Rud’s Syndrome

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Rud’s syndrome (RS), basically composed of ichthyosis, mental deficiency and hypogonadism, is a rare hereditary disease. Some varying dermatologic, neurologic, endocrinologic, ophthalmologic and musculoskeletal abnormalities have coincided with RS. No case of RS has been documented from Asian countries except one from Japan. We describe a 16-year-old girl who presented with lamellar ichthyosis, mental retardation, hypogonadism, short stature, alopecia, sparse eyebrows, strabismus, cataracts, and congenital dislocation of the hip. To our knowledge, RS coexisting congenital dislocation of the hip herein is the first case in English literature. (Ann Dermatol 12(3) 206~210, 2000).

Key Words : Rud’s syndrome, Lamellar ichthyosis, Mental retardation, Hypogonadism

Ichthyosis can be associated with a variety of other systemic disorders, among which a syndrome consisting of ichthyosis, infantilism, hypogonadism, epilepsy, tetany, anemia and polyneuritis was first described by Rud in 1927. Since then, mental retardation, some new neurologic and endocrinologic abnormalities had been added in most of the reports describing Rud’s syndrome (RS). RS needs to be differentiated from other syndromes that are made up of a similar combination of multisystemic disturbances.

We report a case of a 16-year-old Korean female who had distinct RS with lamellar ichthyosis, mental retardation and hypogonadism. Aside from those hallmark components, short stature, alopecia, strabismus, cataracts, and congenital dislocation of the hip were combined. We also reviewed the literature of RS.

CASE REPORT

A 16-year-old Korean girl was referred to Dermatology by Orthopedic Department for skin problems. The extremities including flexural areas and the trunk were covered with large platelike scales in a mosaic pattern (Fig.1 & 2). In some areas, the scales were centrally attached with raised borders. The scales tended to be largest and separated by superficial cracking over the lower extremities, and to a lesser extent, over the upper extremities as well. Ichthyotic change became apparent at the age of 2 to 3 years. She continued to complain about itching on the whole body. Lips, mucous membranes, palms and soles were spared, but increased creases were observed on the palms. Both of her eyebrows were sparse (Fig. 3). There was neither pubic nor axillary hair growth. Large patches of alopecia were found on the scalp (Fig. 4).

On admission, her weight and height was measured as 35kg and 122cm, respectively. She had no significant medical problems before admission. She had strabismus and once underwent phacoemulsification for the treatment of cataracts. She has long suffered from limping gait due to a dislocated hip. Her menstrual cycle has not yet started.

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The dull-looking facies (Fig. 3), slurred and distracted speech, and weak vocabularies were suggestive signs of mental deficiency. Because she was unable to follow the regular curricula, she was sent to the specialized teaching institution run by the government. Her family was financially supported by social welfare.

In the complete blood cell count with differential count, white blood cells, hemoglobin, platelets were within normal limits. Erythrocyte sedimentation rate (33 and 50 mm/hr) and C-reactive protein (1.7 mg/dl) were elevated. Values for serum electrolytes, glucose, liver enzymes, creatinine, urea nitrogen, and complements were normal. Serologic tests for syphilis and hepatitis were negative. In hormonal analyses, thyroid stimulating hormone, free thyroxine, prolactin, adrenocorticotropic hormone, 17-ketosteroid were normal, but follicle stimulating hormone (FSH, 2.6 mIU/ml), leutinizing hormone (LH, 3.7 mIU/ml), estradiol (9.8 pg/ml), dehydroepiandrosterone sulfate (DHEA, <0.2 µg/dl) were decreased. With the normal range of low density (beta) lipoprotein, total serum cholesterol (263 mg/dl) was increased, and high density lipoprotein (33 mg/dl) was decreased in serum lipoprotein electrophoresis. Urine analysis for proteinuria, vanillylmandelic acid, 5-hydroxy indoleacetic acid were not remarkable. Radiologic investigations demonstrated no abnormality in the skull view, otherwise the dislocation of the left hip with corrective osteotomy in pelvic view (Fig. 5). Computed tomography of the brain was not done.
Fig. 5. Radiologic view of congenital dislocation of the left hip after corrective osteotomy with implant.

Fig. 7. Pedigree of the family. Arrow denotes proband. The parents and three of the siblings were unaffected.

No evidence for epilepsy was found in the electroencephalography. The chromosomal study showed no abnormality. No retinitis pigmentosa was detected by ophthalmologist.

A skin biopsy specimen from the leg revealed moderate hyperkeratosis and a layer of granular cells with no acanthosis or papillomatosis (Fig 6).

DISCUSSION

RS is known to be inherited as autosomal recessive trait, and X-linked mode cannot be ruled out. None of the patient’s family members was affected with RS (Fig. 7). The triad of ichthyosis, mental retardation and hypogonadism is regarded as the most common features associated with RS. Less common features represent epilepsy, short stature, chromosomal abnormalities, obesity, muscular atrophy, visual and hearing disturbances, diabetes mellitus, retinitis pigmentosa, and polyneuritis. Meanwhile, owing to the fact that some of RS are overlapped with other syndromes linked to the ichthyoses and that they do not constitute a single nosologic entity, the definition of RS may be at times confusing. Even the use of this term is debatable. Major differential diagnosis includes Refsum’s disease, Sjoegren-Larsson syndrome, KID syndrome and Netherton’s syndrome (Table). Kissel et al. reported coexistence of RS and Sjoegren-Larsson syndrome in the same family.

The chief skin manifestation of RS indicates X-linked ichthyosis, lamellar ichthyosis or nonbullous congenital ichthyosiform erythroderma. The occasional skin manifestations are acanthosis nigricans, alopecia, hyperkeratosis or hyperhidrosis of the palms and soles. Maldonado et al. offered a classification of RS in 3 groups: neuroichthyosis with hypogonadism, neuroichthyosis with spasticity, neuroichthyosis without hypogonadism. The cases of RS were largely reported from European countries such as France, Russia, Poland, Switzerland, Romania, Spain and Italy. In these reports, most of the patients were females widely aged from infancy to adulthood. It is notable that all the cases were involved in ichthyosis, mental deficiency and hypogonadism, and less frequently in epilepsy and chromosomal abnormalities. Interestingly, in our case, we list involvement of the eyes and skeletal system that have least likely been affected in prior reports.

It is proposed, when diagnosing RS, that serum hormonal and lipoprotein assays should be of much help. As these kinds of simple and less expensive screening tests can be available almost in every hospital, results of which will give concrete clues for lack of secondary sex characteristics and for specific lipoprotein patterns of ichthyoses. In cases that X-linked ichthyosis is accompanied by RS, serum cholesterol sulfate, or fast beta band is raised. Addi-
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Table: Systemic variants of ichthyosis, cited and summarized from reference 4.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mode of inheritance</th>
<th>Age of onset</th>
<th>Clinical appearances</th>
<th>Associated features</th>
</tr>
</thead>
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<tr>
<td>Rud’s syndrome</td>
<td>autosomal or X-linked recessive</td>
<td>infancy</td>
<td>lamellar ichthyosis</td>
<td>dwarfism; mental deficiency; hypogonadism; epilepsy</td>
</tr>
<tr>
<td>Refsum’s disease</td>
<td>autosomal recessive</td>
<td>childhood</td>
<td>mild, variable ichthyosis</td>
<td>polyneuritis; nerve deafness improves with dietary</td>
</tr>
<tr>
<td>Sjoegren-Larsson</td>
<td>autosomal recessive</td>
<td>birth</td>
<td>mild lamellar ichthyosis</td>
<td>restriction of phytic acid spastic paralysis; mental</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td></td>
<td></td>
<td>retardation; macular retinal degeneration</td>
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<tr>
<td>KID syndrome</td>
<td>autosomal dominant and recessive</td>
<td>birth or childhood</td>
<td>dry, erythema, verrucous plaques, progeria appearance</td>
<td>keratitis; neurosensory deafness, squamous carcinoma</td>
</tr>
<tr>
<td>Netherton’s syndrome</td>
<td>autosomal recessive</td>
<td>birth or infancy</td>
<td>ichthyosis linearis circumflexa, trichorhesis invaginata</td>
<td>stunted growth; mental retardation</td>
</tr>
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tionally, electroencephalography (EEG) and chromosomal analysis should be performed to confirm the diagnosis of RS. Epileptic traces on EEG can be selectively determined in RS.4 Xp (short arm of chromosome X) deletion may be related to stunted growth, hypogonadism and anosmia11. In X-linked ichthyosis, gene mapping with X-Y translocations placed the steroid sulphatase gene at the Xp 22.3 locus12. Linkage between the transglutaminase 1(TGM-1) locus and lamellar ichthyosis was proved13. In our case, not only failure of sexual development but also decreased values for FSH, LH and estradiol can be in favor of hypogonadotropic hypogonadism. However, it appears to be a drawback not to proceed with the studies necessary for uncovering the cause of hypogonadotropic hypogonadism. Some authors insisted that RS could be the variant of X-linked ichthyosis. Because our case had lamellar ichthyosis instead of X-linked ichthyosis, we did not check the level of cholesterol sulphatase. Based on the normal outcomes of EEG and chromosomal study in our case as compared with the cases in Europe, epilepsy and genetic mutations in RS seem to possibly occur in terms of ethnic discrepancy. The findings in our case illustrate RS uniquely with congenital dislocation of the hip which is postulated to be one of the auxiliary components though a coincidence cannot be excluded.

Histological findings of lamellar ichthyosis generally demonstrated mild to marked hyperorthokeratosis, a normal to increased granular layer and acanthosis5, 14. As to our biopsy specimen, we observed moderate hyperkeratosis and a layer of granular cells, reflecting that histological categorization of ichthyosis can somehow vary.

The treatment for ichthyotic skin in RS was not satisfactory. Topical keratolytic agents and topical vitamin A(retinoid) or vitamin D(calcipotriol) preparations can be beneficial, but sometimes irritating15. Systemic retinoid therapy with isotretinoin or acitretin can induce much improvements, but possible adverse effects must be considered16. We treated this patient with topical emollients and corticosteroids first. After the itching was considerably relieved, urea and calcipotriol ointments were alternatively administered, leading to a good effect.

REFERENCES