Hypomelanosis of Ito. Neurological Complications in 34 Cases

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ABSTRACT: We studied 34 Spanish children with hypomelanosis of Ito. This disease has an incidence of 1 per 1000 new patients consulting a paediatric neurological service, or 1 per 8000-10,000 unselected patients in a children's hospital. About 94% of our patients show noncutaneous abnormalities. Mental retardation (IQ below 70) was present in 64.7%; another 14.7% had an IQ between 70 and 90, usually associated with poor school performance. Four children exhibited autistic behaviour. Seizures of various types were present in 53% of cases. Other skin alterations in addition to the typical hypomelanosis were observed in 38% of our cases: café-au-lait spots, angiomatous nevi, nevus marmorata, nevus of Ota, Mongolian blue spot, heterochromia of the iris or hair, and other nonspecific pigmentations. Other associated disorders occur inconsistently and include macrocephaly, microcephaly, hémihypertrophy, kyphoscoliosis, coarse facial features, genital anomalies, inguinal hernia, congenital heart disease, hypertelorism, and abnormalities of the teeth, feet and eyes. Autosomal dominant inheritance is demonstrated in some but not all cases.

RÉSUMÉ: Complications neurologiques chez 34 cas d'hypomélanose d'Ito Nous avons étudié 34 enfants d'origine espagnole atteints d'hypomélanose de ito. L'incidence de cette maladie est de 1 par 1000 nouveaux patients dans un service de neurologie pédiatrique, ou de 1 par 8000-10,000 patients consécutifs dans un hôpital pour enfants. Environ 94% de nos patients ent des manifestations au niveau de tissus autres que la peau. Un retard mental était présent chez 64.7% (Ql au dessous de 70); 14.7% avaient un Ql entre 70 el 90 et présentaient habituellement des difficultés scolaires. Quatre enfants avaient un comportement autistique. Cinquante-trois pourcent présentaient des manifestations épileptiques de types variés. Trente-huit pourcent de nos cas présentaient d'autres changements cutanés en plus de l'hypomélanose typique: taches café-au-lait, naevi angiomateux, naevus marmorata, naevus d'Ota, tache mongolienne, hétérochromie de l'iris ou des cheveux et autres pigmentations non-spécifiques. D'autres anomalies associées se retrouvent de façon sporadique: la macrocéphalie, la microcéphalie, l'hemihypertrophie, la cyphoscoliose, un faciès fruste, des anomalies génitales, la hernie inguinale, la maladie cardiaque congénitale, l'hypertélorisme, des anomalies des dents, des pieds et des yeux. Une hérédité autosomale dominante a été démontrée dans certains cas, mais pas chez tous.

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Hypomelanosis or incontinentia pigmenti achromians was described by Ito in 1952.[1] It is the most common of the group of diseases known as 'melanophacomatoses'. Its frequency is exceded only by neurofibromatosis, tuberous sclerosis, and Sturge-Weber disease amongst neurocutaneous disorders. The abnormal skin lesions consist of hypopigmented zones as spots with irregular borders, streaks, whorls or patches. The importance of this neurocutaneous disease has always been defined by neurological components, principally mental retardation and epilepsy, which are observed in more than half of cases.[2]

We describe the findings in our personal series of 34 cases of hypomelanosis of Ito (HI). All patients were examined on the Paediatric Neurology Service between August 1965 and December 1986, at the «La Paz» Children's Hospital in Madrid, Spain. All patients were referred because of their neurological disorders. This report consitutes the largest series of this disease published to date.

Material and Observations

Our series consists of 34 Spanish patients, most of whom were referred because of mental retardation and/or seizures. Some were referred from the Dermatology Service because of neurological disturbances. Ages at the time of first visit ranged from 2 months to 10 years (Table 1). Twenty were male (58.8%) and 14 were female (41.2%). Most children, 29 (85.3%), had been born after an uncomplicated pregnancy, while in 5 cases the mothers had experienced minor problems that included vaginal infection, hypertension and anemia in one, hyperemesis gravidarum in two, hepatitis in the first trimester and metrorrha-

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gia in the eighth month in one, and leukorrhea during the first trimester in one. Deliveries had been routine after a gestation of 38-42 weeks in 20 cases; five patients (14.7%) were born at less than 38 weeks, and two (5.9%) were delivered after 42 weeks. Five patients had a birth weight of less than 2500 grams, one of whom was the twin of a child with normal birth weight.

Table 1: Neurologic and Extra-Neurologic Complications of Hypomelanosis of Ito — Neurological Abnormalities

Case	Sex	Age	Genetic	Extra-Neurological	General findings	Seizures	EEG	Psychometric status	Neuroradiology	Evolution
1	M	7m	Parents related	Macrogenitalia Coarse face and hands. Hypomelanosis of iris	Macrocephaly	Several types	Abnormal	Autistic	Normal	Lennox-Gastaut Autistic
2	F	9y	—	Coarse general aspect	—	Generalized tonic-clonic	Abnormal	Autistic	Normal	Autistic
3	F	1y	Grandmother with hypo-melanotic area	Strabismus; Body asymmetry	Macrocephaly Hypotonia	Infantile spasms	Hypsar-rythmia	Profound MR (Autistic)	Normal	Dead at 15 m (no necropsy)
4	F	10y	—	—	—	Focal	Focal abnormalities	IQ: 71	Normal	Moderate MR
5	F	8y	—	—	—	Generalized tonic-clonic	Abnormal	IQ: 109	Normal	Normal
6	F	15m	—	Dorso-lumbar kyphosis feet abnormalities	Microcephaly	Focal	Abnormal	MR (IQ: 50)	Brain atrophy (CT)	Improving
7	M	3y	—	Facial hemi-hypertrophy	Hypotonia Macrocephaly	No	Normal	IQ: 133	—	Normal
8	F	4y	—	Dorso-lumbar kyphoscoliosis	Macrocephaly	No	Focal abnormalities	IQ: 20	Brain atrophy (pneumo) Normal angiography	Profound MR
9	F	4m	—	—	—	No	Focal abnormalities	MR (IQ: 50)	Normal (CT)	MR
10	M	4y	—	Cryptorchidism	—	No	Abnormal	IQ: 62	Normal (CT)	Moderate MR
11	M	16m	—	Café-au-lait spots; Hypospadius; Megalocornea; Hypertelorism; Short nose; Cervical ribs	Macrocephaly	No	Normal	MR (moderate) (IQ: 65)	Normal (CT)	Moderate MR
12	M	6y	—	—	—	No	Normal	IQ: 89	Normal (CT)	Borderline
13	M	4y	—	—	Microcephaly Hypotonia	Infantile spasms at 6 m	Hypsarryth-mia at 6 m. Abnormal at 4y	Profound MR (IQ: 30)	—	Profound MR Seizures (not controlled)
14	F	7y	Brother with seizures	—	—	Focal	Focal abnormalities	IQ: 47	Normal (pneumo)	Lost to follow-up
15	F	5y	Uncle with hemihyper-trophy	Hemihypertrophy	—	No	Normal	IQ: 30	Normal (pneumo)	Severe MR
16	M	15m	—	Inguinal herniae Microcephaly	Macrocephaly	Generalized; partial; myoclonic	Focal abnormalities	Severe MR (IQ: 30)	Normal (CT)	Severe MR Seizures (poorly controlled)
17	M	5½y	—	Microcephaly (moderate)	Irritability	Generalized; partial; myoclonic	Focally abnormal	IQ: 99	Normal (CT)	Irritability Seizures (controlled) Poor school performance

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Case	Sex	Age	Genetic	Extra-Neurological	General findings	Seizures	EEG	Psychometric status	Neuroradiology	Evolution
18	F	29m	—	Bilateral occular nevus of Ota. Angiomatous nevus in the cheek and leg. Mongolian spot on back and both gluteal areas	—	No	Normal	IQ: 106	Normal (CT)	Normal
19	M	2½y	—	Tetralogy of Fallot Asymmetrical ears	—	No	Normal	IQ: 80	—	Borderline
20	M	5y	Two brothers with HI without neurological (disorders)	—	—	No	Normal	Autism	Normal (CT, MRI, angiography	Autism
21	M	2m	—	—	Hypotonia	Myoclonic, focal and tonic-clonic	Abnormal	Severe MR (IQ: 20)	Normal (pneumo)	Death at 1y (no autopsy)
22	M	4y	—	Hemihypertrophy Several abnormalities of eyelids, hair, nose, teeth, ears	—	No	Normal	IQ: 63	Normal (pneumo)	Slow improvement
23	M	6y	—	Hemihypertrophy	—	No	Normal	IQ: 33	—	Lost to follow-up
24	M	5m	Aunt with seizures	—	—	Generalized tonic-clonic	Abnormal	IQ: 50	—	Slow improvement
25	F	7y	—	Asymmetrical breasts. Abnormal fingers and left foot	—	No	Normal	IQ: 55	Normal (pneumo)	Lost to follow-up
26	M	18m	—	Umbilical and inguinal herniae	—	No	Normal	IQ: 86	Normal (pneumo)	Slow improvement
27	M	6m	Two cousins, an uncle, and grandmother (all paternal) with seizures	Café-au-lait spots	—	Focal	Abnormal	IQ: 109	Normal (pneumo)	Improvement to normal
28	F	3½y	Paternal grandmother and aunt with seizures	Coarse general aspect	—	Generalized tonic-clonic	Abnormal	IQ: 30	Asymmetrical ventricles (pneumo)	Seizures poorly controlled; Severe MR
29	F	4y	—	—	—	No	Normal	IQ: 47	Normal (pneumo)	Slow improvement
30	M	17m	Mother with café-au-lait spots	—	—	Focal	Abnormal	IQ: 100	Normal (CT)	Normal; Seizures (controlled)
31	M	10m	—	Agiomatous nevus	—	Focal	Abnormal	IQ: 108	Normal (CT)	Normal; Seizures (controlled)
32	M	6y	Mother and maternal grandmother with HI	Café-au-lait spots	Macrocephaly	Generalized tonic-clonic	Abnormal	IQ: 69	Cortical atrophy (CT)	Minimal improvement; Seizures (controlled)
33	F	1y	—	Atrial septal defect (cardiac)	—	Generalized tonic-clonic	Abnormal	Severe MR (IQ: 50)	Cortical atrophy (CT)	Severe MR
34	M	6y	—	Asymmetrical lower limbs	—	Generalized tonic-clonic	Abnormal	IQ: 80	Cerebral hemiatrophy (CT)	Improvement Seizures (controlled)

Key: CT = computed tomography; IQ = intelligence quotient; MR = mental retardation; MRI - nuclear magnetic resonance imaging; pneumo = pneumoencephalography

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Cutaneous lesions of the HI type were observed at the first examination (Figures 1 and 2). It was difficult to determine the genetic pattern of the disease in many of our cases. The incidence of cutaneous lesions amongst other members of the family was low. The mother and grandmother of one case and the mother of another showed café-au-lait spots. A grandmother of an additional case had hyperpigmented skin. An uncle of one patient had facial hemihypertrophy.

Additional skin lesions associated with HI were observed in 13 cases (38%): café-au-lait spots in 3; angiomatous nevus in 1; nevus marmorata in 1; nevus of Ota in 1, persistent Mongolian blue spot in 1; and nonspecific hyperpigmentation in 4 cases. Two patients exhibited heterochromia of the iris. Case 18 of our series had a combination of skin lesions that included venous angioma of one facial cheek, nevus fuscuceruleus of Ota of both sclerae, and large Mongolian spots covering both gluteal regions and almost the entire back.

Associated noncutaneous abnormalities in our series were: macrocephaly (cephalic perimeter greater than 90th percentile) in 8 patients (23.5%); microcephaly (less than 10th percentile) in 2 cases (5.9%); cardiac tetralogy of Fallot in 1 and atrial septal defect in 1; asymmetry of the body with total or partial hemihypertrophy in 4 cases (11.8%); asymmetrical breast development in 1; inguinal or scrotal hernia in 2 (5.9%). Genital anomalies such as macro- or microgenitosomy, hypospadius, or cryptorchidism were found in 4 boys (11.8%). Skeletal alterations such as kyphosis, scoliosis, hyperlordosis, or rudimentary ribs were present in 8 cases (23.5%). Other musculoskeletal abnormalities such as genu recurvatum, pes valgus or pes cavus were found in 5 patients (14.7%). Minor anomalies included coarse facies, scaphocephaly, hypertelorism, short nose and wide philtrum, low set and deformed ears, megalocornea, imperfect implantation of the teeth, and strabismus.

Seizures were complications in 18 patients (53%). These were generalized major motor in 9 cases, partial in 4, infantile spasms in 2, and Lennox-Gastaut syndrome in 1 case. Epileptic crises of several types occurred in 2 patients. Complete therapeutic control was difficult or impossible in 4 children. Clinical and electroencephalographic follow-up examinations were performed in 31 patients (91.2%). Abnormalities in the EEG were found in 18 cases (53%), in general corresponding to those presenting seizures. A borderline abnormal nonparoxysmal EEG was found in 8 patients.

Mental development ranged from normal to severe retardation with autistic behavioural features (Table 2). An IQ below 70 was observed in 22 patients (64.7%). Four children exhibited autistic behaviour (11.8%). The IQ in 5 cases was between 70 and 90 (14.7%). Only 7 patients (20.6%) showed an IQ higher than 90.

Discussion

Hypomelanosis of Ito has been described as an uncommon disease occurring predominantly in females and in non-white populations.[3,4] Most reviews of the topic are biased in tabulat-

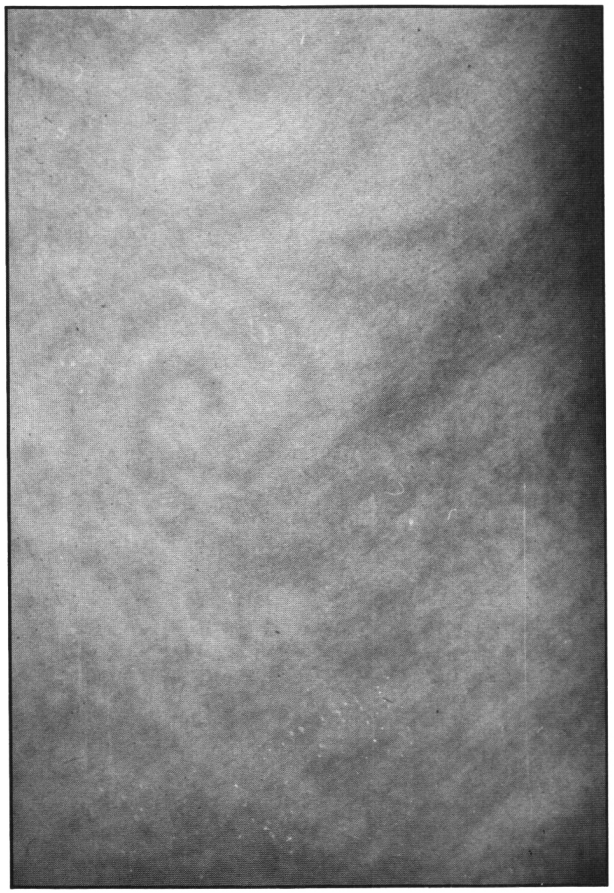

Figure 1 — Hypopigmented lesions in the form of streaks and whorls in the skin of a 4-year-old child with hypomelanosis of Ito.

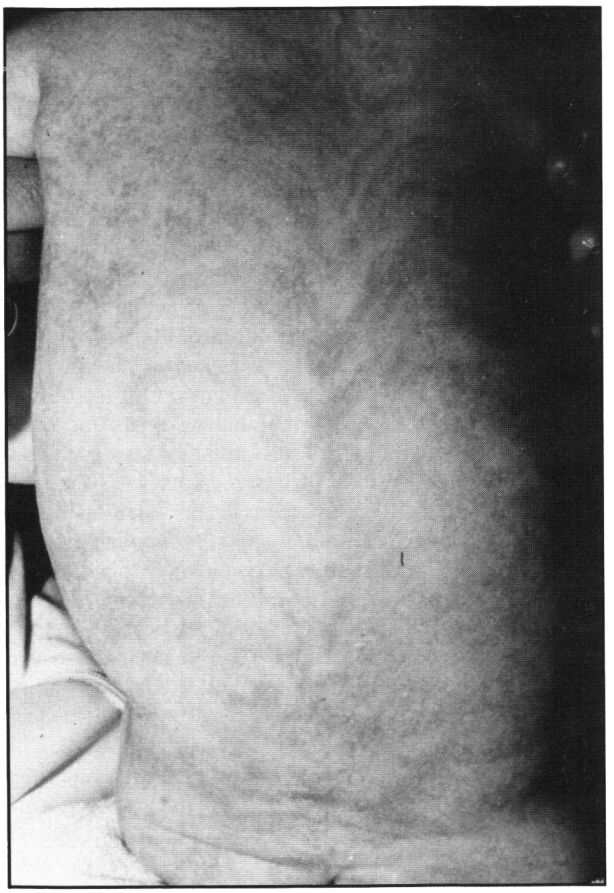

Figure 2 — Whorled hypopigmented lesions on the back of a 5-month-old infant with hypomelanosis of Ito.

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Table 2: Hypomelanosis of Ito and Intelligence Quotient (IQ)

IQ	Patients	%
90	7	20.58
70-90	5	14.7
50-70	5	14.7
50	13	38.23
Autistic	4	11.76

ing only those cases published in English, while ignoring the numerous cases published in other languages. As well, it is our impression that only a small percentage of cases seen in clinical practice are actually reported, and that the disease may be more common than is appreciated. We observe one in 8,000 to 10,000 new patients in our hospital, and one per 1,000 new patients consulting our Child Neurology Service. Both the hospital and the Child Neurology Service are referral centres for all of Spain, specializing in the rarest and most severe diseases. All 34 cases in our series were white, of Spanish ethnic origin. We also found a predominance of males/females of 20/14. We conclude from our own data and previous publications that the frequency of the disorder is higher than expressed in the literature, affects all races and is worldwide in distribution, and probably there is no significant difference between the sexes.

The detection of hypomelanotic zones is easier in people with pigmented skin; fair-skinned individuals may require a Woods lamp to demonstrate the cutaneous lesions. Ultraviolet light was not used in our study. Furthermore, hypomelanotic zones in the skin may be difficult to diagnose at birth or may pass undetected until the neurological disturbance is investigated. Depigmented patches may even be thought to be normal skin while normally pigmented surrounding areas are mistaken as abnormal, particularly in Mediterranean countries where most people have a naturally darker complexion. However, some type of dermatological alteration was observed within the first year of life in about 70 percent of the patients in our study.

Although the hypopigmented lesions are the result of a decreased number of melanocytes, as well as the number and size of melanosomes,[5,6] the pathogenesis of the disorder is still incompletely understood and histopathological examination of the lesions reveals only nonspecific findings. Ultrastructural studies disclose fewer than normal melanosomes and incomplete melanization,[7] though these findings also occur in the hypopigmented skin lesions of tuberous sclerosis and other hypomelanotic diseases.[8,9] Cutaneous lesions additionally associated with HI include café-au-lait spots, Mongolian blue spot, nevus marmorata, angiomatous nevi, nevus fuscuceruleus of Ota, as well as zonal hypomelanosis of the iris.[3,5,12-14] Changes in hair colour arising from hypomelanotic areas of the scalp also are observed. Diffuse alopecia,[5,15] white or greyish-white trichorrhexia, and mottled hair are the most common findings. The patient in our series with this disorder showed alopecia of a zone of the scalp until 3-4 years of age, at which time trichorrhexia and grey-white hair appeared. Sweat glands and fingernails also may be abnormal.[3,5,15,17] Noncutaneous abnormalities are reported to occur in 76 percent of patients,[5] but were found in 94 percent of our patients. The cutaneous nevus of Ito is reported to undergo malignant transformation very rarely.[37]

A wide variation of neurological involvement is reported in the various series of patients with HI. The reports fall into two categories, series by dermatologists who usually report a lower incidence of neurological disturbances, and series by paediatricians and paediatric neurologists who find a higher incidence of nervous system involvement. All of the 94 percent of noncutaneous disorders of our series and 100 percent of other series[18] had neurological disease. In other series, lower incidences of 40,[19] 50,[5] or 61[4] percent are reported. The most frequent neurological disorder is mental retardation. Approximately 67 percent of our patients had an IQ below 70, and 14.7 percent were between 70 and 90, borderline retarded by European standards. Similar average IQs have been described by other authors.[3,13,20,21] Autistic behaviour is exhibited by some patients and was observed in four of our patients; three of these had suffered severe seizures previously, but autism was found in one patient who had never had seizures or other neurological symptoms. Children with HI and mental retardation frequently present an early onset of seizures, especially infantile spasms or other forms of myoclonic epilepsy. Not all retarded cases have epilepsy, however. In our series, 27 patients had an IQ of less than 90, but only 18 had seizures. This proportionate difference is found in review of the literature as well. Seizures commonly first appear within the first year of life and often are refractory to anticonvulsant drugs. Mental retardation is almost universal in such cases.

Macrocephaly is a frequent finding[3,13,17,22,23] and was documented in 23.5 percent of our cases. Microcephaly also is observed,[19,24,25,26] though less frequently. Pneumoencephalography usually shows no gross structural abnormalities. Computed tomography (CT) and nuclear magnetic resonance imaging (MRI), by contrast, may disclose localized or generalized cerebral atrophy[10,11,27,28] or cerebellar hypoplasia,[20,21] especially in cases with clinical neurological deficits. A low attenuation coefficient of the white matter has occasionally been found by CT.[26] Neuronal heterotopia may be demonstrated by MRI in cases where CT has failed to reveal these lesions.[26] No angiographic abnormalities have been described, nor were they found in several of our patients who were studied by angiography.

Cerebral abnormalities may be either ipsilateral[26] or contralateral[22,27] to the hemihypertrophic side of the body. The extent of the hypopigmented cutaneous lesion does not correlate with either the severity of neurological disease or with the neuroradiological or histological findings. Asymmetrical breast development was seen in one girl of our series and was previously described.[1,13,16] Hemihypertrophy of part, or the entire side, of the body was found in 20 percent of our patients. Hypertrophic areas are on the same side as the hypomelanotic skin. Bilateral hypertrophy is found in some cases with generalized HI. These patients commonly have coarse facies and macrocephaly. Partial or complete hemihypertrophy may be observed in other neurocutaneous disorders, such as tuberous sclerosis, neurofibromatosis, Sturge-Weber disease, cutis marmorata telangiectatica congenita, and nevus unis lateralis.[29] In our opinion, this feature is a nonspecific sign of neurocutaneous disease.

Oral anomalies consist of defective dental implantation, conical teeth, partial anodontia, or dental hypoplasia or dysplasia.[20,30,31] Defective enamel, also is found, and hamartomatous cuspids protruding from the dental crowns of permanent teeth might be histological reminiscences of odontomata.[14,32] Bifid uvula and submucosal cleft palate are rarer anomalies.

Nonspecific alterations of the eyes or of ocular motility occasionally are present. These include strabismus, nystagmus,

hypertelorism, micro-ophthalmia, atrophy of the choroid, corneal opacity, and optic nerve hypoplasia.[3,5,12,13,16,20,22,34]

Congenital cardiac disease is occasionally reported and was found in two of our patients (cases 19 and 33). Single kidney or defective genitalia such as micropenis and cryptorchidism are seldom mentioned,[13,17,35] but these anomalies and others were observed in our patients (see Table 1). Some disorders, such as limb malformations and facial clefts could be explained by a disruption in the interaction between neural crest cells and underlying mesenchymal precursors of the affected structures.[33] Neural migrational defects with heterotopia or altered neurons suggests a second trimester disturbance of neural crest cellular migration.[23]

Chromosomal abnormalities have been documented in some cases: mosaic trisomy 18,[21] a balanced translocation between chromosomes 2 and 8 with the formula 46XXt(2,8)(q^{37}.2p21.1),[28] mosaicism of 45SY,-14,-21,+t(14q,21q) and 46XY,-14, -21, +t(14q,21q) + mar in a 1:2 proportion.[24] Although most cases of HI have been reported as sporadic, autosomal dominant inheritance also has been observed.[7,12,17,20,34] In our opinion, these 'sporadic cases' are formes frustes and asymptomatic carriers who transmit the disease to their progeny as an autosomal dominant trait. Hypomelanotic spots or nevus of Ota in close relatives of patients with HI,[7,17,34] also observed in our series, probably are significant. However, autosomal recessive inheritance may be operative in some cases.[10,34]

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