Reviewer’s report

Title: Autonomic neuropathy in Fabry disease: a prospective study using the Autonomic Symptom Profile and cardiovascular autonomic function tests.

Version: 2 Date: 24 December 2009

Reviewer: Raphael Schiffmann

Reviewer’s report:

Biegstraaten et al. provide interesting data regarding characterizing the autonomic abnormalities in patients with Fabry disease. This is a welcome addition to the literature in Fabry disease. The following are the (compulsory) revision is needed in my view:

1. The healthy control group has to be better described. How were they selected?

2. Table 1: please separate clearly for each group those on ERT and those without. We need to know what were for example the MSSI for ERT and non-ERT. We need to know the age of ERT vs. non etc. The idea is really to account as much as possible for possible confounding effect of ERT.

3. Table 2 and the text: I don’t see the usefulness of reporting the percent of patients with non-zero score. What is important is the absolute (raw) score in Fabry vs. healthy controls. Otherwise it looks like the healthy are not that healthy. It is surprising to me for example that healthy individuals have as many people with bladder dysfunction complaints. In this table too please separate the ERT from the non-ERT.

4. I agree with the conclusion that the abnormalities described are due to end organ dysfunction rather than to the neuropathy. However, this conclusion was reached by our group already in a number of primary (non-review) papers:

Sweath: Schiffmann et al Muscle and Nerve 2003


5. The HRV abnormalities in 19 boys and its correction with ERT is actually described in Ries et al. 2006.

6. I do not understand the separate influence of the hypertrophy as an explanation of the abnormal HRV rather than the effect of the small-fiber neuropathy. Rather, it is likely that the end organ that is relevant here is the conduction system not the hypertrophy per se. Decreased HRV is seen in children without LVH (see Ries et al. 2006 above). This is also relevant to the last sentence of the first paragraph of page 10. ...the disease itself. It is all due to the disease itself.
7. Regarding patients on ERT: we need to know their ages and how long they were on ERT. Do the authors think the ERT plays any therapeutic role vis a vis the parameters they measured or if not is ERT just a marker for relatively severe disease?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have received speaking fees, honoraria and research support from Shire Human Genetic Therapies. This company provides a form of enzyme replacement for Fabry disease.