High cholesterol diet found to help mice afflicted with Pelizaeus-Merzbacher disease

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(Medical Xpress) -- In people and most animals, the nerves that carry electrical signals from one part of the body to another must have a protective coating (called a myelin sheath) to allow signals to travel properly. When problems arise that prevent the sheath from forming, a variety of symptoms occur depending on the part of the body impacted. When it happens in the brain, the result is generally fatal. Such is the case with Pelizaeus-Merzbacher disease, where the duplication of the proteolipid protein gene 1 (PLP1) causes the over-expression of the protein in myelin (PLP) which leads to it becoming stuck inside the cells, thus preventing the sheath from being created; sadly, very little can be done for patients with the disease. Now new hope is on the horizon as researchers at the Max Planck Institute in Germany have found that feeding mice that have been genetically altered to give them Pelizaeus-Merzbacher disease, show improvements when fed a diet high in cholesterol. The team has published the results of their study in the journal *Nature Medicine*.

Nerve networks in human and animals can be thought of in similar terms to electrical wiring used in homes and other commercial buildings. Each metal wire is covered in a protective plastic casing to keep in heat and of course the electrical current. If the casing is damaged or missing, shorts occur leading to loss of electricity or in some cases fires. In biology, loss or damage to the casing, or sheath that covers nerves prevents electrical signals from being transmitted properly. Multiple sclerosis is one well known disease that comes about as a result of such damage, though in this case, it's due to an autoimmune disease attacking the sheath. With

Pelizaeus-Merzbacher disease, as noted, the sheath never gets a chance to form rather than it being damaged afterwards.

In their study, the researchers found that feeding mice a diet high in cholesterol led to a reduction in symptoms as compared to those fed a normal diet. In looking closer at why that may be, they found that added cholesterol didn't stop the overexpression of PLP, rather it helped it escape from the cells and then to be incorporated into the myelin sheath. They note that they found the best results when starting the mice on the changed diet when they were still very young.

The researchers are careful to point out that thus far no tests have been conducted to see if the same might be true with people, but doubtless that will happen very soon. They also note that the high cholesterol diet doesn't cure the disease in the mice, it simply reduced the symptoms. Further tests will have to be done to find out if the simple change in diet will continue to help the mice indefinitely, or if it simply delays the inevitable progression that eventually leads to death.

More information: Therapy of Pelizaeus-Merzbacher disease in mice by feeding a cholesterol-enriched diet, *Nature Medicine* (2012) doi:10.1038/nm.2833

Abstract
Duplication of PLP1 (proteolipid protein gene 1) and the subsequent overexpression of the myelin protein PLP (also known as DM20) in oligodendrocytes is the most frequent cause of Pelizaeus-Merzbacher disease (PMD), a fatal leukodystrophy1 without therapeutic options2, 3. PLP binds cholesterol and is contained within membrane lipid raft microdomains4. Cholesterol availability is the rate-limiting factor of central nervous system myelin synthesis5. Transgenic mice with extra copies of the Plp1 gene6 are accurate models of PMD. Dysmyelination6, 7, 8 followed by demyelination9, 10, secondary inflammation and axon

damage contribute to the severe motor impairment in these mice9, 10. The finding that in Plp1-transgenic oligodendrocytes, PLP and cholesterol accumulate in late endosomes and lysosomes (endo/lysosomes)9, 11, 12, 13, prompted us to further investigate the role of cholesterol in PMD. Here we show that cholesterol itself promotes normal PLP trafficking and that dietary cholesterol influences PMD pathology. In a preclinical trial, PMD mice were fed a cholesterol-enriched diet. This restored oligodendrocyte numbers and ameliorated intracellular PLP accumulation. Moreover, myelin content increased, inflammation and gliosis were reduced and motor defects improved. Even after onset of clinical symptoms, cholesterol treatment prevented disease progression. Dietary cholesterol did not reduce Plp1 overexpression but facilitated incorporation of PLP into myelin membranes. These findings may have implications for therapeutic interventions in patients with PMD.