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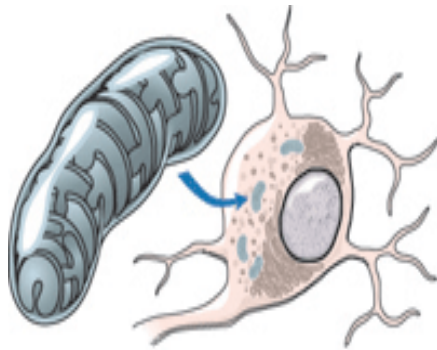
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RETT SYNDROME AND MITOCHONDRIAL FUNCTION

IRSF Asked the Experts, and we thank our key advisor Alan Percy, MD, *Director UAB Rett Center at the University of Alabama Civitan International Research Center* for commenting:

Recent discussions regarding a possible connection between Rett syndrome (RTT) and mitochondrial dysfunction has generated significant interest. The basis for these discussions relates in part to the common features of RTT on the one hand and disorders of mitochondrial function on the other. These common clinical features include hypotonia, delayed development or frank regression of previously acquired milestones, seizures, and problems with growth. None of these features is specific to RTT or disorders of mitochondrial function. While RTT is characterized by specific diagnostic criteria and *MECP2* mutations in most, disorders of mitochondrial function may have a quite varied clinical picture and may be associated with mutations not only of nuclear DNA but also of the much smaller mitochondrial DNA



component. Hence, when faced with some combination of these features and in the absence of satisfying the diagnosis criteria for RTT, physicians may consider mitochondrial disorders as well as specific neurodevelopmental disorders including RTT. In many instances, disorders of mitochondrial function

display a stuttering course with periods of regression in relation to some external event such as an acute illness followed by stabilization until the next regression. However, the first instance of regression

might not be sufficiently typical to distinguish the two clinical problems from each other. When coupled with laboratory abnormalities consistent with a mitochondrial disorder such as abnormal plasma lactate and pyruvate or pathologic abnormalities on tissue biopsy, a more extensive search for a biochemical or

ABOUT THE INTERNATIONAL RETT SYNDROME FOUNDATION

IRSF is the world's leading private funder of basic, translational and clinical Rett syndrome research, funding over \$21M in high-quality, peer-reviewed research grants and programs to date. Annually, IRSF hosts the world's largest gathering of global Rett researchers and clinicians to establish research direction and priorities while exchanging ideas and the most recent information. IRSF is the most comprehensive non-profit organization dedicated to providing thorough and accurate information about Rett syndrome, offering informational and emotional family support, and stimulating research aimed at accelerating treatments and a cure for Rett syndrome and related disorders. IRSF has earned Charity Navigator's most prestigious 4 star rating. To learn more about IRSF and Rett syndrome, visit www.rett Syndrome.org or call IRSF at 1-800-818-RETT (7388).

genetic mitochondrial explanation is often conducted. As described below, reports of such investigations have not yielded consistent findings sufficient to justify in RTT the implementation of dietary therapies typically employed in disorders of mitochondrial function.

Anecdotal reports have implicated mitochondrial dysfunction in individuals with RTT. To-date, no systematic study of mitochondrial function in individuals with RTT has been presented as to whether these findings represent a primary or secondary effect, that is, are they involved directly in the clinical features of RTT or do they reflect effects of these clinical features on mitochondrial function. Prior to identification of mutations in *MECP2* in 1999, several reports appeared related to mitochondrial structure and function [1-19].

However, since 2001, publications on a possible role for mitochondria in the pathogenesis of RTT have been very few [20, 21].

The majority of the early reports involve structural abnormalities of mitochondria detected by studies using the electron microscope [1-6, 8, 12]. In most, chemical measurements of lactate and pyruvate in blood, two markers of abnormal mitochondrial function, were normal. Three reports identified no structural abnormalities [7, 9, 10]. One of these [10] also identified no abnormalities in plasma lactate and pyruvate or in brain lactate by magnetic resonance spectroscopy and a separate study found no abnormalities in plasma [13]. A more relevant evaluation of lactate and pyruvate levels with respect to mitochondrial dysfunction involving the central nervous system is their measurement in cerebrospinal fluid (CSF). In this regard, a study of CSF lactate and pyruvate did demonstrate abnormally high levels in a subset of girls with RTT [11]. However, these elevations correlated directly with those who had hyperventilation,

breathholding, or both. Other pre-*MECP2* investigations evaluated mitochondrial DNA for mutations [15, 17]. While polymorphisms (normal variations) were found, no systematic abnormality in mitochondrial DNA has been identified [14, 16, 18]. Along the same lines, increased levels of oxygen free radical were demonstrated in blood platelets into which mitochondrial DNA had been transferred. The findings suggested a susceptibility to premature cell death as compared to controls [19]. To-date, these results have not been reproduced independently.

Two recent studies build on knowledge of the role of *MECP2* mutations in RTT. Using the *Mecp2*-null mouse (an animal model for RTT) and special molecular genetic measurements, mice with neurological symptoms were shown to overexpress the nuclear gene for ubiquinol-cytochrome c reductase core protein 1 (*Uqcrc1*). *MeCP2* protein interacts with the promoter region of *Uqcrc1* suggesting that mitochondrial dysfunction is involved in the pathology of this mouse model [20]. A direct relationship to RTT in humans remains to be established. This year, investigators in Australia reported gene expression results from postmortem brain tissue of individuals with RTT and normal controls [21]. One gene related to a mitochondrial enzyme, cytochrome c oxidase subunit 1, had reduced expression in RTT tissue raising the possibility that loss of *MeCP2* function could be responsible. However, whether this is a primary or secondary finding remains to be established and provides an important target for further investigation.

In summary, while mitochondrial abnormalities related to structure and function have been reported, sufficient information is lacking as to the precise role of such abnormalities in RTT. At present, no evidence exists to support the use of nutritional supplements designed to enhance mitochondrial function.

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