in three cases. Only one patient received postoperative chemotherapy because of the involvement of microscopically optic nerve section.

Conclusion: Chemoreduction combined with partial exenteration can be useful in orbital retinoblastoma.

Trial registration: Registration number:chiCTR-ORC-17013231 ; registration time: 3 /11/2017. Retrospectively registered.

Retinoblastoma (RB) is the most frequent intraocular malignant tumor in children with a reported incidence ranging from 1 in 15,000 to 1 in 18,000 live births in the United States[1], while is higher in the developing countries, particularly in Asia and some Latin American countries[2]. In neglected or untreated RB patients , the tumor can break through the eye wall and becomes a huge mass occupying the orbit, that is called orbital RB and classified as stage □ RB according to the International Retinoblastoma Staging System (IRSS)[3] . The incidence of orbital RB is becoming rare in industrialized countries, ranging from 6.3% to 7.6% [4], but it is not an unusual feature in developing and under developed world [5][6]. Orbital RB is one of the major contributors to mortality and carries a poor prognosis for life [7][8]. The presence of

orbital invasion is associated with 10-27 times higher risk of metastasis when compared to cases without orbital extension [9]. However, there is no proven definitive therapy or management protocol for orbital RB. It continues to remain a challenging disease to treat because of its complex nature. The traditional treatment is orbital exenteration alone which is unlikely achieve surgical clearance and also leads to unrecoverable damage of appearance. In recent years, systemic chemotherapy has been reported to improve overall survival (OS) from less than 20% to 60% to 70% in patients with overt orbital retinoblastoma [10][11][12] , but the RB cells may be still exist in the eyes and the orbits. So chemotherapy combined with surgery are needed to achieve reasonable results. In this study, we collected orbital RB patients in our hospital, and prospectively investigated the outcome and compliance of the chemotherapy combined with partial exenteration in orbital RB patients.

Patients and methods

Between July 2008 and August 2010, among 92 patients referred for RB to our department, six (6.52%) presented with extensive RB with one case of bilateral orbital mass and five cases with unilateral orbital mass, one of whom had ipsilateral parotid gland mass. This population comprised five boys and one girl, aged 2 to 4 years. Three received eyeball enucleation before, and three didn't receive any treatment. An initial staging assessment was systematically performed at diagnosis (bone marrow aspirate/bone marrow biopsy, lumbar puncture with cerebrospinal fluid cytology, and axial magnetic resonance imaging), and the assessments were negative in all six patients.

Initial treatment consisted of chemotherapy combining of carboplatin, vincristine and etoposide(VEC), as described in the treatment of extraocular forms of RB [13]. All patients received six courses of carboplatin-vincristine-etoposide (Table 1). A first evaluation was performed after completion of chemotherapy. For all patients the efficacy of chemotherapy was assessed by computed tomography (CT) and/or magnetic resonance imaging (MRI).

Table 1 Dose and usage of VEC chemotherapy

Drug	Daily dose		Period
	≤ 36months	＞36 months	
carboplatin	18.6mg/kg	560mg/m^2	D_1
vincristine	0.05mg/kg	1.5 mg/m^2	D_1
etoposide	5mg/kg	150 mg/m^2	D_1,D_2

Patients with no signs of progression were performed the partial exenteration six months after completion of the chemotherapy. However, the partial orbital exenteration in our study was different from traditional surgery. After the chemotherapy, the orbital mass was significantly smaller so that we can only enucleated the tumor mass in the orbit and tried to keep the patient's conjunctiva and other healthy orbital tissue for the secondary implantation. The intraoperative assessment determined the involvement of conjunctiva and the integrity of the zone of posterior section.

Postoperative treatment was determined by the results of surgery and histological examination of the surgical specimen. The indication for postoperative chemotherapy was based on the finding of the optic nerve sections and the histological results. Post-treatment follow up was based on clinical and radiological examinations.

To restore the patient’s appearance, about 2 years after partial exenteration, the patients will receive secondary hydroxyapatite orbital implantation and wear artificial eye.

All patients were enrolled after written informed consent from their guardian, and the institute's ethics committee approved the study protocol (Ethics Committee of Xiangya Hospital).

This study was non-randomised and adhered to Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) guidelines .

Results

The clinical courses of the patients were summarized in Table 2. The preoperative assessments showed clinical regression of all cases (Figure 1, 2). Four patients with no signs of progression received the operation. The intraoperative assessment showed that parts of the conjunctiva was involved, and calcified tissue connected to the eyeball. The orbital soft tissue around the eyeball and calcified tissue was fibrotic and adhesive to

the lesion. The optic nerve section was sufficiency posterior. Postoperative histological examination of the surgical specimens showed largely fibrosis tissue with a small amount of calcified component in the orbit, while RB tumor still existed in the eyeball. Optic nerve resection margins were healthy in three cases. The tumor invasion was visible in the optic nerve resection in one patient. This patient received additional three courses of chemotherapy after operation. Four patients received secondary hydroxyapatite orbital implantation and wore the prosthetic eyes about two years after the partial exenteration. The results were satisfactory in appearance (Figure 1, 2). These four patients were followed up for five years, and they all developed as well as others of the same age.

Unfortunately, one patient died of intracranial metastasis after five courses of chemotherapy, and one patient died of abandoning treatment.

Of course, there are certain side effects of chemotherapy, such as hair loss, vomiting, diarrhea, granulocyte reduction which can be self-recovery after drug withdrawal.

Table 2 Clinical summary of the patients

Patients (age)	Clinicoradiological features	Neoadjuvant treatment	Evaluation	Exenteration histology	Postoperative treatment	Post-treatment response
1 (2.8 years)	Bilateral orbital mass	6 carboplatin-vincristine-etoposide	Clinical: regression; CT: tumor reduction	Retinoblastoma, No residual optic nerve invasion	None	22 months Survive
2 (2 years)	Unilateral obital mass	6 carboplatin-vincristine-etoposide	Clinical: regression; CT: tumor reduction	residual calcified tissues, no tumor	None	14 months Survive
3 (4.3 years)	Orbital portion of optic nerve involved and ipsilateral parotid gland mass	6 carboplatin-vincristine-etoposide	Clinical: regression; CT: tumor reduction CSF(-)	Retinoblastoma, Macroscopic invasion of optic nerve resection margins	3 VEC	16 months Survive
4 (3.8 years)	Unilateral obital mass	5 carboplatin-vincristine-etoposide	Clinical: regression; CT: tumor replase; brain metastasis	/	/	Died
5 (2.5 years)	Unilateral obital mass	6 carboplatin-vincristine-etoposide	Clinical: regression; CT: tumor reduction	Retinoblastoma, No residual optic nerve invasion	None	20 months Survive
6 (3.5 years)	Unilateral obital mass	1 carboplatin-vincristine-etoposide; then abandoned	Clinical: progression; CT: not done	/	/	Died

Discussion

For the orbital RB, traditional treatment method is the orbital exenteration combined with external beam radiotherapy, which can lead to significant appearance damaging and high risk of life-threatening. The secondary plastic surgery is extremely difficult due to significant soft tissue atrophy of the facial region. Both physical and mental developments of children are seriously affected. How to treat the orbital RB effectively, meanwhile, to improve the survival rate and quality of life of patients, is becoming an important issue of the ophthalmologists in the developing countries.

Chemotherapy used in RB patients began in the 1990s, and now it is becoming a first-line treatment for intraocular RB. Chemotherapies for intraocular phase of RB currently include of vincristine, etoposide and carboplatin, those dose are different among the research institutions. The chemotherpy we used in the study is referring to Oncology Department, Children's Hospital of Philadelphia in U.S [13]. Our results showed the orbital tumors were significantly reduced to near extinction after VEC chemotherapy in all 6 patients (7 eyes, 100%), four of the six children received partial exenteration instead of exenteration and remained alive after five-year follow-up. However, the drugs can't pass through the blood-brain barrier very well, so the effect on central neuron system metastases is poor. One patient in our hospital died of brain metastases after five courses of chemotherapy, and was presumed to have brain metastases before the last chemotherapy. Although we didn't detect any cancer cell in this patients' cerebrospinal fluid before chemotherapy, but it may be false negative result. Therefore, we recommended multiple examinations of cerebrospinal fluid for orbital RB patients. And unfortunately, one patient in our study died because his parents gave up the treatment.

Although the orbital tumor of some children could be significantly reduced after chemotherapy, there still existed the residual tumor in the eye[12]. It was also certified by pathological examination in the study. So further surgery was needed to eradicate the tumor. Radhakrishnan et al. [12]recommended that only enucleation was needed after neoadjuvant chemotherapy. In our opinion, we recommended partial orbital exenteration was a better way since the tumor may not only exist in the eyeball but also in the orbit. On the consideration of the secondary plastic surgery, the partial orbital enucleation performed in the study was different from traditional surgery. We kept the patient's conjunctiva and other healthy orbital tissue maximally, which could create favorable conditions for the secondary plastic surgery.

However, the treatment of RB does not end with enucleation or exenteration.

Prosthetic rehabilitation of the patients is of the equal importance. Improving appearance will help them to reintegrate in today's esthetic conscious society, thereby improving their quality of life. Previous studies about orbital RB were only concerned about the survival rate, little was reported whether patients accepted cosmetic surgeries and restored better appearance. In our study, about 2 years after partial exenteration, four patients received secondary hydroxyapatite orbital implantation and wore artificial eyes. The facial appearances are improved by the above operations. Therefore, Chemoreduction combined with partial exenteration may be a good method for orbital Rb patients. It can not only save the RB patients life, but also improve these patients appearance and quality of life.

The main side effect of chemotherapy is ototoxicity or renal toxicity after the application of carboplatin. Smits and his colleagues tested 25 RB children's hearing receiving carboplatin chemotherapy, and found no abnormalities during follow-up of 25 months[14]. The similar results are also observed in China. Patients received VEC chemotherapy have normal hearing and renal function, while they might have mild bone marrow suppression, but no serious infections. There are also reports the application of etoposide may result in the secondary tumors[15], especially in children who are hereditary RB. In the 5 years follow-up, we have not yet found the occurrence of secondary tumors in children.

Since orbital RB is a rare disease, and will occur more rarely because of the widely use of chemotherapy on intraocular RB, we could not obtain the enough sample to reach to the scientific conclusion about the survival rate of orbital RB patients and effectiveness of the treatment reported in this study. It is the limitation of the study. But we think it is still of importance to similar case, and further observation is needed to evaluate the survival condition and life quality of the patients.

List of abbreviations

RB: retinoblastoma; VEC:carboplatin, vincristine and etoposide

Declarations:

Acknowledgments

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Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Authors' contributions:

Professor Tan , Professor Xu and Doctor Liu contributed significantly to the patients' treatment and follow-up; Professor Tan, Doctor Liu , Doctor Wang contributed significantly to the acquisition of data , data analysis and manuscript writing. All the authors have read and approved of the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in compliance with informed consent regulations and the Declaration of Helsinki. The study protocol was approved by Xiangya Hospital Ethics Comittee. Informed consent was obtained from the parents of the patients for the study.

Consent for publication

Consent for publish was obtained from the patients'parents in this study.

Competing interests

The authors declare that they have no competing interests.

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Legends:

Fig 1: The appearance and CT performance of a patient before, after chemotherapy and after artificial eyes wearing
A1-A5: before chemotherapy ;B1-B5:after chemotherapy;C1-C5:after artificial eyes wearing. A2, B2 and C2: CT scanning with axial position; A3, B3 and C3: CT scanning with coronal position; A4; B4 and C4:CT scanning with sagittal position of right eye; A5, B5 and C5: CT scanning with sagettal position of left eye.

Fig 2: The appearance of a patient before and after complete treatment.
A: before chemotherapy; B: after chemotherapy; C: after partial exenteration ; D: after secondary hydroxyapatite orbital implantation and artificial eye wearing.

Figure 1

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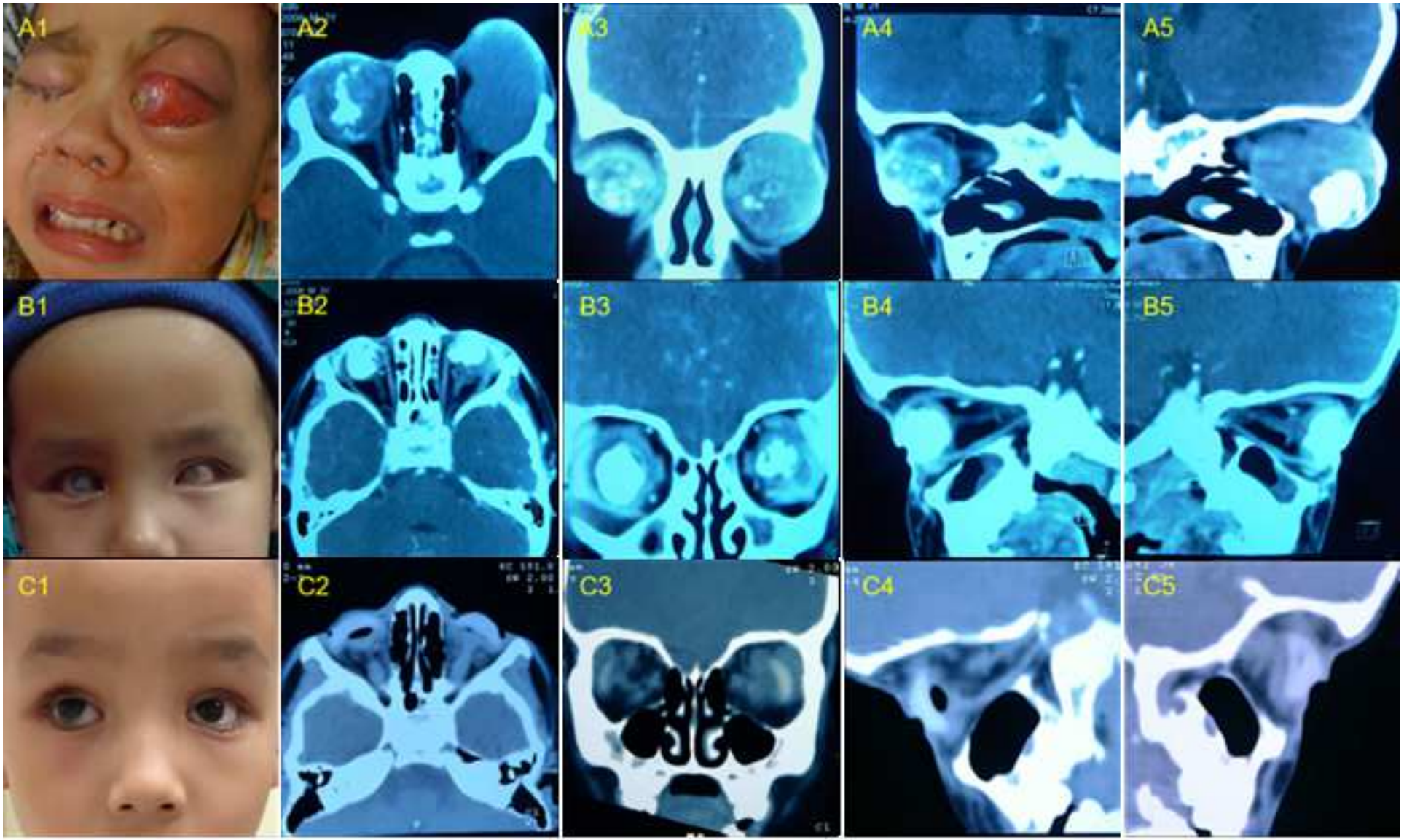

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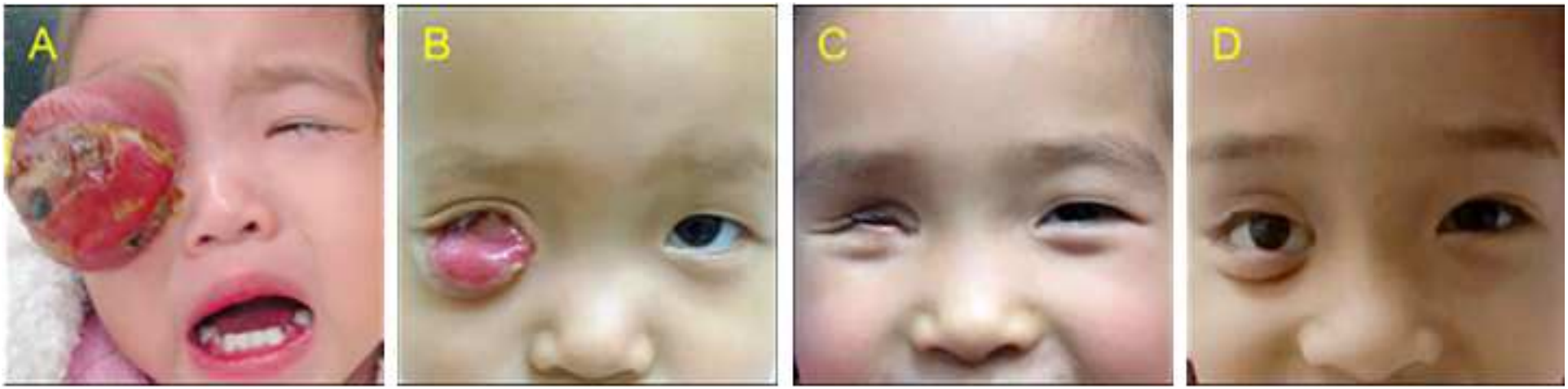

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