

European Rett Syndrome Conference 2013
Maastricht, Netherlands



The 3rd European Rett conference was held in Maastricht from the 17th to 19th October 2013. Although principally a conference about Rett syndrome, there were 4 podium presentations and 4 poster presentations about CDKL5. This report focuses on those parts of the meeting relevant to CDKL5 although I have covered other aspects which I thought were of interest.

The first talk was from Dr. Steinbusch who is Professor of Neuroscience at Maastricht University. He has an expertise in both Parkinson's and Alzheimer's Diseases. He presented some observations about the similarity in brainstem dysfunction between these conditions and Rett syndrome that he felt might help in the understanding, for instance, of MeCP2-mediated autonomic dysfunction and therefore provide possible future therapeutic strategies. Given that there may well be an autonomic element to the CDKL5 disorder, this is something that may be relevant to us. There were a number of subsequent presentations by other researchers on brainstem dysfunction in Rett syndrome, particularly in relation to respiration and sleep.

Professor Angus Clarke from Cardiff gave an excellent presentation regarding the potential for a cure for Rett and the potential hazards associated. He discussed the issues of raising hopes and having to manage unrealistic expectations if unsubstantiated claims were being made regarding cures. He emphasised the responsibility researchers have to fully obtain informed consent when recruiting families to clinical trials, especially regarding the potential hazards that a particular treatment approach might involve. Again, these are issues that families with children who have a CDKL5 disorder will almost certainly face in the future.

Wendy Gold, a researcher in Professor Christodoulou's unit in Sydney, gave a presentation on dysregulation of mitochondrial bioenergetics which may contribute to disease progression in Rett syndrome - again a subject that might be relevant to CDKL5. They looked at the accumulation of free radicals in skeletal muscle and suggested that reducing these should be considered in developing future therapeutic treatments. Subsequent talks looked at the role of ω - polyunsaturated fatty acids (PUFA's) in the treatment of Rett syndrome; some of this research has previously been reported.

<http://g35.aktiweb.no/Kundearkiv/9449/MineDokumenter/Genes%20Nutr%202012.pdf>

There was a presentation on 2 sibling girls who have the same CDKL5 mutation but who have had different presentations. They are now 7 years and 1 year of age and have a healthy brother between them. Germline mosaicism - which is suspected - has been excluded in the father.

There were 2 very good and very technical presentations on the molecular biology of CDKL5. The first was from Charlotte Kilstrup-Nielsen from the University of Insubria, Italy. Their research has shown that levels of the CDKL5 protein are highly regulated. Stimulation through depolarisation causes a rapid induction of the protein. However, clearance of the protein (degradation) is also rapid and seems to occur over just a few minutes. This implies that the controls of CDKL5 levels are complex and one does therefore tend to wonder how the proponents of protein therapy as a therapeutic strategy for the treatment of CDKL5 would overcome this. The second talk was from Maurizio Giustetto from Turin, who discussed his work on knockout mice. He presented work undertaken on the characteristics of the mice including the molecular and anatomical deficits and their behavioural changes. This work has yet to be fully published and has been funded in part by the IFCR.

Stephanie Fehr presented some data from the International CDKL5 Disorder database. She gave a presentation on treatment regimens used for epilepsy. The median time of onset of seizures was 6 weeks and seizures occurred daily in 88% of cases. Anti-epileptic drugs were the commonest treatment with the use of 3 or more being the most frequent. Almost half had been on the ketogenic diet at some point although this had reduced to just under a third. Vagal nerve stimulation had been used in 23%. She concluded that epilepsy remains severe for most individuals but not refractory for all.

Stephanie also had 2 poster presentations from the database. One was on development and gross motor function. There were 76 females and 21 males on who data was available, 88% had impaired gross motor function and milestones, when achieved, were delayed. Independent walking was seen in 17% of females and one male, while sitting was reported in 56% of females and 21% of males. Overall, males tended to be more severely affected than females. Their second poster was in relation to gastro-intestinal (GI) problems. They reported on 83 individuals on who data was available. They found that the majority (86%) had had a history of GI problems at some point. The commonest was constipation (76%) followed by reflux (75%). A gastrostomy had been performed in 22 cases and 13 had had anti-reflux surgery. CDKL5UK also presented the results from a parent survey on the same subject. Of 90 responses about 75% reported reflux, 25% had a g-tube for feeding and about 20% had had a Nissen's Fundoplication. Although only about 15% reported constipation (bowels open less than 3 times a week) at the time of the survey, nearly 50% were taking medication to support bowel function. Overall, the results between the 2 posters were fairly similar, which is not surprising, given that the populations being sampled may be similar. This also endorses the function of the International Database.

The final poster on CDKL5 was from The Netherlands regarding respiratory and sleep disorders. This was a poster presenting data that has already been published in the literature.

<http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2012.04432.x/abstract?deniedAccessCustomisedMessage=&userIsAuthenticated=false>

Overall, this was a very good conference. The philosophy of inviting, clinicians, researchers and families to the same meeting works very well, and provides an excellent opportunity for families to quiz and learn from the experts. The next conference for CDKL5 will be from the 25th to 27th April 2014, in Bologna, Italy. Hope to see you there.

Martyn Newey
October 2013.