Progressive vitiligo, mental retardation, facial dysmorphism, and urethral duplication without chromosomal breakage or immunodeficiency

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Abstract

A boy, born to first cousin parents of Algerian origin, first presented at the age of 9 years with growth failure, mental retardation, and dysmorphic facies. Progressive vitiligo developed from the age of 12 and distal duplication of the urethra was later recognised. The basis of this syndrome remains to be determined; autoimmune disease, chromosomal breakage syndromes, and other neurocutaneous syndromes have been excluded.

Neurocutaneous syndromes are a well classified group of disorders, and new entities are described regularly. We report here a boy who presented with retarded growth, moderate microcephaly, mental retardation, progressive vitiligo, and urethral duplication. Neither immunodeficiency nor chromosomal breakage could be detected. Thus, this clinical association may represent a new syndrome.

Case report

This boy is the fourth child of first cousin Algerian parents whose first three children were normal. He was born in Algeria and his weight and length were said to be normal at birth. However, his psychomotor development was considered to be slower than it had been in his three sibs. The child was first admitted to our unit at the age of 9 years. His height was 115 cm (-3 SD), weight was 18.5 kg (-2 SD), and head circumference was 50 cm (-2 SD).

Mild facial dysmorphism was noted with a beaked nose and a high, narrow palate. Moderately severe mental retardation was also present (IQ 65 on the Stanford-Binet scale). Complete blood cell count, serum and urine electrolytes, and liver tests were normal, as were serum and urine amino acid chromatography. The karyotype (enzymatic denaturation, 15 metaphases studied) did not show any cytogenetic abnormality. At the age of 12 vitiligo was first noted.

The patient was readmitted at the age of 15 years. His height was 140 cm (-3 SD), weight was 29 kg (-2.5 SD), and head circumference was 50 cm (-3 SD). The facial dysmorphism (fig 1) and mental retardation were still present. Disseminated vitiligo was also noted (fig 2). Physical examination showed moderate macrogenitosomia and two separate urethral meatuses, while pubertal development was progressing. Ophthalmological examination proved normal, as did total skeletal radiographic examination. Antinuclear factors, anti-DNA autoantibodies, and Waaler-Rose latex test were negative in serum. Complement components were normal and the search for numerous serum autoantibodies was negative (anti-smooth muscle, anti-mitochondria, anti-thyroid, anti-gastric, anti-insulin, and anti-islet cells). Thyroid hormones, ACTH, and cortisol plasma concentrations were normal. A second karyotype was performed (cultured with trimethoprim, 58 metaphases studied) and no evidence of fragile X was found. At the age of 17, his height was 155 cm, his weight was 35 kg, and his head circumference was 51 cm. Vitiligo had progressed and the skin

Figure 1 Facial profile of the child showing the mild dysmorphism (beaked nose) and the vitiligo.

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Received 30 July 1991.
Revised version accepted
2 January 1992.

Figure 2 (Left) vitiligo at the age of 15, (right) increase of the vitiligo at the age of 17.

was almost completely hypopigmented (fig 2). Mental retardation was unchanged. There was still moderate macrogenitosomia with two visible urethral meatuses (fig 3). Cystography showed a distal duplication of the urethra, ending with two meatuses. Audiometric testing, cerebral magnetic resonance imaging, and abdominal ultrasound examination were normal. The results of immunological studies are shown in the table. No evidence of immunodeficiency was found. A third karyotype was performed without addition of chromosome

Figure 3 Moderate macrogenitosomia with two visible urethral meatuses.

breakage inducing agents (R banding after stimulation with phytohaemagglutinin and IL2): no chromosomal breakage was observed in 50 mitoses (Dr Aurias, Institut Curie, Paris).

Discussion

Our patient presented with retarded growth, mental retardation, progressive vitiligo, and urethral duplication, with normal immunological and cytogenetic studies. The close parental consanguinity suggests that this disorder is transmitted as an autosomal recessive trait.

Vitiligo is known to be a marker for certain autoimmune diseases, such as thyroid or Addison's disease. These disorders were excluded in our patient since plasma hormone concentrations were normal and no autoantibodies were found. Vitiligo has also been reported in syndromes such as the Ermine phenotype,¹ but our patient had no evidence of hearing loss.

Several possibly related neurocutaneous syndromes have been previously described. Lison *et al*² and Mukamel *et al*³ reported two families with consanguineous parents, in whom several sibs presented with spastic paraparesis, muscle wasting, mental retardation, skeletal deformities, and cutaneous manifestations (greying hair and hypopigmented and hyperpigmented lesions). A syndrome of spastic paraplegia, cutaneous lesions, and dysarthria was reported by Bahemuka and Brown,⁴ but the skin rash was confined to the face. Our patient had no evidence of paraparesis, no skeletal deformities, and his cutaneous lesions were different from those reported in these studies.²⁻⁴

In our patient, the absence of chromosomal and immunological defects excludes chromosomal breakage syndromes such as Fanconi's anaemia, Bloom's syndrome,^{5,6} xeroderma pigmentosum, and ataxia telangiectasia.^{7,8}

Finally, the diagnosis of Nijmegen breakage syndrome was suspected since it includes most of the clinical manifestations of this patient.^{9,10} However, the lack of serious infections and of chromosomal abnormality strongly argues against this diagnosis.

Therefore, our patient seems to have a syndrome different from previously reported neurocutaneous syndromes and from the chromosomal breakage syndromes.

Immunological studies.

Serum immunoglobulins (g/l)

IgG: 16

IgA: 1.35

IgM: 0.9

Vaccinal antibodies

Antipoliomyelitis type 1: 1/640

Antipoliomyelitis type 2: 1/1280

Antipoliomyelitis type 3: 1/640

Antitetanus: 0.250 U/ml

Lymphocyte populations (%)

T3: 72

T4: 41

T8: 12

Mitogen and antigen responses of blood lymphocytes

PHA: 203 (N > 15)

Tuberculin: 24 (N > 5)

Candidin: 31 (N > 5)

Tetanus toxoid: 16 (N > 5)

We are grateful to Dr Aurias for performing the search for chromosomal breakage.

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