Alteration of serum lipid profile, SRB1 loss and impaired Nrf2 activation in *CDKL5* disorder

This is a study by researchers from Italy and the US examining whether children with CDKL5 have abnormalities in their cholesterol regulation and also whether there is evidence of something called oxidative stress. So - before we start, a quick biochemistry tutorial!

Cholesterol isn't just about eating too much fat and clogging up your coronaries!! It has an essential role in the structure and function of cell membranes. When it comes to cholesterol and your arteries, low density lipoproteins (LDL's) and high density lipoproteins (HDL's) are the bad guys and good guys respectively. LDL's deposit cholesterol into your arteries – that's bad - while HDL's hang on to cholesterol and transport it to the liver where with the help of a receptor called SRB1, the cholesterol is removed and partly excreted from the body. As I'm sure we all know, drinking red wine increases your HDL levels – so that's good...right!!

Oxygen (in addition to red wine) is vital to life. In cells, oxygen is used to produce cellular energy. However, there is a down side in that this process also produces toxins – things called free radicals, a term you might recognise. Fortunately, cells have a defence mechanism for dealing with free radicals. However if that mechanism becomes unbalanced then a toxic environment can develop in cells – something called oxidative stress – and that's bad. A molecule called Nrf2 is involved in the activation of these defence mechanisms. In normal conditions Nrf2 sits around in the cytoplasm of the cell apparently doing nothing in particular. However, in the presence of oxidative stress, it moves (translocates) into the nucleus of the cell where it acts on various genes that initiate the defence mechanisms. As such it is known as a transcription factor.

So, what's all this got to do with us and CDKL5? Well, previous studies have shown that the regulation of cholesterol metabolism is impaired in Rett syndrome and it has been suggested that this may ultimately contribute to the phenotype of the Rett disorder. Other studies have suggested that an imbalance producing oxidative stress may also contribute to the Rett disorder in some circumstances. It is thought that oxidative stress can somehow block the function of the SRB1 receptor thereby causing an increase in cholesterol levels – that's also bad. In this study, the researchers have looked to see if there is a similar dysregulation in the CDKL5 Disorder.

Method - The authors studied 16 females (aged 2 to 18 Years) who had a CDKL5 mutation. A further 30 healthy females were recruited to act as controls for the purposes of comparing results. Blood tests were performed after all the girls had fasted overnight. These were used to obtain what is called a serum lipid profile (this gives values for the blood levels of cholesterol, triglycerides, LDL's and HDL's).

Skin biopsies were obtained from 4 girls with a CDKL5 mutation and 4 controls. These were used to obtain cells called fibroblasts, which were then used to study the mechanisms involved in cholesterol regulation and oxidative stress. In particular, 2 markers were studied. Firstly the SRB1 receptor for HDL and secondly the transcription factor Nrf2.

Results

Serum lipid profiles – blood results showed that the girls with a CDKL5 mutation had a higher serum lipid profile compared to the control group. The increased levels seen were statistically significant in all but the levels of triglyceride.

Fibroblast studies - the authors found that the levels of SRB1 receptor were significantly reduced in fibroblasts from the CDKL5 girls compared to the controls. This was possibly due to under-production of SRB1 through interference with its translation (production) from its mRNA or possibly due to an effect after it had been translated from its mRNA. In fact, its mRNA was significantly increased – suggesting that the cells were trying to compensate for the low levels of SRB1. The authors suggest that the reduced level of SRB1 might account for the increased lipid profile. The authors also demonstrated that levels of Nrf2 were lower in CDKL5 fibroblasts compared to controls – suggesting at least a vulnerability to developing oxidative stress. Furthermore, on inducing an oxidative stress challenge, activation and translocation of Nrf2 into the nucleus was clearly reduced in CDKL5 fibroblasts compared to the controls.

This work therefore demonstrates that both abnormal cholesterol regulation and oxidative stress occur in the fibroblasts of children with CDKL5. These biochemical abnormalities are common to both CDKL5 and Rett syndrome which may reflect the overlap in molecular pathways affected in the 2 conditions.

Note – This is a study of rather complex mechanisms and clearly there may be a whole lot more to discover about these and their related pathways. Furthermore, these studies were performed in fibroblasts and there is some evidence to suggest that the situation, particularly in relation to Nrf2 and oxidative stress, may actually be very different in neurons. A further difficulty here is understanding cause and effect and in particular, how relevant these abnormalities are in contributing to the overall phenotype we all see.

So, if there is a significant problem in CDKL5 with cholesterol regulation and oxidative stress then this may have implications. Firstly, it might indicate new treatment strategies. Secondly, as said above, cholesterol does have a role in cell membrane function including that of the neuron, so there may be effects here that need to be explored further. Finally, I have always thought of CDKL5 as being a relatively stable condition, that is, while there might always be potential for improvement with appropriate therapy, there isn't necessarily a reason why things should deteriorate – apart from, perhaps, in relation to uncontrolled seizure activity. However, oxidative stress is increasingly being recognised as having a role in the development of various neurodegenerative diseases, which by definition are progressive conditions. For us, therefore, this raises the possibility that if oxidative stress is a significant issue in CDKL5, then regardless of whether it is cause or effect, if left untreated it could turn what might otherwise be a stable condition into a progressive one. We should therefore watch this space carefully…