Arch Psychiatr Nervenkr (1983) 233 : 111-124

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

Cerebral Gigantism Associated with Jaw Cyst Basal Cell Naevoid Syndrome in Two Families

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Summary. We report 9 subjets from 2 families with the syndrome of cerebral gigantism, seven of the patients also had jaw cyst basal cell naevoid syndrome. Neurological, radiological, somatic and biochemical features of this hitherto unreported association are described. Neurological symptoms included mild hydrocephalus, ventricular malformation, cerebellar syndrome, intracranial calcification, oculomotor disturbances, EEG abnormalities and rarely, mild peripheral nervous disorders. A disturbance of calcium metabolism appears to be a prominent feature of the genetically determined nonprogressive syndrome.
Key words: Cerebral gigantism - Macrocephalus - Jaw cyst - Basal cell naevoid - Bone metabolism - Alkaline phosphatase - Genetics

Zusammenfassung. Es werden zwei Familien mit 9 Fällen von cerebralem Gigantismus (Sotos-Syndrom) mitgeteilt, von denen 7 ebenfalls das Kieferzysten-Basalzellnaevoid-Syndrom von Binkley und Johnson sowie Gorlin und Goltz aufwiesen. Die neurologischen, radiologischen, somatischen und biochemischen Befunde bei dieser bisher nicht bekannten Syndrom-Assoziation werden beschrieben. Unter den neurologischen Zeichen finden sich Makrozephalus mit leichterem Hydrozephalus, Ventrikelabnormitäten, Kleinhirnsyndrom, intracranielle Verkalkungen, okolomotorische Störungen, EEG-Veränderungen, leichte peripherneurologische Störungen und psychomotorische Entwicklungsstörungen. Eine Alteration des Calciumstoffwechsels mit Isoenzymerhöhung der alkalischen Phosphatase und leichter Parathormonvermehrung scheint ein wesentliches Kennzeichen dieses genetisch bedingten, nicht-progredienten Syndroms zu sein.

Schlüsselwörtrer: Cerebraler Gigantismus - Makrozephalus - Kieferzysten-Basalzellnaevoid-Syndrom - Knochenstoffwechsel - Alkalische Phosphatase - Genetik

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Introduction

In 1964 Sotos et al. described a new syndrome, cerebral gigantism (CG) in children. It was characterized by excessive rapid growth, acromegaloid features without evidence of pituitary dysfunction and nonprogressive cerebral disorder with mental retardation. Since then there have been more than 100 case reports. While Ott and Robinson (1969) reviewed 33 cases, Maes et al. (1976) found 83 cases in the literature and added another patient. Sakano et al. (1977) reported or reviewed 21 cases from Japan. Thus, a typical syndrome has been established including rapid growth in childhood, cranial dysmorphia with macrocrania, hypertelorism and antimongoloid slant, unusual arm span, frequency of kyphoskoliosis and mild mental retardation. Focal neurological deficit was absent in the 5 children originally described by Sotos et al. (1964) except for moderate incoordination with generalized clumsiness which in later case reports appeared to be the most prominent neurological symptom. The occurrence of seizures was noted in 7 out of 32 cases (Ott and Robinson 1969). Other authors reported abnormal EEGs without convulsions. Although there was early recognition of the syndrome in monozygotic twins (Hook and Reynolds 1967; Lecornu et al. 1976) a genetic determination of the malformation was only confirmed later (Goumy et al. 1979).

Individual features of CG have also been noted in another genetic disorder, the "jaw cyst basal cell naevoid syndrome" or "basal cell naevus syndrome" (BNS) (Binkley and Johnson 1951; Gorlin and Goltz 1960). The coexistance of these syndromes, however, has not to our knowledge been reported. In this paper we describe our findings in 9 subjects from 2 families with concominant occurrence of CG and BNS in the same individuals.

Case Reports

Case 1

A 45-year-old father of three children, was seen for the first time in 1974 for migraine headaches, which had occurred since puberty with a frequency of approximately one attack per month. In addition, he complained of recent severe diffuse headache and irritability. The previous history was uneventfull with the exception that he had suffered from undernutrition and tuberculosis of the lung from the age of 16 to 19 years. The patient had undergone previous surgery on several occasions for cysts in both jaws and maxillae. He reported that this father, killed at the end of the war, was tall, that his mother (75 years) was still alive and that in her family psychiatric cases, including several suicides, were known. No information about his sister or further family could be given.

On examination the patient showed proportional gigantism with 193 cm body length, arm span was 246 cm, head circumference 60 cm, chest circumference 87 cm. On the trunk there were multiple colourless or brownish naevi from the size of a pinhead to a pea, and numerous pits. He had marked macrocephalus with bulging of the parietal bones, slight hypertelorism and an antimongoloid lid axis. There was a divergent strabismus and a nystagmus on horizontal gaze to the right more than to the left. Tendon reflexes were normal on the upper and weak on the lower extremities, with muscle mass moderately developed and hypotonic. There were no further neurological abnormalities. The psychic status was peculiar with the patient appearing irritable, slightly depressed but eager to undergo all examinations. There was no

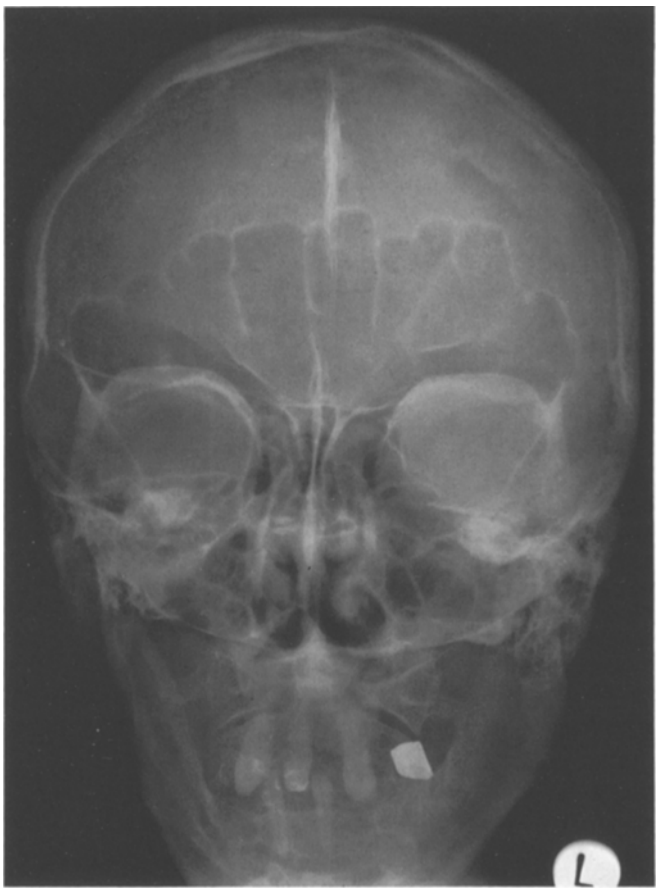

Fig. 1. Case 1, a.p. radiography of the skull showing macrocephalus with cranial dysmorphia, bilateral jaw cysts, calcification of falx cerebri and internal carotid artery

intellectual deficit. The EEG showed a well developed but irregular alpha-rhythm of 8 to 12/s and diffuse theta-waves, and no photic driving.

In 1977 the patient complained of weight loss, severe nocturnal headache without scotoma or nausea, sleep disturbances, adynamia and epigastric pain. He reported a permanent feeling of cold and an absence of temperature sensation. He still showed a nystagmus on lateral gaze, slightly dissociated to the right, slight decrease of optokinetic nystagmus to the left, divergent strabismus and a weakness of convergence of the eye balls. On the left planta pedis there was an ulcer with a torpid border and serous secretion, which the patient reported had appeared 3 years ago and never healed. The neurological status was unchanged except for a decrease of all sensory modalities, especially of thermaesthesia on the lower extremities, more pronounced distally and on the left side. Neurography showed a normal conduction velocity of the median nerve (57 m/s), decreased velocity (34 m/s) and decreased action potential (500 μV) of the right peroneal nerve. On the left side no action potential could be recorded for the distal and proximal peroneal and tibial nerves. During the following 2 years the patient frequently complained of headache and epigastric pain, but with use of analgesics and spasmolytics the headaches were less frequent. The EEG showed general slowing of rhythms, dysrhythmia and slow waves over the temporal areas.

Thorough medical examinations including gastroscopy revealed no abnormalities. He developed some weakness of foot elevation on the left side, and tendon reflexes were now

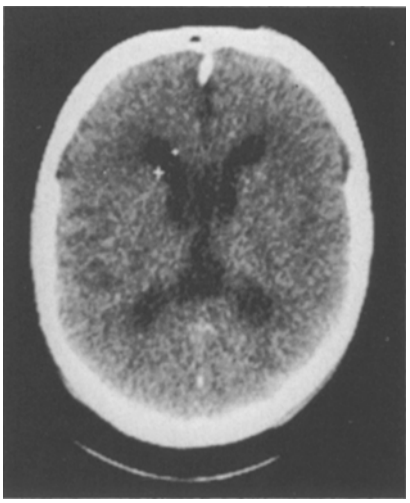

Fig. 2. Case 1, computer tomography scan showing moderate hydrocephalus and median cyst

markedly decreased. The sensory deficit was unchanged, skin temperature on the feet was decreased between 0.3° to 1.8°C on the left with respect to the right side. The ninhydrin test showed absence of sweating of the feet. On neurographical examination the conduction velocities of the peroneal and tibial nerves were decreased to 31 and 29 m/s, respectively. The recorded action potentials were small ($800 + 500\,\mu V$).

Radiological Findings. On first admission X-ray examination of the skull showed a macrocephalus with bulging of the frontal bones and asymmetry of the frontal sinuses, elevation of the right os petrosum, pronounced calcification of the falx cerebri, calcification of the carotid artery at the level of the siphon, very marked formation of cysts and protrusion of the mandibles on both sides (Fig. 1). Pneumoencephalography showed internal hydrocephalus and a double contour in the centre of the cranial cavity (Fig. 2). The spine showed a primary fusion of the vertebral bodies C-6 and C-7 with hypoplasia of the right arch and the processus articularis of C-7, cervical osteochondrosis, marked dorsal kyphosis and changes of the bone structure typical for osteoporosis or osteomalacia.

Computer tomography at the age of 50 years showed a symmetrical ventricular system which was enlarged in all parts. The width of the anterior horns was 52 mm. The lower parts of the third ventricle were unapparent, while the lateral ventricles were displaced by a large cavum vergae.

Biochemical findings in serum (transaminases, aldolase, creatine kinase, creatine, creatinine, bilirubin, urea, electrophoresis, cyclic AMP) were normal. Cyclic GMP was low (0.6 pmol/ml). Only the alkaline phosphatase activity was found repeatedly to be elevated (234 mU/ml), the γ-glutamyltranspeptidase was 43 mU/ml. Amino acid analysis in plasma showed glutamine to be slightly elevated, though 24 h amino acids excretion was normal. The final medical examination in 1979 showed evidence of hypothyroidism, and cytogenetic examination revealed a 46,XY normal male karyotype.

Case 2

This patient, the son of case 1, was seen for severe behavioural problems in childhood. Delivery had been complicated, birth weight was 3.5 kg, birth length 55 cm. There was a retardation of psychomotor development, and a strabismus and a nystagmus had been noted since birth. Because of the retardation and his autistic behaviour, he was admitted to the paediatric department where an internal hydrocephalus was diagnosed. Later on he showed accelerated growth, and at 10 years of age his body length was above the 97th percentile. The testes were

Table 1. Clinical features in patients with CG and BNS

Case number	1	2	3	4	5	6	7	8	9
Age at last examination	52	22	18	17	42	19	18	16	12
Sex	M	M	F	M	F	M	F	M	F
High birth weight	u	+	+	+	u	+	+	–	+
High birth length	u	+	+	+	u	+	+	–	+
Retarded development	–	+	+	–	–	+	+	–	–
Retarded puberty	u	+	–	u	+	+	+	–	u
Gigantism macrocrania	+	+	+	+	+	+	+	+	+
Cranio-facial features	+	+	+	–	+	+	+	–	+
Advanced bone age	u	–	+	u	u	+	–	–	u
Skeletal dysplasia	+	u	+	u	+	+	+	u	+
Changes in bone structure	+	u	+	u	+	–	–	u	(+)
Increased alkaline P'ase	+	+	+	u	+	+	–	(+)	(+)
Jaw cysts, basal cell naevus	+	+	+	–	+	+	+	–	+
Subcutaneous tumours	+	–	–	–	+	+	+	–	–

+ means symptom present; – symptom lacking; u unknown

undescended, dermatoglyphics were abnormal, there was adipositas. Neurological examination showed a horizontal congenital nystagmus and a convergent strabismus of the left eye. He was operated on for strabismus when 9 years old and and for septal deviation when 15 years old. The first of a series of jaw cyst operations was performed in his 11th year.

By his 18th year the patient showed marked gigantism (Table 1) with a body length of 197 cm, though the arm span was less than the body length. The head was dolichocephalic with prognathia, and there was a bilateral scapula alata with hypoplasia of the m. suprascapularis. He had genu valga, the muscle mass was rather purely developed and hypotonic, and coordination was awkward, though there was no ataxia. Neuroophthalmological examination showed a partial ptosis on both sides, heterochromia of the iris, the beginnings of a cortical cataract on the left side and a congenital pendular nystagmus.

On psychiatric examination the patient stammered, and the intellectual testing (HAWIE) showed a mean IQ of 66 but only slightly subnormal IQ in a language and culture free test (Raven). His psychomotor behaviour was slow, pedantic and inhibited; the EEG was nonspecifically abnormal with increase of theta activity and flat slow waves over a background of predominantly fast alpha rhythms.

Radiography of the skull showed a biparietal diameter of 17.4 cm, and there was calcifcation of the tentorium. Pneumoencephalography revelaed an internal hydrocephalus and a median cyst communicating with the ventricular system (Fig. 3). There was moderate cortical atrophy and a large accumulation of air under the tentorium cerebelli.

Laboratory examinations at age 22 years showed a moderate increase in alkaline phosphatase activity to 261 mU/ml, while other routine values of serum and CSF were normal. At this age the patient had attained a body length of 201 cm. He lived in an institution for handicapped youths, where his behaviour was satisfactory, except for numerous fugues, lasting for several days. There was no evidence of epileptic attacks.

Case 3

This patient, the daughter of case 1, had a birth length of 60 cm and birth weight of 4.4 kg. A strabismus had been noted since birth, and there was psychomotor retardation, the child could not sit up until 11 months and did not learn to stand and walk until the end of the second

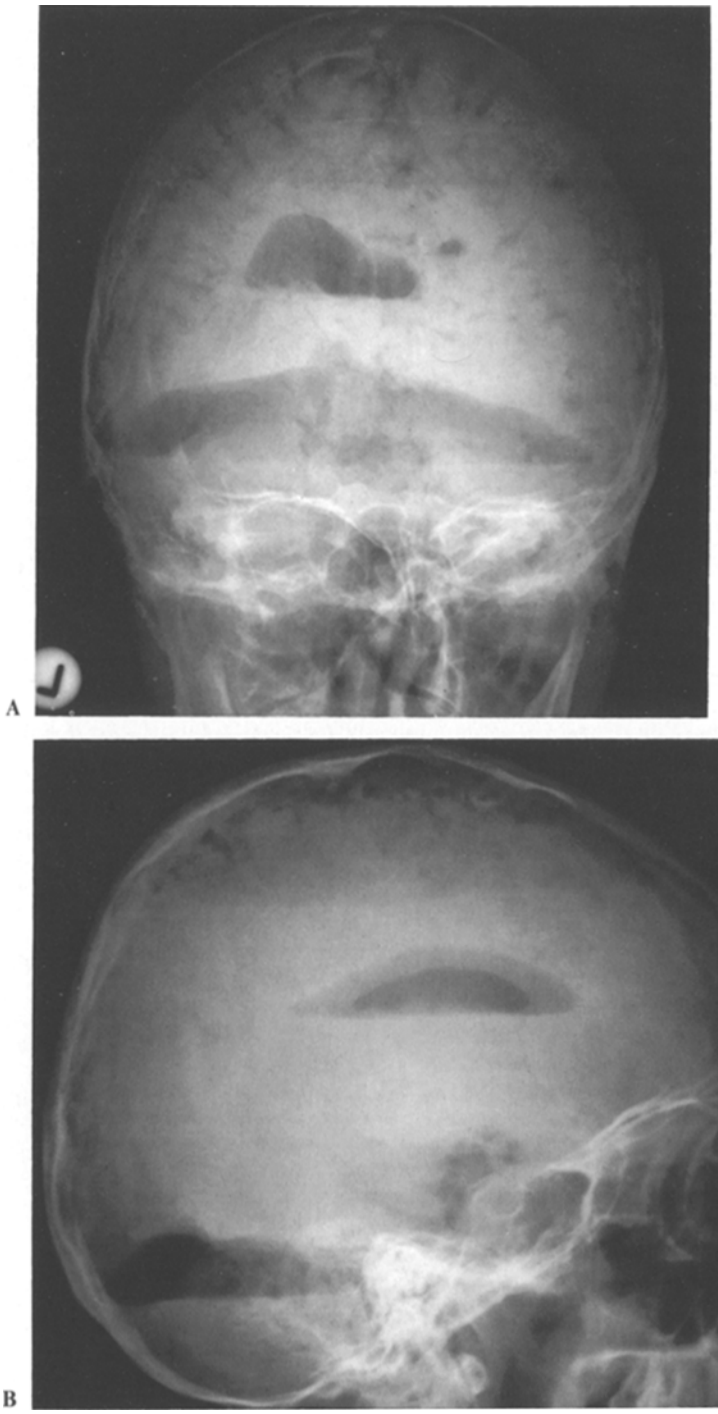

Fig. 3A, B. Case 2, pneumoencephalogram. **(A)** a.p. projection showing enlarged ventricles, cortical atrophy, median cyst and air accumulation below the tentorium cerebelli; **(B)** lateral view demonstrating extension of the median cyst (dark figure projecting into image of left lateral ventricle)

year. At 15 months the body length of 89 cm was above the 97th percentile. There was macrocrania, marked strabismus, pendular nystagmus, ptosis and ocular torticollis. Radiography of the extremities showed an advanced bone age of 1 year. Pneumoencephalography revealed a symmetrical internal hydrocephalus. The child was anaemic with a haemoglobin of 8.1 g/dl and an erythrocyte count of 3.5 million. Other routine laboratory tests were normal, except for an aminoaciduria with increased excretion of taurine, serine, glycine, glutamic acid, alanine and γ-aminobutyric acid (three fold). This finding, however was not confirmed on subsequent examinations.

During the following years the child showed excessive growth, the body length was 177 cm at 12 years and 7 month. However, levels of growth hormone, TSH, prolactin and gonadotrophins were all normal. The patient was treated with high doses of oestrogens for more than 4 years, and growth decreased only slowly, the body length was 190 cm at 17 years of age. By this time the patient had had repeated operations for follicular jaw cysts. Basal cell naevi and pits were also present. She had gigantism (Table 1), macrocrania with hypertelorism, antimongoloid slant and slight prognathia. Neurological examination showed no major deviations except for a hypotonia of the muscles and some awkwardness of movement with no ataxia or dysdiadochokinesia. Neuroophthalmological examinations showed spontaneous and latent nystagmus only on monocular testing. The horizontal vestibulo-ocular reflexes were abnormal, vestibular nystagmus was not suppressed by fixation. In addition there were vertical disturbances with saccades during pursuit movements, with no smooth compensatory movement because of lagophthalmia. Vertical vestibular nystagmus was not suppressed by fixation. Vertical optokinetic nystagmus was preserved. The ophthalmological examination revealed preretinal and intraretinal foci near the papilla which were not further characterized. Acuity of vision after correction was 0.9 on the right and 0.6 on the left side. The EEG and conduction velocities of peroneal and tibial nerves were normal.

Radiography showed macrocephalus, dolichocephaly, hypertelorism, a bridged sella turcica and calcification of the falx cerebri and tentorium. Computer tomography revealed a moderate internal and slight external hydrocephalus, a median cyst and a marked enlargement of the cerebellar cisterna, indicating cerebellar atrophy (Fig. 4). There was a fusion of the C-6 and C-7 cervical vertebral bodies, very similar to the findings in her father, but with torticollis to the right. On the right side there was a bifid 6th rib.

Routine laboratory findings were normal except for a moderate increase in alkaline phosphatase (284 mU/ml) and an increase in serum α_2-globulins to 11.5%. Basal serum growth hormone and prolactin levels were 3.2 and 6.9 mg/dl, respectively. All night monitoring of hormones showed a decreased growth hormone peak (7.3 mg/dl) during the first sleep cycle and additional small peaks during later cycles while prolactin increased normally during the second half of night sleep. Serum cyclic AMP was 6.9 and cyclic GMP was 0.7 pmol/ml. Excretion of calcium and phosphate, CSF cytology and proteins were all normal.

Case 4

This case, the second son of case 1, had a normal development except for increased birth weight and length and excessive growth in childhood. At the age of 17 years his body length was 198 cm. His general appearance, neurological and psychic status appeared normal. Radiography of the skull showed macrocrania but otherwise no abnormalities. There was no evidence of jaw cysts or dermatological symptoms, and further detailed examinations were not possible.

Case 5

A 38-year-old mother of four children (cases 6–9) was seen for migraine headaches, which had occurred since puberty. She was the youngest of 8 siblings, her father was 48 years old and her mother 42 years old when she was born. The father had a body length of 192 cm while her mother was small, he had been killed at the end of the war, therefore no further information about any other family members was obtained. The patients early development was normal, though her first operation for jaw cysts was at 12 years of age, with delayed puberty and

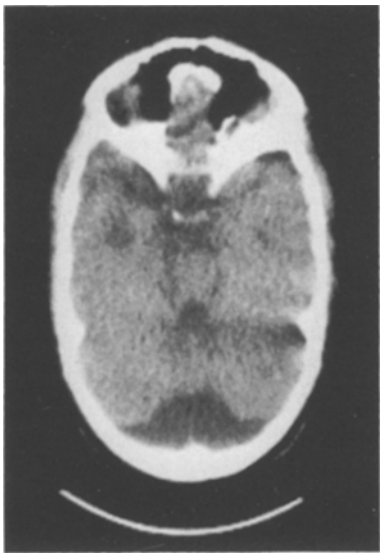

Fig. 4. Case 3, computer tomography scan demonstrating enlarged cisterna magna

Table 2. Serum alkaline phosphatase activity in three patients, determined according to Ohlen and Richter (1971)

Patient	Diagnosis	Bone isoenzyme (% total)	Liver isoenzyme (% total)	Intestinal isoenzyme (% total)	Total (mU/ml)
Case 5	CG and BNS	75.3	16.2	8.5	223
Case 6	CG and BNS	70.1	11.3	18.6	231
Case 8	CG	59.2	14.0	26.8	321
Mean:		68.2	13.8	18.0	258
Normal values:		<70	<10	<20	60–200

first menses at 17 years of age following hormonal treatment. Her four deliveries were complicated.

On admission the patient complained of premenstrual migraine, orthostatic vertigo, frequent dorsalgia, paraesthesias and feeling cold in both feet and nocturnal paraesthesia in the right hand. She had had 11 operations for jaw cysts. She reported repeated appearances of very small red papulae which developed within a year to small brownish naevi with painful inflammation on the skin of the hands, legs and head. She had several colourless naevi the size of a pea on the face and a flat subcutaneous fibroma-like tumour the size of a penny on the right tibia. The body length was 170 cm, arm span 167 cm, body weight 65 kg, she had marked kyphosis, macrocrania (head circumference 59 cm), slight hypertelorism and a slight antimongoloid lid axis. There was exophoria of the right eye, light mydriasis with preserved pupillary reflexes and light diminuition of vision on the right side, nystagmus on horizontal gaze to the right, bilateral hypacusis. Further neurological examination revealed a lesion of the right median nerve at the wrist with slight weakness, but no atrophy of the thenar. On neurographical examination the distal latency was prolonged to 5.6 ms, the action potential was reduced to 8 mV, though the conduction velocities of median, ulnar and peroneal nerves were normal. There was a moderate decrease of vibrational sense on the left leg. The EEG showed an

unstable alpha rhythm and a paroxysmal dysrhythmia with sharp alpha and theta waves over both temporal regions. Psychiatric examination was normal, except for moderate depression, and there was no intellectual deficit.

Radiological examination showed a slight asymmetry of the thorax, the arch of the first thoracic vertebra was not closed. There was a bridged sella turcica and a marked calcification of the falx cerebri. The skull, humerus, femur and vertebrae showed multiple small patchy clearings.

Biochemical examinations showed a moderately increased activity of alkaline phosphatase (251 mU/ml), normal acid phosphatase (8.7 mU/ml), normal γ-glutamyltranspeptidase. The increase in alkaline phosphatase was due mainly to the increase in the bone isoenzyme (Table 2). Parathormone was elevated (5.9 mU/ml), and other routine laboratory examinations were normal.

Case 6

This boy, the son of case 5, had a birth weight of 3.5 kg, a birth length of 53 cm and the head circumference at birth was 37 cm. His psychomotor development was retarded, and at the time of examination, the 14-year-old patient attended a special school for retarded children. The child had undergone several operations for jaw cysts, and naevoid cell tumours were found on the face and trunk. At 10 years of age an advanced bone age (13 years), scoliosis and shortening of the fourth metacarpal bone of the hands had been noted. He complained of attacks of diffuse headache with increased irritability and some nausea. His height was 176 cm, his body weight 56 kg. He had typical macrocrania and orofacial dysmorphia (Fig. 4), a high arched palate, moderate kyphoscoliosis, scapulae alatae, marked hypotonia of muscles, and sexual development was that of the beginning of puberty. Neurological examination showed awkwardness of movement with no clear ataxia. There was weakness and atrophy of the small muscles of the hand and foot; on neurographic examination the conduction velocities of the median and peroneal nerves were 62 m/s and 51 m/s, the action potential, however, of the small toes' extensor muscle was reduced to 5 mV. All sensory modalities were normal. The EEG showed a 8.5–9/s alpha rhythm, increased fast beta waves over the anterior regions, dysrhythmia with sharp waves over the temporal regions. Psychological examination revealed debility with increased irritability.

Radiography showed macrocephalus, large frontal sinuses, a small bridged sella turcica and marked calcification of the falx cerebri and the tentorium. The spinal vertebrae showed kyphoscoliosis and a dysplasia of the second and third thoracic vertebrae. Computer tomography showed symmetrical, markedly enlarged ventricles; the width of the anterior horns was 60 mm; enlarged cisterna cerebellum medullaris and slight anterior cortical atrophy.

Laboratory examination showed a slight increase in alkaline phosphatase (338 mU/ml) and acid phosphatase (17.8 mU/ml) activities and a normal serum amino acid pattern. At 19 year of age alkaline phosphatase activity was 235 mU/ml with preponderance of the bone isoenzyme (Table 3). Parathormone was slightly elevated (4.9 mU/ml), at this age his body length was 190.5 cm, arm span 189 cm, body weight 71.2 kg.

Case 7

The details of this patient, the second child of case 5, are given in Table 1. Her birth weight was 4.5 kg, birth length 59 cm. Psychomotor development was less retarded than that of case 6, though she had difficulties in school. She had had several operations for jaw cysts in childhood. On examination at age 14 years, puberty was delayed and she complained of rare attacks of frontal headache. She showed gigantism, macrocrania and orofacial dysmorphia with hypertelorism, antimongoloid slant and prognathia. There was a moderate kyphoscoliosis, narrow thorax, scapulae alatae, and on the right palm there were several reddish naevi and typical pits. Above the right knee there was a pea-sized subcutaneous tumours of hard consistency. There were no fovea coccygis. Her neurological examination was normal, except for poor development and hypotonia of muscles and some awkwardness of movements. Psychological testing revealed a weakness of concentration and calculation, otherwise no deviations

and average intelligence (IQ 103). The EEG showed a nonspecifical pathological tracing, similar to that of the brother. Neurographic examination was normal.

Radiological examination showed macrocrania, small bridged sella turcica, marked calcification of the falx cerebri and a flattened head of the right femur. Computer tomography showed a symmetricall slightly enlarged ventricular system, normal cisternae and slight atrophy of the frontal cortex.

Alkaline phosphatase activity was 362 mU/ml when she was 14 years and 149 mU/ml at the age of 18 years. Other laboratory examinations including serum amino acids and parathormone (3.4 mU/ml) were normal. At the age of 18 her body length had reached 173 cm, arm span was 167 cm, body weight 56.7 kg.

Case 8

This child, the son of case 5, had a birth weight of 3.0 kg, a birth length of 50 cm, and his development was normal. However, at age of 16 a jaw keratocyst was suspected. Radiography of the skull showed no major abnormalities, no calcification of falx cerebri. His height was 178.5 cm, arm span 181 cm, body weight 65.3 kg. Alkaline phosphatase activity was 240 mU/ml, and parathormone levels were normal (2.4 mU/ml).

Case 9

This girl, the fourth child of case 5, had a birth weight of 4.0 kg, a birth length of 57 cm. She was first examined at 10 years of age, and her development had been normal except for the development of jaw cysts in the previous year. Neurological examination was normal.

Radiological examination showed macrocrania, small bridged sella turcica, fine calcifications of the falx cerebri and first grade cervical ribs. Laboratory examination showed alkaline phosphatase activity to be 442 mU/ml, with serum electrophoresis, amino acid pattern and other findings normal.

Subsequently she should abnormally rapid growth. At 12 years of age she was 162.5 cm tall, the arm span was also 162.5 cm and body weight 47.4 kg.

Discussion

The concomitant occurrence of "cerebral gigantism" and "jaw cyst basal cell naevoid syndrome" in two unrelated families suggests a genetic relationship between these two syndromes, well described earlier as isolated entities (Sotos et al. 1964; Binkley and Johnson 1951). Both syndromes were fully expressed in 7 of our 9 cases while one (case 4) was a giant without any signs of BNS and another (case 8), also of tall stature, had only a suspicion of a jaw keratocyst but no proof of BNS. The mode of inheritance is compatible with an autosomal dominant mode and a high degree of expression, though the exact mechanism remains unknown. Chromosomal analysis performed in some of our patients revealed no abnormalities, similar to other reports of CG (Goumy et al. 1979). Probably, mutation had occurred in the father and mother respectively, of the siblings, and, in case 5 the advanced age of her parents at her birth has to be noted.

It appears that BNS is more common than CG. However, in our two families CG showed a greater expression than BNS (Table 1). A coincidental occurrence of the syndromes is improbable and that the accelerated growth and tall stature were incidental also appears unlikely. No endocrinological cause of gigantism was found, and all major features of Sotos' syndrome of CG were present. The syndrome is characterized by connatal macrosomia and postnatal gigantism with

acceleration of bone growth, macrocrania, typical cranial dysmorphia including frontal bulging, prognathia, moderate hypertelorism and antimongoloid lid axis. Also various degrees of psychomotor and mental retardation and motor incoordination occur as a nonprogressive neurological disorder (Sotos et al. 1964). Congenital hydrocephalus (family 1 and 2) is a typical feature of CG (Sotos et al. 1964; Ott and Robinson 1969), and the presence of a median cyst (family 1) has been reported earlier (Poznanski and Stephenson 1967; Lecornu et al. 1976). Additional features of CG include high arched palate (Sotos et al. 1964), peculiar configuration of dorsum sellae and kyphoscoliosis (Ott and Robinson 1964), abnormal EEG and abnormal dermatoglyphic pattern (Ott and Robinson 1964; Le Marec and Lecornu 1976). All our patients studied in adulthood present with tall stature and macrocrania (despite hormonal treatment during adolescence in one case) while in the literature recession of growth in the first or second decade and normal adult body height were frequently observed (Sotos et al. 1964; Hook and Reynolds 1967). All the 5 patients in Sotos' report were isolated cases, and sporadic cases prevail in the later publications although familial cases have been observed (Hook and Reynolds 1967; Lecornu et al. 1976).

Genetic relationships between CG and BNS are suggested by occasional reports of the presence in BNS of high birth weight (Kahn and Gordon 1967), tall stature (Boyer and Martin 1958; Clendenning et al. 1964, case 4; Codish et al. 1973), larger than normal cranial circumference and hypertelorism (Rittersma 1972), and cranial dysmorphia (Summerly and Hale 1965; Kahn and Gordon 1967). Most of these symptoms were frequently seen in connection with the multiple skeletal abnormalities in BNS. Moreover, neurological symptoms have been repeatedly observed in BNS. Besides neoplasias of the brain (medulloblastomas and astrocytomas) cerebral developmental anomalies (agenesis of corpus callosum, Binkley and Johnson 1951; intracerebral cysts, Taylor et al. 1968) and cerebral atrophy (Codish et al. 1973) were described. Numerous authors reported nonspecific EEG changes and some found mental retardation and intellectual deficits. A "borderline" level of intelligence was also stated in cases of CG. In both syndromes this appears to be the consequence of cerebral atrophy.

The *neurological picture in CG* has been described as nonprogressive, consisting mainly of various degrees of motor incoordination or "awkwardness" (Sotos et al. 1964). In at least some cases of BNS progressive neurological disease has been described (Esser and Bohnert 1980). The neurological symptoms of our patients are summarized in Table 3. The most marked neurological symptoms were congenital nystagmus, motor incoordination and muscle hypotonia. These symptoms can be attributed to the marked cerebellar atrophy, evidenced by pneumoencephalography and computer tomography. A cerebellar syndrome was also reported in BNS by Codish et al. (1973) and Esser and Bohnert (1980). The latter authors discuss a paraneoplastic process as a cause of this syndrome in their patient, also presenting optic atrophy and pyramidal signs. In our patients the absence of malignancies as well as the lack of progression and the morphological findings argue against such a hypothesis. Peripheral nervous disorder is uncommon in CG as well as in BNS. In our case 5 median nerve involvement was most probably due to local compression in the carpal tunnel. In cases 1 and 6, however, there was evidence of axonal neuropathy, possibly related to a metabolic disturbance present in the syndrome.

Table 3. Neurological symptoms in the syndrome of CG with BNS. Numbers indicate patients with symptom present, numbers in brackets patients examined

Neurology
psychomotor retardation 4 (9)
motor incoordination, awkwardness 4 (9)
hypotonia 5 (9)
irritability 3 (9)
low IQ 2 (9)
headache 4 (9)
abnormal EEG 5 (7)
peripheral nervous disorder 3 (8)
Neuroophthalmology
strabismus 4 (9)
congenital nystagmus 4 (9)
unilateral ptosis 1 (9)
cataract 1 (7)
fundus abnormality 1 (7)
heterochromia of iris 1 (8)
Neurootology
hypacusis 1 (9)
Neuroradiology
internal or communicating hydrocephalus 5 (5)
median cyst 3 (5)
cerebellar atrophy 3 (5)
macrocephalus 8 (9)
intracranial calcification 7 (9)
bridged sella turcica 7 (9)

Although electrophysiological examinations and pneumoencephalography or computer tomography could not be performed in case 4 and 8, clinical examinations showed no nervous system symptoms in these subjects with no BNS. Table 3 points to the variable expression of neurological symptoms in BNS. Hypothetically CG can be regarded as one of these expressions, and severe neurological, opthalmological, psychic and skeletal disorders as well as ectopic calcifications appear to be related to BNS. That all symptoms typical of BNS as jaw cysts, basal cell naevi, porokeratosis, vertebral and rib deformations, intracranial calcifications and others were observed in our patients with BNS but not in the patients with only CG, suggests pleiotypic rather than specific responses to one or more genes.

While *biochemical studies* on CG patients showed no disturbances in growth hormone levels and inconclusive involvement of somatomedins (Sakano et al. 1977), studies of BNS have centred, in part, on calcium metabolism. Several authors found diminished responses to parathormone (Gorlin et al. (1965; Clendenning et al. 1964; Murphy 1969) and relationships between BNS (and CG) and pseudohyperparathyroidism have been discussed (Clendenning et al. 1964),

though no definite conclusions have been possible (Rittersma 1972). Parathormone levels were determined in 4 of our patients (family 2) and were raised in two of them (cases 5 and 6). Infantile cataract has rarely been reported in CG (Yeh 1978) BNS (Rittersma 1972), and only one of our patients (case 2).

A remarkable finding in our patients with BNS and CG was an increase in serum alkaline phosphatase activity present in at least 8 of the patients. Cryer and Kissane (1978) reported increased alkaline phosphatase in a giant with a hypophyseal adenoma and multiple endocrine abnormalities, but in this case there was also a hepatic malignancy. The enzyme has not been reported to be increased in CG or BNS, and also enzyme histochemistry of jaw cysts showed no alkaline phosphatase activity (Rittersma 1972). In our patients increased parathormone levels appeared to correlate with the elevation of the bone isoenzyme of alkaline phosphatase (Table 2). This suggests that the increase in alkaline phosphatase activity may be due to stimulation by parathormone. Our syndrome, thus, bears relationships to hyperparathyroidism. However, calcium and phosphate excretion when measured, were not altered in the sense of hyperparathyroidism or pseudohyperparathyroidism, similar to patients with BNS (Rittersma 1972).

An abnormality of calcium metabolism appears to be prominent in our patients as suggested by the radiological picture resembling osteomalacia or osteoporosis, the presence of ectopic calcifications even in juvenile cases and a tendency to frequent bone fractures noted in cases 1 and 3. Its precise nature and its relationship to gigantism, neuroectodermal dysplasia and cyst formation remains to be determined.

Acknowledgement. The help and advice of numerous collegues of the neurological, pediatric, ophthalmological, dermatological, internal and dentistry departments of the University of Freiburg is gratefully acknowledged. Especially we thank Dr. P. Burmeister, Freiburg, for the determinations of PTH and Dr. M. Kienholz, Aschaffenburg, for the determination of APase isoenzymes. Dr. Riemschneider, Karlsruhe, kindly performed the computer tomography scans.

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Received December 27, 1982