Appendix S1

SUPPLEMENTARY MATERIAL

Clinical features of patients with hyaline fibromatosis syndrome

Patient 1 died at the age of 2 years due to failure to thrive and complications of severe and chronic diarrhea, and protein-losing enteropathy. The parents of the proband were referred for genetic counseling and prenatal diagnosis. They were first cousins and healthy with no family history of genetic diseases. The patient was born by vaginal delivery after a full-term pregnancy. At the time of birth there were minimal manifestations related to disease but he started to show progressive flexure of the swollen large joints which were clearly painful at ~6 months of age. The growth parameters were normal at birth, but weight, height and head circumference at 18 months of age were 5.1 kg, 68 cm and 44 cm, respectively. The patient showed enlargement of tissues of the gingival and perioral region, and there were several masses in perianal area. He was not ambulatory and could not speak. The hair was blond and there were regions of hyperpigmentation in lateral malleoli and lumbar area. His face was typical of hyalinosis patient with low set and prominent ears, deep seated eyes and proptosis.

Patient 2 was a 1.5 year-old girl born by planned Caesarean section after an uneventful full-term pregnancy. The parents were healthy second cousins. Their first child succumbed in the second year of his life to complications of HFS. The weight, height and head circumference of the patient at birth were 3.5 kg, 48 cm and 34 cm, respectively. During the neonatal period, the patient showed apparent flexural contractures of joints and "frog-legged" position due to limitation in movements of joints (Fig. 1f). Main reasons for initial referral of the patient were severe pain induced by movement, severe chronic diarrhea, protein-losing enteropathy, feeding problems and failure to thrive. Her weight was about 6 kg, i.e., below the second percentile. Low set and prominent ears, deep seated eyes, depressed nasal bridge, gingival hyperplasia and multiple pearly papules on her face and nuchal area were evident (Fig. 1e, g). Areas of livid red hyperpigmentation were noted at the prominent sites of body, e.g., in lateral malleoli, wrists and elbows. Thickened skin was palpable on examination.

Patient 3, a 3.5-year-old girl was the only child of healthy consanguineous, first cousin parents. The mother noticed decreased fetal activity during her pregnancy, and the proband was born by elective Cesarean section. The family history was negative for birth defects and genetic diseases. The birth weight, height and head circumference were 2.7 kg, 51 cm and 35 cm, respectively. At birth, the patient showed unilateral congenital equinovarus and swollen and painful joint contractures. Cutaneous findings consisted of thickened skin, subcutaneous nodules under the earlobe and the nuchal area, hyperpigmented skin over bony prominences and fleshy perianal plaques. There was no history of chronic diarrhea and brain function was apparently normal. Patient was alert and could speak and comprehend well. She had coarse facial features, including proptosis, low set and prominent ears, and depressed nasal bridge. There was a nodular tumor developing on the head (Fig. 1a). Following intensive physiotherapy she was ambulatory with the use of walking aids.

Patient 4, a 1-year-old girl, was the only child of distantly related consanguineous parents. Their first child also succumbed in the first year of her life with similar disease manifestations, including severe and chronic diarrhea, weight and height were 3.7 kg, and 60 cm, respectively. Flexural contractures of joints and limitations in movements of small and large joints with pain were noted. The patient also had immunodeficiency, and infantile pyloric stenosis (managed by surgery). She had coarse facial features, including proptosis, low set and prominent ears, and depressed nasal bridge. There were no masses in perianal area or enlargement of tissues of the gingiva.