Progress Report "Clinical Outcome Measures for Gene Therapy Trial in Infantile and Juvenile GM2".

Since we initiated the project on 2/1/2011, we have made progress on all 3 aims. Retrospective data on juvenile patients has been collected and analyzed (**aim 1**). We have established a clinical severity score and used it to prospectively assess both infantile and juvenile patients (**aim 2**). We have collected brain MRIs on infantile and juvenile GM2 patients and together with two expert neuroradiologists, we have developed a MRI rating scale (**aim 3**).

Studies and Results

1. Retrospective data on 10 juvenile patients has been collected by surveys and compared both to the literature (Maegawa et al 2006) and to adult onset Tay Sachs patients. Age at onset was 2.1 years (range 1- 4 years) compared to Maegawa 1.8 years (range 1.5-2.5 years). Age at diagnosis was 5.6 +/- 4 years in our retrospective juvenile cohort compared to Maegawa 3.2 years (no range given). A comprehensive summary of 55 late onset patients, including a comparison of symptom latency in juvenile versus adult onset patients, will be presented by Padmaja Yerramilli-Rao at the *WORLD symposium* (San Diego, February 2012).
2. Prospective data was obtained in 6 infantile and 5 juvenile patients. A prospective version of the previously published retrospective clinical severity score (Pediatrics 2011) was applied to infants and a new clinical severity score for juvenile patients was developed and applied as well. The average age of infantile patients was 20.5 months. The average age of juvenile patients was 55.2 months. A neuropsychologist performed the Vineland Scale for Adaptive Living Skills .
3. In order to develop a brain MRI scoring system two expert neuroradiologists from Minnesota and Boston reviewed a total of 10 brain MRIs of infantile GM2 patients. The average age at time of MRI was 11.8 months (range 9-18 months). All (10/10) patients displayed myelin abnormalities on the MRI with relative preservation of myelin in the splenium and genu of the corpus callosum. These findings were accepted as platform presentation at the *American Society for Neuroradiology* (NYC, 2012). Since the abstract we have collected an additional 5 brain MRIs and reviewed myelination status in more detail. Interestingly, the scoring system applies well to juvenile patients as well but the deep gray matter structures are not involved as in the infants.

Significance

The studies shed light on clinical progression in childhood GM2 and are of direct relevance to eligibility criteria and recruitment efforts in the upcoming human gene therapy trial. Outreach to other countries and continents will be important in order to enhance awareness, early diagnosis and possible future recruitment. Our MRI studies have allowed us to develop a 16 point MRI rating scale and show severe changes in specific brain structures of infantile GM2 patients. Due to the lack of serial images in this population it remains unclear whether conventional imaging is a good biomarker to track disease progression. However, an understanding of the conventional imaging changes is necessary at entry into the study and in preparation to use advanced MR techniques (DWI, MRS).

Plans

We will continue to enroll patients in our prospective studies and continue with follow-up evaluations in order to assess the rate of disease progression. Together with our neuropsychologist we are also developing Quality of Life scales specific to GM2 based on the Vineland Scale and prior survey material. We will assess interrater variability of our MRI scoring system and correlate the MRI findings with age, developmental milestones and clinical symptoms. Dates for meetings to design the gene therapy trial have been set.

References:

Maegawa, G.H., et al., The natural history of juvenile or subacute GM2 gangliosidosis: 21 new cases and literature review of 134 previously reported. Pediatrics 2006. 118(5): 1550-62.

Bley A, Giannikopoulous O, Hayden D, Kubilus K, Tifft CJ, Eichler FS. Natural History of Infantile GM2 Gangliosidosis. Pediatrics 2011. 128 (5): 1233-41.