CHALLENGES TO TREATMENT OF INHERITED METABOLIC DISORDERS: THE SAUDI EXPERIENCE

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Saudi Population & Genetic Diseases

- High consanguinity rate
- Large family size
- Tribal structure
- Presence of isolates & semi-isolates

Treatment Challenges
Professionals-Related Challenges

- Shortage of:
  - Metabolic physicians
  - Metabolic nutritionists
  - Counselors

Number of metabolic physicians

- 2:758
- # births/year
  - ~450,000
- ~ 600 new cases/year
- ~ 100 new cases/metabolic physician/year
- ~ 40 new cases/metabolic physician/year

Number of metabolic dietitians

- 2:300 new cases/metabolic dietitian/year

Professionals-Related Challenges

- Inadequate assessment of neuropsychological outcome
- Inadequate professional education/awareness:
  - Delay in instituting treatment
- Generalization of the false impression of poor outcome in IMD:
  - Delay of prompt and properly aggressive ICU interventions
Laboratory-Related Challenges

• Shortage/Unavailability of biochemical diagnostic facilities
• Confirmatory tests are not available
  – Enzyme assay
  – Metabolites (pterins)
  – Complementation studies (MMA)
  – Mutation detection

• MS/MS related:
  – Fractionation of plasma isoleucine and leucine levels

• Delay of lab results:
  – Biochemical assessments for follow up cases

Disorders-Related Challenges

The National Neonatal Screening Program

• Organic Acidurias
  - Methylmalonic acidemia
  - Propionic acidemia
  - Isovaleric acidemia
  - Glutaric acidemia I
  - HMG CoA lyase def.
  - Beta-ketothiolase deficiency
  - 3MCC
  - Biotinidase deficiency

• Aminoaciopathies
  - PKU
  - MSUD

• FAOD
  - MCAD

• UCD
  - Citrullinemia
  - Argininosuccinic aciduria

• CHO disorders
  - Galactosemia

• Endocrine disorders
  - Congenital hypothyroidism
  - Congenital adrenal hyperplasia

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Organic Acidurias - Diagnostic Issues

- Confirmatory tests are not available
  - Enzyme assay
  - Complementation studies (MMA)
  - Mutation detection
- $B_{12}$ responsiveness assays (MMA)
  - in-vivo and in-vitro

Organic Acidurias - Treatment Issues

- Nutrition:
  - Formula/synthetic food:
    - Cost
    - Availability
  - Evaluation of nutritional status:
    - Shortage of specialized/dedicated metabolic nutritionists
    - Inadequate frequency of follow ups
    - Inadequate family/nutritionist communication
    - Inadequate nutritional laboratory assessments

Organic Acidurias - Treatment Issues

- Carnitine / Biotin / Glycine:
  - Availability
  - Physicians knowledge (ER physicians, Pediatricians)
- Bicarbonate:
  - Improper correction of severe metabolic acidosis:
    - Cerebral edema
    - Prolongation of imbalanced acid-base status

Organic Acidurias - Complications

- Acute complications:
  - Dialysis:
    - Lack of experts/experience on using hemodialysis
    - Delay of instituting dialysis in cases of severe unresponsive metabolic acidosis:
      - Call for guidelines

Organic Acidurias - Complications

- Chronic:
  - Neuropsychological outcome:
    - Shortage of pediatric psychiatrists and psychologists to assess neuropsychological outcome
    - Inadequate neurological evaluations for CNS deficits
    - Lack of psychosocial support and interventions
  - Renal complications:
    - Lack of interest/experience of adult nephrologists to follow organic acidurias cases.
    - The burden of kidney transplantation:
      - The Priority

Organic Acidurias - Complications

- Chronic:
  - Recurrent Pancreatitis
    - Prolonged hospital stay – recurrent
    - Hospital-acquired infections
    - The need for TPN – availability / cost
    - Social impact
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MSUD - Diagnostic Issues

- Mutation detection assays are not available:
  - Prevention
- MS/MS related:
  - Unknown plasma isoleucine level:
    - Over treatment
    - Improper a.a. supplementation
    - Skin changes
    - Poor growth
    - Unnecessary interventions:
      - High dextrose/insulin infusion
      - ICU care
      - Dialysis
      - Delay of hospital discharge

MSUD - Treatment Issues

Nutrition

- Formula/synthetic food:
  - Cost
  - Availability
- Shortage/lack of amino acids (Val, Ile) supplements
- Evaluation of nutritional status:
  - Improper use of MS/MS for follow ups instead of plasma amino acids analysis
  - Shortage of specialized dedicated metabolic nutritionists
  - Inadequate frequency of follow ups
  - Inadequate nutritional laboratory assessments
  - Inadequate family-nutritionist communication
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MSUD - Complications

- Acute complications:
  - Dialysis:
    - Lack of experts/experience on using hemodialysis
    - Delay of instituting dialysis in cases of severe leucine encephalopathy
    - Delay of the results of plasma amino acids:
      - On presentation
      - For monitoring
    - Clinical judgment – based intervention: not always accurate
    - Call for guidelines

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  - Dialysis:
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PKU
PKU - Diagnostic Issues

• Enzyme / Pterine measurements / Mutation detection assays are not available:
  – Confirmation of the hyperphenylalaninemia variant
  – Prevention

• No uniformity of protocols to detect biopterin metabolism defects
  – Biopterin metabolism defects
  – Biopterin-responsive PKU

PKU - Treatment Issues

Nutrition

– Formula/synthetic food:
  • Cost
  • Availability

– Underutilization of plasma amino acids analysis

– Evaluation of nutritional status

• Sinemet / BH4 / 5HT:
  – Availability
  – Cost

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UCD - Diagnostic Issues

• Enzyme and mutation detection assays are not available:
  – Confirmation
  – Prevention

• Spurious serum ammonia result – Unnecessary/Delay of interventions:
  – ICU care
  – Dialysis
  – Delay of hospital discharge

UCD - Treatment Issues

Nutrition

– Formula/synthetic food:
  • Cost
  • Availability

– Evaluation of nutritional status:
  • Underutilization of plasma amino acids analysis for follow ups
  • Shortage of specialized/dedicated metabolic nutritionists
  • Inadequate frequency of follow ups
  • Inadequate nutritional laboratory assessments
  • Inadequate family/nutritionist communication

UCD - Treatment Issues

– Arginine:
  – Availability

– Unavailable sodium phenylbutyrate (I.V.)

UCD - Treatment Issues

• Acute decompensation:
  – Dialysis:
    • Lack of experts/experience on using hemodialysis
    • Delay of instituting dialysis in cases of severe hyperammonemia

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MCAD - Treatment

- Management of acute decompensation:
  - Physicians awareness of:
    - Signs of acute presentation
    - The importance of prompt intervention

Galactosemia - Diagnostic Issues

- Detection of partial GALT deficiency

- Unavailable assays:
  - Mutation detection
  - Epimerase

Family/Social - Related Challenges

- Inadequate parents/family education
  - Compliance issues
- Implication of a “Genetic” disease on the family/tribe
- Inadequacy of counseling services
- No support groups
**Family/Social - Related Challenges**

- Inadequate services for other preventive measures:
  - Prenatal diagnosis
  - Preimplantation genetic diagnosis

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**System-Related Challenges**

- Maintaining the chain is a major undertaking:
  - Time of sampling/early discharge
  - Tracking of positive cases
  - Follow up of detected cases

- Efficiency of communication faces hurdles

- The wide geographic area poses a great challenge to every single element of the Program

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**System-Related Challenges**

- Inadequate evaluation of nutritional status:
  - Shortage of specialized/dedicated metabolic nutritionists
  - Unavailability of dietary products (semisynthetic diet, mixtures of a.a., modified protein hydrolysates)
  - Inadequate frequency of follow ups
  - Inadequate family/nutritionist communication
  - Inadequate nutritional laboratory assessments

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**System-Related Challenges**

- Inadequate assessment of neuropsychological outcome:
  - Shortage of pediatric psychiatrists and psychologists to assess neuropsychological outcome
  - Inadequate neurological evaluations for CNS deficits
  - Lack of psychosocial support and interventions

- No plan for multidisciplinary approach
System-Related Challenges

• Lack of:
  – Treatment guidelines
  – Consistency of management interventions
  – Consensus on outcome measures

System-Related Challenges

• The infrastructure of the health care system and integrating the Screening Program

System-Related Challenges

• Facility for diagnosis and treatment:
  – A single comprehensive center (KFSH&RC) serving the whole country
  – The goal of a comprehensive and efficient system may not be achievable
  – The need for more specialized centers

Administration-Related Challenges

Vision of the Program administration
• The comprehensiveness of the Program
  – Integration of follow-ups into the Program

• Pace of the Program expansion:
  • New disorders
  • New centers
  • New labs

• ? who evaluates/plans

Administration-Related Challenges

• Funding issues:
  – Screening (new technologies
  – Diagnosis
  – Management (formulas / medications
  – Follow up and evaluation
  – Education

• Poor involvement of the public/media

• Bureaucracy – not unexpected!
Despite these challenges:

A great opportunity still remains to overcome these issues

- The Program is still in its first stages.
- The high ambition, perseverance, and determination.
- Having the political support and decision has always been attainable.

THANK YOU