

## **NINDS CDE Project Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Neuroendocrine Subgroup**

We grappled with the definition of “Neuroendocrine” because it has been used in ME/CFS in ways that are not always consistent with general medical terminology. The 2003 Canadian Consensus Criteria includes a broad set of symptoms under the “Neuroendocrine” label. As noted in the IOM report, the 2011 ME International Consensus Criteria includes some of these symptoms under the “Energy Production/Transportation Impairments” domain. While we recognized that the symptoms labeled as neuroendocrine are not all neuroendocrine, we included all of them in the list of symptoms because these are all symptoms that ME/CFS patients experience. Later work will need to decide what subdomains are appropriate.

For this initial set of recommendations, we included labs that measure neuroendocrine (or other endocrine) function, particularly ones that have been utilized repeatedly in previous ME/CFS research or which represent standard, common measures of endocrine function. We also developed guidance and case report forms (CRFs) that cover the range of symptoms classified as neuroendocrine by the Canadian Consensus Criteria as we felt these symptoms are important in this disease, regardless of what label they are given. The resultant questions can be used as a set to assess compliance with the Canadian Consensus Criteria (as in the list of key gaps below) and individual questions can also be used as needed to collect data appropriate to the given research study. Some of these questions may be more appropriately placed into the baseline domain.

Material from submitted case report forms was reviewed and neuroendocrine or related items were selected for further review. These were then reviewed for redundancy and for appropriateness of inclusion. We also reviewed background information, and studies to better understand whether differences in laboratory methods needed to be taken into account. The clinician, researcher and patient advocate perspective were considered in developing these recommendations. One subgroup member is the carer for a person with ME/CFS.

We considered the lack of physical stamina of people with ME/CFS and streamlined the received questionnaires to balance the needs of research with that of patients. At least given the current state of knowledge of neuroendocrine manifestations in ME/CFS, the subgroup was able to make recommendations that capture the diversity and complexity of the clinical presentations of ME/CFS. These recommendations will need to be evolved as we learn more. There are gender differences in the application of some of these recommendations, as indicated on the draft CRFs. No specific recommendations have been made for pediatric patients or for severely ill patients.

### **The products of the subgroup was three (3) case report forms (CRF) as follows:**

- 1. Neuroendocrine Labs** - When neuroendocrine labs tend to exhibit fluctuation based upon timing, collection methods should ensure consistency among participants.
- 2. Neuroendocrine/Hypothalamic Symptoms** - The list of questions can be used as a set to assess whether cases meet the Neuroendocrine component of the Canadian Consensus Criteria or used separately.
- 3. Reproductive and Hormonal History**

As noted above, one challenge is the variance in how the term “neuroendocrine” is used in ME/CFS research. A more specific difficulty arises in assessing adrenal function. An AM cortisol may be a desired baseline test, however the standard recommended collection time for a morning cortisol would normally be 6-8 AM. This may be less practical in ME/CFS patients, where collection at this time may constitute a challenge for patients and also may be affected by greater deviations in the timing of patients' circadian hormonal rhythms than those of healthy individuals.

In review of the recommendations certain unmet needs or unanswered questions were identified. These key gaps which will need to be addressed include:

- We recommend that the field move away from using the term “neuroendocrine” to refer to symptoms that are not specific to neuroendocrine abnormalities (as the term is used in clinical medicine), an issue that was also discussed in the IOM report. In terms of clinical data element classification, questions regarding such symptoms could be reclassified.
- Further research is needed to better characterize the effects of disturbances in neuroendocrine function and elucidate the pathophysiological mechanisms leading to such disturbances. In doing so, it will be important to address the limitations of existing research described in the 2015 National Academy of Medicine (NAM, also called the Institute of Medicine or IOM) report. This includes issues with patient sampling and study designs that could not show causality or that did not control for time of day.
- Data elements for assessing reproductive/hormonal status, including whether puberty has been reached. Current subgroup recommendations have CDEs for female reproductive status which include an indicator for menarche in females. However, menarche is not a marker for the onset of puberty. There is no clear male equivalent to menarche, and males overall are less well defined in terms of changes in hormonal status.
- Further refinement of data elements and guidance regarding data collection is needed. Specific considerations include the following:
  - For hormones in which there is diurnal variation such as cortisol, the optimal method for obtaining the most consistent measurements is unclear.
  - It is unclear whether reference ranges should be recommended for certain labs (e.g., TSH, AM cortisol). In some cases, reference ranges may be lab specific so it is difficult to specify a single reference range, but there also may be variation in how certain labs choose reference ranges (for example, sex-specific values for TSH or not). As a corollary, there was disagreement over whether a "normal vs abnormal" field should be included since some labs may make standard measurements of absolute values but provide different lab-based reference ranges.
  - Prior research evidence suggests that disturbances in water handling are present in individuals with ME/CFS (including abnormalities in arginine-vasopressin production and action; see IOM report for further discussion). However, there is not a single standard method for fluid deprivation testing – the current data element does not provide a specific recommendation for fluid deprivation testing methodology.
  - Specifying an appropriate approach to data collection in review of systems that captures changes in symptoms and can be used in measuring changes with exercise or treatment.
- Correlation between endometriosis and use of fertility medication (and other large hormone fluctuations) with disease onset or symptom worsening
- Correlation of pregnancy with disease onset, symptom worsening or symptom improvement.
- Research related to blood sugar regulation issues in ME/CFS patients.