Tamoxifen Treatment for Pubertal Gynecomastia in a Patient with Partial Androgen Insensitivity Syndrome

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Introduction: Androgen insensitivity syndrome (AIS) is a sex development disorder that causes varying degrees of virilization defects in 46,XY individuals. The cases diagnosed with partial AIS (PAIS) can present with many different clinical findings including ambiguous genitalia from female phenotype with cliteromegaly to male phenotype with hypospadias, cryptorchidism, azoospermia, and pubertal gynecomastia. In PAIS patients, pubertal gynecomastia can develop and affect the quality of life. There is no standard protocol for its treatment. Here, we discussed a PAIS patient with pubertal gynecomastia and the effect of tamoxifen, a pure estrogen receptor modulator, in treatment.

Case: The patient admitted to our clinic at 3.2 years of age with ambiguous genitalia and his physical examination revealed Sinnecker stage 3 genital phenotype. Gonads were bilateral testis, internal genitalia were male, and karyotype was 46,XY. There was no testosterone synthesis problem that was revealed with human chorionic gonadotropin stimulation test (stimulated total testosterone: 532 ng/dL). Androgen receptor gene analysis showed two silent mutations (no amino acid changes) in exon 1 (p.Glu213Glu) and exon 7 (p.Ile817Ile). Corrective operations for cryptorchidism and hypospadias were performed and testosterone and dihydrotestosterone gel were used for the treatment of micropenis. When the patient was 12.3 years old, bilateral gynecomastia was observed at stage T3. At 13.5 years old, gynecomastia advanced to stage T4 and tamoxifen treatment 20 mg/day was started. After six months of the therapy, the dose was increased to 40 mg/day. At the 7th month of treatment, a dramatic regression of gynecomasty was observed.

Results: In PAIS patients with pubertal gynecomastia, difficulties in treatment may be observed. Surgery is not recommended because of the side effects such as skin retraction, hypertrophic scar, hypesthesia, and skin excess. Tamoxifen treatment can be an effective therapeutic option especially in PAIS patients with significant pubertal gynecomastia.

Key words: Tamoxifen, pubertal gynecomastia, androgen insensitivity syndrome

Genetic Diagnosis Using Whole Exome Analysis in Two Cases with Malignant Infantile Osteopetrosis

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Aim: Osteopetrosis is caused by autosomal mutations occurring in nine genes (*TNFRSF11A, TNFSF11, TCIRG1, CLCN7, OSTM1, SNX10, PLEKHM1, CA2, LRP5*). Detecting the etiology and providing genetic counseling via individual mutation analysis of all these genes is expensive and time consuming. Whole exome sequencing is currently increasingly used given that the cost and the time needed are similar to that of single gene sequencing analysis. Here, we present two newborns, genetic evaluations of whom were made with whole exome analysis.

Methods: We examined a nine-day-old male patient who was born to non-consanguineous parents and who had bicytopenia and hypocalcaemia and a six-day-old female patient with hypocalcaemia, whose parents were first cousins and elder brother had died due to osteopetrosis. The newborns were diagnosed with malignant infantile osteopetrosis on clinical and radiological grounds. Their DNA samples were extracted from peripheral blood. Exome sequencing data generated in genotypic (India) using HiSeq 2500 sequencer were analyzed in Intergen Genetics Center.

Results: 31382 variants were detected in the first case. Among the possible genes in etiology, a novel heterozygous mutation (c.718G>A), which was predicted to be most likely a disease-causing mutation with in silico analyses, was detected in *CLCN7*. Another mutation was also detected using whole gene Sanger sequencing (compound heterozygous c.398_401delTTGG/c.718G>A). 32 529 variants were detected in the second case. A previously reported homozygous nonsense mutation c.2236C>T in *TCIRG1* was detected and confirmed using Sanger sequencing.

Conclusion: Whole exome analysis is a useful method for diseases in which multiple genes play role in the etiology. It should be kept in mind when heterozygous mutations are detected in autosomal recessive diseases that exome sequencing may not evaluate 5% of coding regions and relevant gene should be reanalyzed by Sanger sequencing.

Key words: Osteopetrosis, novel heterozygous mutation, bicytopenia, hypocalcaemia, exome sequencing