Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Nomination and Prioritization Reports: MPS I and Pompe Disease

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Nomination and Prioritization Work Group

- Dr. Joseph Bocchini, Jr., MD – Chair
- Fred Lorey, PhD
- Dietrich Matern, MD
- Andrea Williams
- Nancy Green, MD

Outline of Presentation

- *MPS I:*
  - *Present review by Nomination and Prioritization Work Group*
  - Discussion and Vote by Committee:

    Move forward to Evidence Review?
- *Pompe:*
  - *Present review by Nomination and Prioritization Work Group* - update
  - Discussion and Vote by Committee:

    Move forward to Evidence Review?

MPS I: Nomination

- Nominator: National MPS Society
  - Barbara Wedehase, MSW, GCG, Executive Director
- Medically serious condition:
  - Defective glycosaminoglycan catabolism (↓α-Iduronidase)
  - Debilitating < 1yr: multi-system (cardiac, pulmonary, CNS, other)
  - Fatal within 1st decade of life; considerable CNS impairment (Hurler Syndrome); Absent enzyme.
    - 40-60% of cases; Symptoms by 6 months
  - Attenuated forms with slower, later progress;
    - Symptoms by 5 years; Less or no CNS; some enzyme activity
- Estimated incidence 1:100,000 in the U.S.,
  - including those within the spectrum of disease.
  - Actual U.S. incidence is unknown.

MPS I: Case Definition & Disease Spectrum

- Case definition and disease spectrum - Yes
- Attenuated forms: Broader spectrum of age and onset:
  - Later symptoms and slower progression;
  - Approximately half of cases
- All forms: little or absent enzyme activity
  - Depends on tissue tested
- Molecular analysis provides good correlation with protein function
- Some uncertain genotype-phenotype correlates:
  - Some variants have unclear impact on enzyme
  - Pseudo-deficiency variant = rare

MPS I: Population-based Newborn Screening & Diagnosis

Recently established algorithm*

- Screen by enzyme activity (MS/MS): low/absent
  - Absent activity: severe form
  - Low activity: generally less severe but serious, but levels are imperfect predictors of severity

  [Multiplex with other LSDs]
- DNA sequencing of α-Iduronidase
  - Predict severity (if mutation is obvious known)
  - May need to sequence gene in family members (e.g. for novel mutations)
  - Technical challenges for some states? (*Fine for Krabbe - NY*)

*Wang, et al. ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Genetics in Medicine, 2011

MPS I: Analytic Validity

- Washington State: 75,000 screened (anonymous) by multiplex (3 enzymes):
- 5 identified below cutoff value: 1 early; 1 attenuated; 1 heterozygote; 2 no identifiable mutation.
  - False positive rate approx. 1:14,000.
- Missouri: Assay development is underway
- Several states (e.g. New Jersey, CA):
  - Currently deliberating about their screening approach

MPS I: Clinical utility

- Treatment improves outcomes:
  - HSC* transplant for the severe form
    - Best < Age 2 yrs;
    - Arrests disease impact on CNS;
    - Lifespan if transplanted vs. not: 15.6 vs. 7.9 yrs (2008)
    - 10-15% mortality, plus 10-15% GVHD, other complications
  - FDA approved therapy: ERT
    - Milder forms: enzyme replacement therapy or pre-BMT.
    - Does not cross the blood–brain barrier, thus does not improve CNS effects for severe form (Intermediate?).

* Hematopoietic stem cell transplant

MPS I: Issues & Recommendation

- **Established overall**: Case definition, Screening and diagnostic protocol, Treatment protocols
  - Appeal of multiplex testing
- **Recommend**: ***Move forward to Evidence Review***

  BUT WITH RESERVATIONS

  – Uncertain: Identifying various forms of MPS, though each type is serious and treatable: Phenotypic spectrum and genotypic mutations
  – Uncertain: Impact of treatment with HSCT and ERT, especially for variants (50% of those identified)
  – Uncertain: Acceptability to parents (e.g. Krabbe experience, other non-oncologic disorders)
  – Uncertain: State NBS laboratory and program challenges
  – Uncertain: Public health impact

MPS I

Nomination and Prioritization:

Comments

and

Questions?

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Nomination: Pompe - Updated

- Previously nominated & reviewed in 2008
  - Nominator: Priya S. Kishnani, MD, Duke University
- Pompe Disease is medically serious:
  - Deficient enzyme Acid α-glucosidase (GAA): Hydrolyzes lysosomal glycogen $\rightarrow$ accumulates in muscle
  - Progressive muscular disease: skeletal +/- cardiac
  - 1/3 have the infant form (early & rapid Sx, cardiac too)
  - Infantile: Symptoms at ~2 months
  - 100% mortality in the first year of life
- Estimated incidence:1/40,000
  - Including Infantile and later onset forms

Pompe: Case Definition and Spectrum of the Disorder

Infantile versus later onset

- Later onset: more variable in timing of onset, its impact on health, treatment issues
- Distinguishing infantile onset from late-onset:
  - Can be challenging
- Pseudo-deficiency: low efficiency enzyme
  - Prevalent among Asian populations
  - Would need to be discerned

Pompe: Population-based Newborn Screening & Diagnosis

- 1st tier screening: GAA enzyme activity level
  - Fluorometry or MS/MS - perform similarly
  - Enzyme levels differ by tissue

  [Multiplexed]

<u>Newly clarified for diagnostic testing</u>*:

- Leukocyte GAA activity
- Followed by GAA gene sequencing
  - Likely to detect infantile, but some uncertain mutations
- (Technical challenges for some state labs? *NY: Fine for Krabbe)*
  - CRIM status (Western Blotting)

*Wang, et al. ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Genetics in Medicine, 2011

Pompe: Analytic validity

- DBS Screen: GAA Enzyme activity
  - Different methods appear comparable (multiplex)
- Prospective pilot data from Washington State (false positive rate: 0.01%).
- Illinois: 8002 screened - 2 false positives (BB 2/20/2012)
- Taiwan: 130,000 infants screened – 4 Diagnosed
  - Repeat blood testing rate: 0.82%;
  - Clinical recall rate 0.091%
- Austria (35,000 babies screened):
  - False positive rate: 0.006%

Pompe: Clinical utility

- Taiwan: 130,000 infants screened
  - 4 diagnosed by NBS in 1st month;
  - 3 diagnosed clinically between 3-6 months
- Children who would benefit from newborn identification and therapy = 1/3 of those identified
- Clinical utility for children in the later onset group: not addressed by the Nominator

Pompe: Treatment

- Defined treatment protocols exist using enzyme replacement therapy (ERT)
- Earlier diagnosis and treatment has been shown to improve outcomes.
- C/W European consensus (2011)
- Open issues: CRIM = cross-reactive immunologic material
  - Some with limited response to treatment

    (CRIM negative) – 20-30% of infantile on treatment (Kishnani 2010)

    - African American common
  - Sensitization: Antibodies to GAA replacement (“Anti-CRIM”)

Pompe: Open Issues

- Identifying late onset disease – 2/3 of cases.
- Challenges in DNA sequencing:
  - How clinically predictive
  - Technical challenges for some state labs.
- ERT: Sensitization to enzyme replacement.

Pompe: Work Group Recommendation

- **Move forward to Evidence Review**
- Review of the specific areas previously deficient:
  - **Improved screening test specificity for infantile form**
  - **Standardized method of diagnosis of pre-symptomatic infants**
  - **Benefit and harm of diagnosing late-onset Pompe disease during infancy**
  - **Review any cost or cost-effectiveness data**
  - **Impact on State Health Departments**
  - **New: Public health impact**

Pompe

Nomination and Prioritization:

Comments

and

Questions?