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Editorial

Neonatal retinoblastoma: understanding the problem better

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Retinoblastoma is a disease that does not discriminate between gender or race; however, it has long been reported there are marked differences in outcomes for patients around the world. Most affected children live in countries of low and middle income, where the mortality from retinoblastoma is about 70%, meaning that of the estimated 9,000 newly diagnosed patients every year, the majority will die.[1] Given that retinoblastoma is a rare disease, gathering more information to increase our understanding helps guide therapy for all children around the world and leads to better treatment outcomes. This is especially so in neonatal retinoblastoma, which is defined as affecting those aged less than 28 days or 44 weeks' gestation if born prematurely. In a 50-year review from Melbourne, Australia between 1939 and 1989, an audit of 17,417 necropsies failed to identify a single case of retinoblastoma in the series of 46 neonatal cancers.[2] In Toronto, Ontario, where there is a large retinoblastoma centre, 17 cases of neonatal retinoblastoma were reported in a total of 102 children with neonatal cancer.[3] Although small series of neonatal retinoblastoma in developing countries have been published,[4] many countries unfortunately do not report their retinoblastoma data. Efforts are being made to report and better understand the global picture of retinoblastoma[3]. Zohari and colleagues make a welcome contribution which again highlights the contrasting clinical picture in developing versus developed countries.

The disparity in retinoblastoma care between developed and developing countries is clearly evident when looking at those diagnosed in the neonatal period. In developed countries, from 7% to 10% of all retinoblastomas and 44% to 71% of familial retinoblastomas are diagnosed in the neonatal period, prompted by a positive family history leading to pre- or postnatal screening.[6] Family history has been reported elsewhere as the primary association reported regarding neonatal retinoblastoma in developed countries.[6] The importance of family history in the management of neonatal retinoblastoma was demonstrated in another study in the United States which showed that family history (67%) exceeded leukocoria (13%) as the most common reason for detection.[7] Altogether, review data shows that 72% in developed countries as opposed to 23% of familial retinoblastoma in developing countries were detected through screening.[6] Similarly, in the series published here,

the authors describe a difference in incidence due to a lack of screening in patients with a positive family history. Of the six patients identified with neonatal retinoblastoma, only two had a positive family history, both of which were siblings, and only one was screened for familial retinoblastoma.

This highlights the importance of patient education and counselling. It is safe to say that no country around the world has a perfect record in this regard. Given that retinoblastoma is a rare disease, we need continued efforts to better educate our colleagues in the medical profession as well as patients regarding the importance of family history and screening in retinoblastoma. This is more important than ever as the landscape continues to evolve with respect to genetic testing and treatment options.

A statement that we should all aspire to realise is that genome-level technologies could make genetic testing a reality for every family affected by retinoblastoma.[1] Our knowledge in this regard continues to grow. Initially, retinoblastoma was thought to be caused uniquely by loss of function of the RB1 tumour-suppressor gene, whereas more recently it has been shown that it can also be initiated by activation of the MYCN oncogene.[8] The vast majority of neonatal retinoblastoma is still however initiated by a germline mutation and therefore likely to result in bilateral disease. Patients with neonatal retinoblastoma pose a considerable challenge as most disease at presentation is advanced and rapidly evolving to involve the posterior pole and macula.[7] This was reported by Zohari and colleagues, as advanced disease was present with four patients (five eyes) having International Intraocular Classification of Retinoblastoma (IIRC) Group E eyes. Despite this, retinoblastoma remains intraocular and curable for 3–6 months after the first sign of leukocoria,[1] another common presentation of retinoblastoma and one identifiable with a simple red reflex check. Even with this in mind, early delivery and treatment remains controversial. Consideration for this is strengthened by the advanced stage of tumours often present at birth and therefore the desire for earlier intervention, when the tumours are less advanced and the burden of disease is less. In Canada, prenatal identification of an RB1 mutation means that obstetric care and premature delivery at 36 weeks' gestation is recommended.[1] Treatment in the neonatal period is a balance between the stage of disease and safety concerns in very young children. For example, systemic or intravenous chemotherapy is indicated in children under four months of age and not intra-arterial chemotherapy.[9] Limiting the morbidity of chemotherapy and concern regarding potential multi-drug resistance in neonates has led to consideration of treatments such as sub-Tenon chemotherapy for small volume tumours.[10]

Regardless of the challenges in diagnosing and treating neonatal retinoblastoma, the results of this study are encouraging. It should always be remembered that enucleation for advanced disease (IIRC Group E) can be a life-saving treatment and this was very appropriately practiced in this series, which reported no deaths and no metastatic disease. This is despite the expectation of germline disease in

neonatal retinoblastoma and bilateral disease developing later. All patients in the study presented here ended up with bilateral disease.

Advanced disease at presentation, rapid disease progression with high recurrence rate, and macular involvement are key factors in the consideration of neonatal retinoblastoma. Lack of awareness and education of surviving patients and also healthcare workers continue to pose challenges in both developed and developing countries alike. As the number of patients around the world with neonatal retinoblastoma inevitably increases, we can all work together to better understand the problem and its unique challenges and to hopefully offer our patients better outcomes in the future.

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