Author's response to reviews

Title: Incidence rates of progressive childhood encephalopathy in Oslo, Norway: a population based study

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Thank you very much for the appropriate comments provided by Referee 1. We have addressed the comments in the following way:

1. Shift from unknown to known diagnoses during the observation period
Some causes of PE such as mitochondrial disorders are more readily diagnosed today than 20 years ago. However, we did not observe a significant shift of the proportion of unknown towards known disorders during the observation period. There was a definite trend towards identifying an exact molecular cause in patients with known diseases. Two sentences have been added to the discussion:

Mitochondrial disorders may have been inadequately diagnosed in Norway. There was a trend towards identifying an exact molecular cause in patients with known diseases.

2. Study population
(i) Proportion of immigrants
The overall proportion of non-western immigrants to Norwegian in the at-risk population was 34.9 % across the study period; 13.4 % in 1985 and 57.4 % in 2004. However, a recent study from Norway has shown that the proportion of children resulting from consanguineous marriages has dropped steadily over the years. Thus, the expected increase of progressive encephalopathy associated with a high proportion of non-western children has to be adjusted to the time trend with lower proportion of consanguinity in this population.

In this paper we have omitted the impact non-western immigrant children poses on the occurrence of progressive encephalopathy. The reason was that ethnic background or origin in a non-western country (parents or grand parents) would not make a difference whether a child would be referred for medical examination. Thus, the at-risk population was only limited to age (birth year) and geographical boundaries.

Base on these considerations we are going to focus separately on non western immigration and PE in a forthcoming study. In the present article we will add the following passage in the discussion:

The potentially increased incidence rate of PE in the non-western immigration population, associated with higher proportion of consanguineous marriages, will be addressed in a separate study.

(ii) Live births
The calculation of at-risk population was based upon live births in Oslo which was an approximation as we did not calculate the influx and efflux of children. Six of 84 cases (7.1 %) were born outside Oslo; all moved to Oslo aged < 1 year of age. One case (1.2 %) moved out during the observation period. We do not believe that births outside Oslo contributed to change the number of person years at risk to such a degree that it would significantly alter the incidence rates.

Incidence rates
Incidence rates and cumulative incidences supplement each other. Both are population measures of disease frequency. The cumulative incidence tells us what proportion of the child population that will have come to suffer from a certain disorder during a certain age span. Incidence rates give more precise information on the number of new cases according to the total number of person years under risk. Incidence rates make good sense when the case fatality is high, and makes it easy to compare age groups or to follow a population over time. Incidence rates are therefore commonly used in epidemiological studies of cancer, and should, in our opinion, be more often employed in studies of neurological disorders.

Age at diagnosis or age at onset of symptoms
Age of onset is presented under results (page 8) and was distributed between neonatal, infantile, early infantile, and juvenile onset. Age at diagnosis is presented below (on the same page) showing that the median age at diagnosis of neurodegenerative disorders was later than for metabolic diseases. The time gap between onset of symptoms and age of diagnosis was not presented. However these data including, case fatality, survival rates, and standard mortality ratio will be addressed in a forthcoming paper on the prognosis of PE.