First reported case of alpha-mannosidosis in the RSA

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Abstract

The first known case of α-mannosidosis in the RSA is reported. Presentation was classic, viz. delayed speech, kyphoscoliosis and hearing loss at the age of 4 years. Among the generally rare inherited lysosomal storage diseases, α-mannosidosis is regarded in Europe and the USA as one of the more common disorders. It is suggested that the apparent underdiagnosis in South Africa may stem from lack of clinical recognition of a condition, which is relatively simple to diagnose biochemically. The clinical and radiological features of the child are described in the hope that clinicians will develop an awareness of the disorder, and include it in the differential diagnosis of deaf children who may also have mild skeletal abnormalities. Antenatal diagnosis of this untreatable condition is possible, so the birth of further affected children in a family could be prevented.

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ALPHA-MANNOSIDOSIS is a lysosomal storage disorder which together with aspartylglycosaminuria, sialidosis and α-fucosidosis, is classified as a glycoproteinosis, since the metabolic defect involves faulty catabolism of the oligosaccharide side chain of glycoproteins. The progressive accumulation of undegraded complex carbohydrate molecules in various tissues leads to a wide clinical spectrum of abnormalities, such as skeletal deformities, psychomotor retardation and somatic manifestation, e.g. facial coarsening and cardiovascular complications.

The first case of α-mannosidosis was described by Öckerman in 1967,[1] and subsequently more than 80 cases[2] have been reported. The condition is biochemically not only well understood but so frequently encountered in Europe and the USA that new cases are seldom published. As this report represents the first recognised South African case of α-mannosidosis, we feel that local clinicians should be made aware of its existence in our population, since it is likely that further cases may exist undiagnosed. There is no treatment for this autosomal recessively inherited condition other than symptomatic management. At present the only approach to the prevention of further affected offspring in a family is that of genetic counselling, prenatal diagnosis and the option of selective termination of affected pregnancies.

Case report

The patient is the second child born to parents of mixed ancestry, who are second cousins, after a period of secondary infertility. The older and younger siblings are clinically normal. Delivery at full term was by caesarean section due to fetal distress and cephalopelvic disproportion. The patient's birth weight was 3 800 g (> 50th centile), head circumference 34,5 cm (50th centile) and the length was given as 50 cm (50th centile). The Apgar score was 4 and 7 at 1 and 5 minutes, respectively. According to the mother, the propositus was a healthy child who attained the milestones of smiling, sitting, and walking within normal limits, but never achieved speech. At 15 months of age a gibbus developed, which was examined elsewhere (see discussion of radiological findings). The patient underwent tonsillectomy at 4 years, after which he was referred to the Ear, Nose and Throat Department of Tygerberg Hospital for evaluation of his delayed speech and possible deafness. A 30 - 40 dB sensorineural hearing loss was found.

On examination, the patient was a large, strong child with a mass of 17,8 kg (90th centile), height 102,4 cm (75th centile) and head circumference on the 50th centile. His face appeared somewhat coarse (Fig. 1) with a notably square jaw and prominent tongue. The fontanelles were closed and the nose, mouth and ears were normal. The thorax showed pectus carinatum. There was a marked thoracolumbar kyphosis and protruding abdomen with an umbilical hernia, but no organomegaly. The cardiovascular, respiratory and genito-urinary systems were normal, as were the limbs. The patient was extremely unco-operative during evaluation, and appeared mentally dull with unintelligible speech. He was found to function on the level of a 3-year-old.

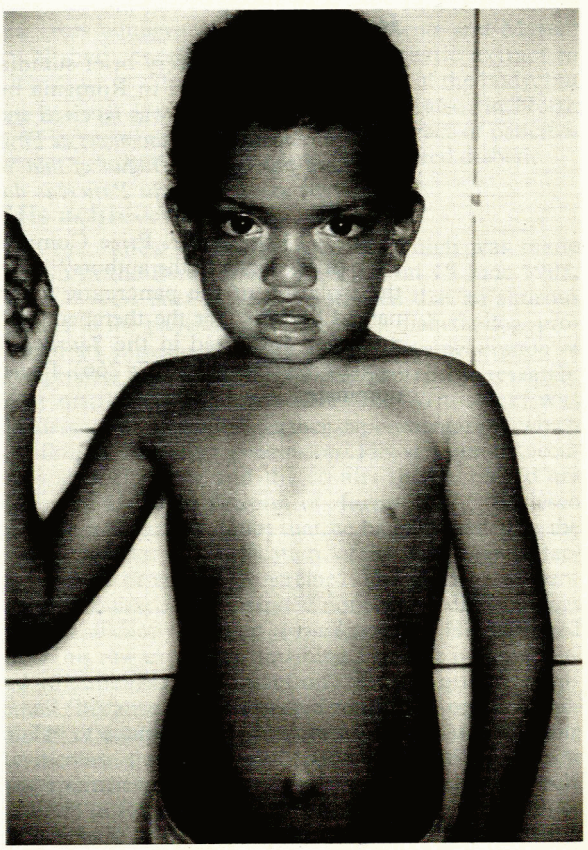

FIG. 1.
Patient at 4 years of age, showing the coarse facies.

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Radiography of the spine showed flattening of the thoracic vertebrae with anterior wedging in the T12/L1 region, hypoplasia of L1 and kyphosis (Fig. 2). The ribs were spatulate, while the skull radiograph showed calvareal thickening and a J-shaped sella turcica. The phalanges were abnormal with coning and broadening of the metacarpals, contributing to an overall pattern of mild 'dysostosis multiplex', which is characteristic of most complex carbohydrate storage disorders.

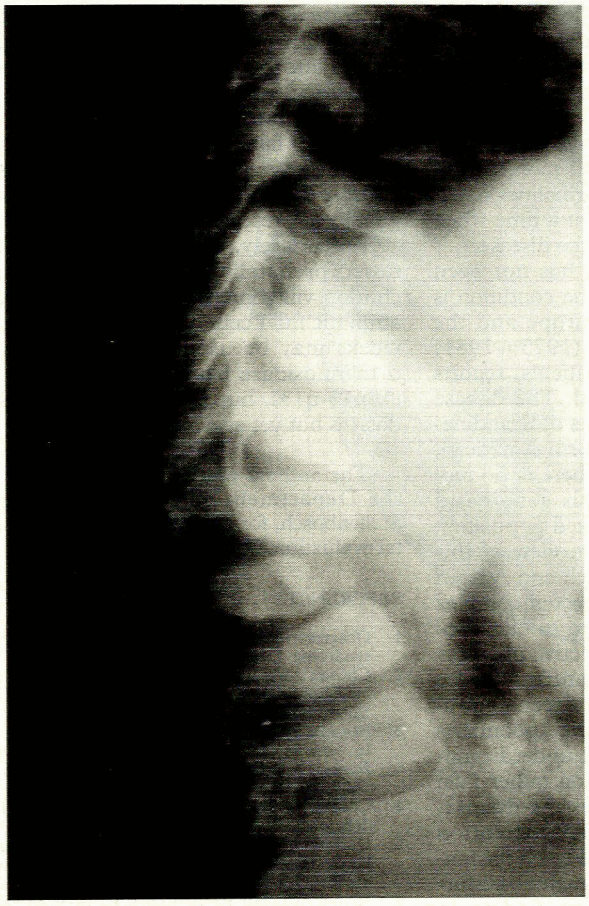

FIG. 2.
Radiograph of thoracolumbar vertebrae (lateral view).

These findings prompted a preliminary clinical diagnosis of mucopolysaccharidosis, but this was excluded by the absence of abnormal or excess mucopolysaccharides in the urine. Thin-layer chromatography of total urinary oligosaccharides, however, showed multiple abnormal bands in the 'rugby jersey' striped pattern typical of mannosidosis (Fig. 3). Neither sialylated oligosaccharides nor free sialic acid was present. The diagnosis of α-mannosidosis was confirmed by the profound deficiency of α-mannosidase activity measured in the serum, Epstein-Barr virus-transformed lymphoblasts and cultured fibroblasts from the patient, while reduced levels in the parents demonstrated their heterozygosity (Table I). Chromosome analysis of the patient was normal.

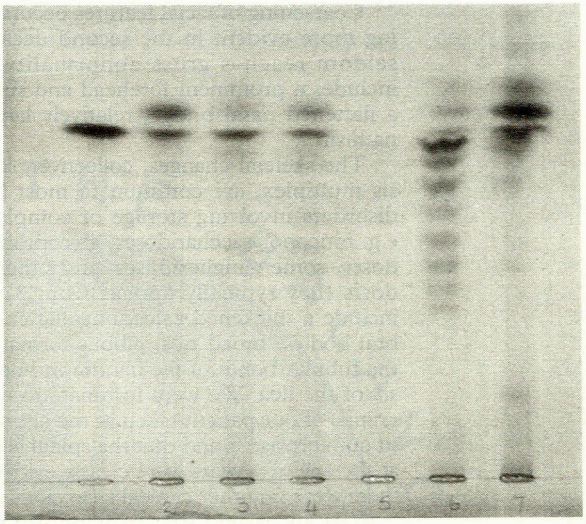

FIG. 3.
'Rugby jersey' pattern of α-mannosidosis (see text).

Urine from the proband's younger sister contained no abnormal oligosaccharides. The older brother, aged 13 years, has not been examined but is reportedly normal. Carrier testing on these siblings was refused by the parents.

Discussion

To the best of our knowledge, this is the first patient with α-mannosidosis described in the RSA. Some authors differentiate between a severe infantile form (type I), with obvious hepatosplenomegaly, severe skeletal involvement and rapid psychomotor retrogression to an early childhood death, and a milder juvenile-adult phenotype (type II).[2] Clinical heterogeneity causes broad overlap of these two categories, and our patient, like the majority of published cases, presented with a history typical of the intermediate or 'moderate' form of the disease.[3]

These patients seem to be healthy at birth, with normal milestones throughout infancy and even sometimes in early childhood. Recurrent respiratory and ear infection become troublesome during the first 2 years of life and gradually lessen with time. Signs of delayed development gradually progress, appearing first at between 1 year and 4 years of age. Delayed development of speech is often the presenting symptom. Hearing loss may be partly due to repeated infections, but sensorineural damage of varying degree seems to be the rule in these children. This may be contributory or causally the reason for the speech and pronunciation defects, but problems in the field of auditory discrimination, auditory perception and auditory memory have also been described.

Apart from clumsiness, ataxia is the most characteristic motor disturbance and often appears as early as 3 years of age. Progressive impairment of motor function follows, but only rarely to the extent of prevention of movement in adult life.

TABLE I.
Alpha-mannosidase measurements

	Serum (nmol/min/ml)	Fibroblasts (nmol/h/mg)	Lymphoblasts (nmol/h/mg)
Patient	0,08	1,82	0,73
Mother	0,58	20,04	55,0
Father	0,32	21,93	80,5
Controls (mean ± SD)	1,19 ± 0,51 (N = 23)	40,03 ± 3,12 (N = 5)	109,0 (N = 1)

Coarsening of facial features occurs with age, becoming more evident in the second decade, although this seldom reaches gross abnormality. Typically, this includes a prominent forehead and supra-orbital ridges, a flattened nasal bridge, relatively large ears and prognathism.

The skeletal changes, collectively known as dysostosis multiplex, are common to most lysosomal storage disorders involving storage of complex carbohydrates, e.g. mucopolysaccharidoses, glycoproteinoses, mucolipidoses, some gangliosidoses, and others. In α-mannosidosis they typically appear from 3 years of age and include a thickened calvarium, flattened thoracic vertebral bodies, broad ribs, gibbus formation, expansion of the tubular bones of the hands, and occasional hypoplasia of the ilea. We were fortunate to obtain early radiographs of our patient taken at the age of 15 months, and to our surprise found that the spinal abnormalities noted at the age of 4 years were clearly evident at a time when there were no other clinical suspicions of the disease.

It is surprising that α-mannosidosis has not been previously diagnosed in the RSA, since the condition is relatively frequently encountered in Europe and the USA. For example, in the 7-year period (1975 - 1981) following the description of the first 6 patients, reports of a further 61 new cases were published. The disease appears to be pan-ethnic, affecting patients of Scandinavian, Western and Eastern European, North American, Arabian, African and Japanese origin.[2] There is no reason to suppose that the α-mannosidosis gene has a lower frequency in the large and very mixed population of the RSA than elsewhere, especially in view of this country's considerable proportion of Dutch and African genes. The majority of patients with suspected complex carbohydrate storage disorders are referred to our laboratory in Cape Town, and the very distinctive oligosaccharide pattern of α-mannosidosis is unlikely to be missed by the thin-layer chromatography screening procedure routinely performed on all urine specimens received. It seems likely that the apparent underdiagnosis resides at the level of clinical recognition rather than biochemical demonstration, particularly as the dysmorphology may be subtle and the clinician's attention focused on the deafness, which is assumed to be the reason for the speech difficulties and poor mental performance. It is hoped that documentation of the findings in this patient will heighten awareness of the condition and aid in the recognition further cases.

By comparison ß-mannosidosis deficiency, although well known in goats and long predicted in man, has only recently been described.[4] Although originally thought to be a milder condition manifesting only in nerve deafness and mental retardation,[4,5] the clinical spectrum has now widened to include gargoyle facies, bone deformities, severe psychomotor retardation[6] and possibly epileptic encephalopathy.[7] Its frequency is as yet unknown, and its very variable presentation may mimic that of α-mannosidosis, and make its definitive diagnosis a biochemical rather than a clinical one.

Although no treatment is available for α-mannosidosis, competent clinical management often allows survival into adulthood. Apart from the inevitable mental retardation and clinical problems, this condition has economic and social implications for the family. Repeated respiratory infections and orthopaedic complications are a drain on family/state resources. Delayed development and deafness will usually necessitate special schooling/training facilities, of which the RSA unfortunately has a paucity at present.

Fortunately, this syndrome may be reliably diagnosed prenatally by means of biochemical assays. A chorion villus biopsy at 9 - 11 weeks gestational age or amniotic fluid cells obtained by amniocentesis at 15 - 20 weeks may be used for this purpose. The gene for α-mannosidase has been mapped to chromosome 19 (19p13-q13), but DNA-based diagnosis of α-mannosidosis is not yet available.

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