

LCHAD...or is it... TFP? : An Update

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In a late evening a few months ago, I opened my e-mail to find a message from a caring mother that read in part “**My daughter...is diagnosed with TFP...She was diagnosed in 1993...as LCHAD and several months ago was diagnosed as having TFP. I have done some research on the computer about TFP, but find it keeps referring me to LCHAD. Do you have a good description of TFP, for me, for anyone in the medical field whom I come in contact with (who has never heard of TFP...which is everyone), and for our FOD support group and for a grass roots group called Save Babies...?**” In this article, I will attempt to first clarify the difference between LCHAD and TFP, which, I admit, can be confusing. Second, I will provide an update of what we have learned about these disorders in the past few years.

LCHAD and TFP: What are they?

Both LCHAD and TFP are proteins (enzymes) that are necessary for fatty acid breakdown in the cell. However, LCHAD is actually part of TFP (which is an abbreviation for trifunctional protein). TFP is simply a complex protein that is composed of LCHAD and other 2 enzymes that are, like LCHAD, necessary to break down fatty acids. This knowledge of the relation between TFP and LCHAD was not known in 1989, when the first case of LCHAD deficiency was described. The fact that LCHAD is part of TFP became known in 1992. After that, it became clear that some of the children who were initially diagnosed as LCHAD, in fact, had TFP deficiency. In MTP deficiency, all the 3 enzymes, including LCHAD, are deficient. So, there are 2 groups of LCHAD children: The first with deficiency of LCHAD alone, and the second with deficiency of LCHAD and the other 2 enzymes. The second group is labeled with TFP deficiency since all the 3 enzymes in TFP are deficient. The majority of LCHAD children belong to the first group (only LCHAD affected). Over the past few years we learned several lessons about LCHAD and TFP disorders.

Lessons from Kids

In 1999, we reported our findings in 24 children with LCHAD and TFP disorders. By enzymatic measurement, we found that 19 of these children had LCHAD deficiency and 5 had TFP deficiency. Although there was some overlap in the clinical features, we noted that, in general, children with LCHAD deficiency presented at few months of age (5 months on average) with liver abnormalities due to accumulation of fat in the liver. A severe form of TFP deficiency affected 3 children who presented primarily with heart problems in the first 2 weeks of life. We found a mild form of TFP deficiency in the remaining two children who

presented at older age (more than 2 years old) primarily with problems in the muscles of the extremities and some neurological abnormalities. Our molecular analysis in these children revealed some important findings. A common mutation for LCHAD was found in all children with LCHAD deficiency either in both copies of the gene or in one copy (the one from the mother or the father). This mutation was not found in any of the 5 children with TFP deficiency. Our research in additional families confirmed these findings. It should also be noted here that few of these children had sudden unexpected death and initially labeled as SIDS.

Lessons from Women

Our research in the past few years has provided an important understanding to an association between LCHAD deficiency in the child and development of liver disease in the pregnant mother while carrying the affected child. The liver disease late in pregnancy is called acute fatty liver of pregnancy “abbreviated as AFLP” which is difficult to distinguish, sometimes, from another condition called HELLP syndrome, which also causes liver disease late in pregnancy and reported to occur in association with carrying a child with LCHAD deficiency. In our families, we found that approximately 70% of the women who carry children with LCHAD deficiency develop AFLP or, to a less extent, HELLP syndrome. In all of these cases, the unborn child had the common mutation in one or both copies of the LCHAD gene. None of the mothers in the families who had children with TFP deficiency had AFLP or HELLP syndrome. This suggested to us that this association between liver disease in pregnancy and fatty acid oxidation disorders in children is primarily unique to LCHAD deficiency. However, we should caution that there are few reports of an association between these pregnancy diseases and other fatty acid oxidation disorders including TFP.

In a recent study of 27 cases of AFLP and 81 cases of HELLP syndrome, we screened the women and the newborns for the LCHAD common mutation based on the mother’s history. In 5 of the 27 pregnancies complicated by the AFLP, the child was LCHAD deficient with either one or two copies of the LCHAD common mutation. This finding led us to an important recommendation: newborns should be screened for the LCHAD common mutation in all pregnancies complicated by AFLP. This is critical because screening the newborn can be life saving, such that a diagnosis will be established before development of the disease, which is potentially treatable. These disorders are treated by dietary modifications including frequent feedings, high carbohydrate and low fat diet, and replacement of fat with “medium chain” fatty acids that do not require LCHAD and MTP for their breakdown. In addition, screening the newborn in these complicated pregnancies and establishing a diagnosis of LCHAD deficiency can be important for genetic counseling including prenatal diagnosis in future pregnancies.

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