Reviewer's report

Title: Optic glioma and precocious puberty in a girl with neurofibromatosis type 1 carrying an R681X mutation of NF1. Case report and review of the literature.

Version: 0 Date: 03 Nov 2015

Reviewer: Assunta Albanese

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The manuscript is a case presentation of a 2.5 years old NF1 girl who presented with central precocious puberty (CPP) and was found to have a chiasmatic optic pathway glioma (OPG) on brain MRI. Genetic analysis of NF1 gene showed a rare R681X mutation. Her puberty was successfully arrested with LHRH analogues and a yearly MRI follow up showed no tumor progression for the following 6 years. The Authors reported this case as the first NF1 patient with R681X mutation who presented with CPP. They hypothesized that the occurrence of CPP could be associated to R681X mutation and concluded that "it might be wise to search for the R681X mutation in children with NF1 associated with optic glioma and/or precocious puberty".

My main comments are that NF1 are not rarely associated with optic glioma in childhood and NF1 is not exceptionally associated with precocious puberty as mentioned by the Authors (Abstract page 3 line 3-4). As described by the Authors on page 4 line 22-23, optic nerve gliomas occur in 12% of patients with NF1 usually within the first decade of life. This is not a rare association.

Page 4 line 24-25: Precocious puberty due to optic glioma has rarely been described in patients with NF1. This is not correct as precocious puberty is one the commonest endocrine disorder in NF1 and it mainly occurs in children with NF1 and optic pathway glioma (1). Also in the cited reference 19 (Habiby et al, 1995), it is reported that CPP is associated exclusively with chiasmatic OPG in the 39 % of cases. The etiology of CPP in NF1 children with OPG is not yet clarified more recent data seem to suggest a causative role of OPG itself rather than the presence of NF1 condition(1,2).

Zacharin et al 1997 paper (22) was cited by the Authors to support the presence of CPP in NF1 children without OPG. This paper was discussed by Bertelloni et al(3) and Habiby et al(4) in their letters to the Editor. Bertelloni concluded that the occurrence of CPP in NF1 children without OPG was not clearly supported by Zacharin's paper. Habiby confirmed Bertelloni's conclusion and added that also children with NF- 1 without OPG are at risk of developing idiopathic CPP as in the non NF1 population.
Overall there are no sufficient evidences to support the Authors' hypothesis of a possible correlation between CPP and R681X mutation in NF1 children with OPG in view of its absence in the remaining 9/10 cases with similar mutation published in the literature. The suggestion to search this mutation in children with NF1 is condition could not be considered appropriate.


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Unable to assess

Does the work include the necessary controls?
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Unable to assess

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No

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