

Valproic acid may be tested in
patients with H3F3A-mutated high-
grade gliomas

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February 15, 2016

Letter to the editor

The first reports [6] of a possible effect of valproic acid in the outcome of patients with glioblastoma were published nearly at the same time as the first ever description of the driver role of histone mutations in a human cancer - significantly enough in pediatric and young adult patients with glioblastoma [8]. Since then, a few retrospective reports have added clinical information that fueled the hypothesis of valproic acid effect in the survival of glioblastoma patients, via HDAC-inhibiting effect. Now, the report of Haggold *et al* [6] may have seemingly poured cold water upon this idea. Without a shadow of doubt, Haggold's report is the best evidence about this question that has been provided so far. Even though someone may put forward a number of well grounded critiques to their findings, this will be mostly worthless given the weaknesses of the previous evidence.

One particular type of bias that seems to be very common in retrospective accounts of would-be repurposed drugs is the *immortal time bias* [7] (aka sur- vivor bias). This kind of problem

arises when one has to forcefully add the pre-therapy events (deaths, in this case) to the non-treated group (because such patients never had the opportunity to receive the therapy of interest, they have died before!). It is very easy and amusing to demonstrate that any such an arrangement of an observational cohort study will necessarily suggest a beneficial effect of the treatment.

As Hapold *et al* has cited [6], our group was the one that originally published retrospective data suggesting a possible effect of valproic acid in pediatric patients with brain tumors. Our original account included a heterogeneous group of patients, but since then, we published other reports studying more homogeneous cohorts of patients, with mixed results [4]. Recently, we presented a poster in a Brazilian Society of Pediatric Oncology Congress with new data on the outcome of diffuse intrinsic pontine glioma (DIPG) patients treated with a contemporary radiochemotherapy protocol and valproic acid [5]. We showed a small cohort of 9 patients with

DIPG treated with valproic acid throughout the observation time. This group of patients had a 6-month survival of 86% and a 12-month survival of 64%. While this could be regarded as reassuring and an indication for further investigation, we acknowledge that the number of patients is too small and any comparison would be severely underpowered. However, one of the mainstays of investigational clinical science (and one that is too frequently forgotten) is to gather prior information about the therapy of interest and the target cohort. Mixed results from mixed groups of patients are hardly conclusive of anything, so we must examine thoroughly the rationale for any proposed treatment.

In this particular case, evidence has been building up that points to a subset of pediatric high-grade gliomas that depends on histone H3.3 (H3F3A gene) mutations [10, 1, 9]. To be specific, pediatric patients with DIPG and midline glioblastomas harboring the H3F3A-K27M mutation comprise a subgroup with a particularly poor prognosis, compared to other patients. Mutations K27M of H3.3 and H3.1 histones define two mutually exclusive DIPG

subgroups that differ in biology, behavior and prognosis [2]. The H3F3A-K27M mutant cells seem to globally lose methylation markers of H3.3 and undergo a bulk derepression of epigenetically silenced genes, while focally gaining methylation H3.3 sites, thus repressing the expression of selected genes [3]. Even though its mechanism is incompletely understood, it is possible that H3F3A-K27M may render tumor cells more sensitive to HDAC inhibitors like valproic acid. So, there is a strong rationale from recently-gathered evidence for the use of HDAC inhibitor drugs in patients with H3-mutant tumors. Most of them will be children, adolescents and young adults with DIPG and midline glioblastomas. We propose that future trials exploring this possibility select the patients by this molecular marker, including DIPG and glioblastoma patients with H3F3A-K27M mutation, and excluding other patients that may not benefit from the treatment.

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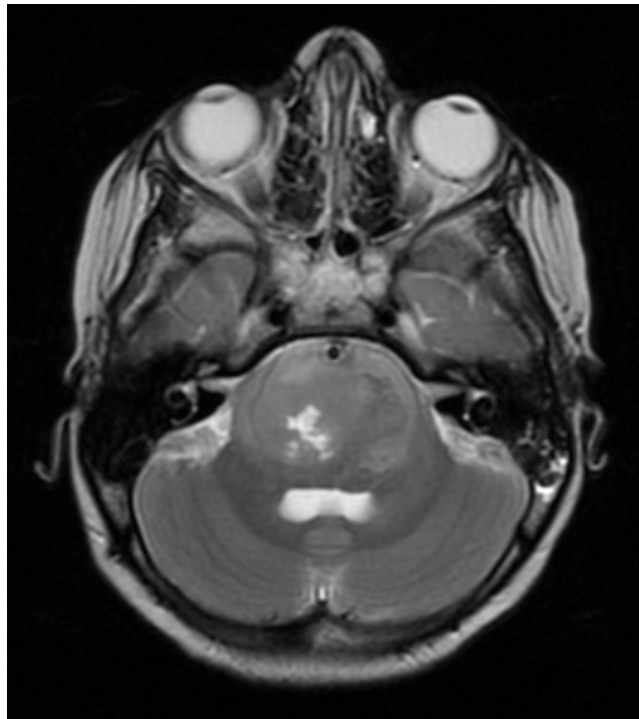


Figure 1: Figure 1: T2-weighted MRI showing the characteristic image findings in DIPG. A diffuse pons enlargement with T2-signal alteration. Basilar artery is "engulfed" in the pathologically enlarged pons