Hypergonadotrophic Hypogonadism In 2 Siblings With DIDMOAD Syndrome and Its Associations

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POSTER No. P-0572

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Hypergonadotrophic Hypogonadism with DIDMOAD

Background: Wolfram syndrome

- Rare hereditary / sporadic neurodegenerative disorder also known as **DIDMOAD** [WFS1 gene mutations - encodes an endoplasmic reticulum membrane protein called "**Wolframin**" that is expressed in **pancreatic beta cells and neurons**.]
- Insulin-dependent diabetes [**non-autoimmune**] optic atrophy, central diabetes insipidus, and sensory neural deafness.

Hypergonadotrophic Hypogonadism with DIDMOAD

Background: Wolfram syndrome

- Neurological and psychiatric manifestations
- Delayed puberty
- Central hypogonadism
- Anterior pituitary hormone dysfunctions –
 - **Secondary adrenal insufficiency**
- Urodynamic abnormalities
- Limited joint motility
- Cardiovascular and gastrointestinal autonomic neuropathy
- Heart malformations

Wolfram syndrome

Hypergonadotrophic Hypogonadism with DIDMOAD

Aim

- To describe **hypergonadotrophic hypogonadism** in the rare genetic autosomal recessive syndrome (**Wolfram Syndrome**) in 2 sisters.

Hypergonadotrophic Hypogonadism With DIDMOAD

Methods: A. Sibling 1

- Full term normal delivery;
- **Age 8** : Diabetes insulin dependent
- **Age 13** : Optic Atrophy
- **Age 18**: Diabetes insipidus
- **Age 16**: Menarche
- **Age 17**: Secondary amenorrhea,
 - Serum FSH :87.5 mIU/ml,
 - LH : 29.9 mIU/ml,
 - Testosterone: 6.9 ng/dl,

Hypergonadotrophic Hypogonadism With DIDMOAD

Methods: A. Sibling 1

- **US Abdomen**:
 - Small sized uterus,
 - Bilateral ovaries hypoplastic / agenesis
- **Age 17**: Bilateral minimal high frequency sloping hearing loss
 - **Right ear** PTA 25db, **Left ear** 23.3 db

Hypergonadotrophic Hypogonadism With DIDMOAD

Methods: A. Sibling 1

- **Short Stature**:
 - Height 146 cm; % ile: 0%; Z-score :-2.64;
 - Weight 39.4 kgs; % ile: 0%; Z-score :-3.13;
 - BMI-for-age 18.5; % ile:13%; Z-score :-1.11;
- **Serum Growth Hormone post clonidine**:
 - 6.99 ng/ml

Hypergonadotrophic Hypogonadism With DIDMOAD

Methods: B. Sibling 2

- Full term normal delivery;
- **Age 4**: Diabetes insulin dependent;
- **Age 15**: Optic Atrophy;
- **Age 17**: Diabetes insipidus;
- **Age 15**: Menarche;
- **Age 16**: Secondary amenorrhea,
 - Serum FSH 87.8mIU/ml,
 - LH 31.7 mIU/ml,
 - Testosterone 16.3 ng/dl.

Hypergonadotrophic Hypogonadism With DIDMOAD

Methods: B. Sibling 2

- **US Abdomen**:
 - Small sized uterus,
 - Bilateral ovaries hypoplastic / agenesis,
 - Left side hydronephrosis;
- **Age 16**:
 - Left minimal hearing loss [Left ear 16db].
 - Right normal hearing [Right ear PTA 10db].

Hypergonadotrophic Hypogonadism With DIDMOAD

Methods: B. Sibling 2

- **Short Stature**:
 - **Height** :151 cm; % ile: 3%; Z-score : -1.87;
 - **Weight** : 40.2 kgs; % ile: 0%; Z-score : -2.89;
 - **BMI-for-age** 17.6; % ile: 5%; Z-score : -1.61;
- **Serum Growth Hormone post clonidine**:
 - 7.94 mg/ml.

Hypergonadotrophic Hypogonadism With DIDMOAD

Conclusion

- Wolframs syndrome being a **progressively devastating multisystem degenerative disorder** can have myriad other manifestations than the classically described features.
- **Premature death** occurs by the fourth decade of life.
- **Short stature** is a common feature in WFS.
- **Hypogonadism** may be hypogonadotropic or hypergonadotrophic [more reports in males].

Samatvam – Jnana Sanjeevini

Dr S S Srikanta

Big shot Doc who gives free insulin

Diabetes runs in the blood of Bangalore-based Dr S S Srikanta. Which is why when you ask the good doctor how many children he has, prompt comes the reply: "I have 7,800 diabetic children all over India!" Through Samatvam, a medical trust he

Childhood Diabetes Clinics, Residential Diabetes Camps and Patient Parent Support Groups

Location of mutations leading to Wolfram Syndrome

The genetic mutation that causes this disease takes place on the WFS1 gene of chromosome 4p16, or the upper arm of the fourth chromosome, and leads to the inability to produce a protein called Wolframin.

Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype

■ **Insights into Wolfram syndrome.** (a) Natural history of WS. The proportion of patients (density) for each clinical feature at onset age, measured as a nonparametric probability density distribution, is plotted. (b) Probability of development of WS clinical features by age group. The probability of developing each of the clinical features over age, calculated using a life-table analysis, is displayed.

Genetics in Medicine (2013) 15, 497–506

Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype

■ (d) Order of clinical feature onset in WS. The order in which each clinical feature appears is shown as the percentage of patients with that clinical feature. DM (n = 385); OA (n = 322); HD (n = 189); DI (n = 148); ND (n = 67); UD (n = 72). DE, deceased; DI, diabetes insipidus; DM, diabetes mellitus; HD, hearing defects; ND, neurological, psychiatric, and developmental defects; OA, optic atrophy; UD, urological or renal defects; WS, Wolfram syndrome .

Genetics in Medicine (2013) 15, 497–506