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Primitive megalencephaly in children: natural history, medium term prognosis with special reference to external hydrocephalus

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Abstract. We studied 74 children with primitive megalencephaly retrospectively with attention directed to familial megalencephaly, birth history, enlarged pericerebral subarachnoid space (SAS) (idiopathic external hydrocephalus), head and statural growth dynamics, developmental and school prognosis, morphological findings and development of subdural haematoma. In the megalencephalic children, no significant differences were found between those with normal or those with enlarged pericerebral SAS. Out of 62, 31 children (50%) were already megalencephalic at birth. Of 74, 37 children (50%) showed variable degrees of developmental delay which in 18 was transient. Eight out of 74 were mentally retarded. Of 52 children at school age, 42 attend normal schools and 10, of whom 7 are mentally retarded, attend special schools. Three children showed subdural haematoma resulting from apparently minor trauma or occurring spontaneously. We suggest that idiopathic external hydrocephalus represents a variant of primitive megalencephaly with transient increase of intracranial pressure and that it could predispose to the development of idiopathic (spontaneous or non-traumatic) subdural haematoma.

Key words: Childhood – Hydrocephalus – Megalencephaly – Subdural haematoma

Introduction

A large number of infants and children with excessively large heads do not have hydrocephalus, subdural haematoma or rarer causes of macrocephaly. Their brain volume is too large, i.e. they are megalencephalic. Some of these children have a well known condition associated with megalencephaly (neurofibromatosis, tuberous sclerosis, cerebral gigantism) or more exceptional syndromes. In the majority, however, no specific disease entity can be recognized, and a number of these children have relatives with large heads. These children are referred to as primitive megalencephaly (PMG), sometimes familial. Increased use of CT-scan has shown that some of these children have large pericerebral subarachnoid spaces (SAS) – a condition also called "idiopathic external hydrocephalus" (IEH) – and/or moderate enlargement of the ventricular system. These, however, cannot account for the very large and excessively rapid and persistent head growth. Some of these children also have delay in early development, and this combination of findings is of great concern to the practicing paediatrician.

Few studies have tried to evaluate medium term neurodevelopmental outcomes, assess head growth dynamics, describe precisely neurological and morphological findings in megalencephalic infants and children, or to study the relationship between IEH and PMG.

To understand the natural history, prognosis and relationship of PMG and IEH, we retrospectively studied 74 children and tried to answer the following questions:

1. Do PMG and IEH represent variations of the same entity?
2. How does their occipito-frontal circumference (OFC) grow?
3. What is their developmental and school prognosis?
4. Is there a subgroup with homogeneous morphological and neurological findings leading to a new syndrome?
5. Does IEH really predispose to the development of spontaneous non-traumatic subdural haematoma?

Patients and methods

The children in this study had all been referred for neuropaediatric evaluation of macrocephaly and/or associated problems in neurological development and thus represent a selected population.

Head circumference was measured at the maximal OFC and macrocephaly was defined by an OFC superior to the 90th or 97th percentile on the Swiss standard growth curves for neonates and infants respectively [8, 11].

Cerebral structures and/or pericerebral spaces were evaluated neuroradiologically (CT scan: $n = 33$, air pneumoencephalography: $n = 5$), by echography ($n = 5$) or by transillumi-

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Abbreviations: CSF = cerebrospinal fluid; DD = developmental delay; IEH = idiopathic external hydrocephalus; OFC = occipito-frontal circumference; PMG = primitive megalencephaly; SAS = subarachnoid space

nation ($n = 13$). Pericerebral SAS were considered enlarged when a transillumination halo was symmetrically equal or superior to 5 cm or when neuroimaging revealed unusually large pericerebral SAS. Ventricular or pericerebral SAS dilation, however, never accounted for the macrocephaly alone. Megalencephaly was diagnosed when a child showed macrocephaly *and* when hydrocephalus or subdural haematoma could be ruled out either by neuroradiological methods ($n = 43$) or by clinical criteria alone ($n = 31$). The latter method applies mainly to the older cases in which invasive diagnostic methods were not justified and in which the combination of clinical data and follow up observation clearly excluded these diagnoses. Children with megalencephaly associated with a known condition (tuberous sclerosis, neurofibromatosis, metabolic condition) or a rare syndrome (cerebral gigantism or Sotos syndrome) were excluded from the study. After records reviewal, 25 cases were excluded because of normal OFC ($n = 16$), poor data ($n = 6$), hydrocephalus ($n = 1$), isolated subdural haematoma ($n = 1$) or Sotos syndrome ($n = 1$). The children in this study thus have primitive megalencephaly. Through direct or indirect examination (a questionnaire was sent to all patients' paediatricians), 53 patients were re-evaluated within the last 6 months.

Neurological and developmental assessment was made in each case. Developmental delay in the younger children (< 2 years) refers to those children with clear-cut retardation in motor (most with associated hypotonia) or language development but who did not have global mental retardation or evidence of specific neurological signs indicative of one particular form of cerebral palsy. This assessment was not based on standardized tests, but was a clinical judgment taking into account the normally wide range of occurring variations. Persistence of "clumsiness" or need for speech therapy in the older children was also considered as "developmental delay" (DD). Non-genetic convulsive disease were considered as epilepsy as opposed to genetic seizures (focal Rolandic, Petit Mal, Grand Mal, generalized spikes-waves) because the latter are known not to be associated with PMG. Children without DD, mental retardation, cerebral palsy or epilepsy were considered neurologically normal. Signs of increased intracranial pressure were defined as a bulging fontanelle, diastasis of cranial sutures, dilation of scalp veins and the setting sun or "eye-popping" phenomenon [3]. School is very selective in the Canton de Vaud. School evaluation was done earliest after the 1st year of primary school (6–7 years old), and normal attendance to regular school was considered as reflection of a probably normal intelligence.

Familial megalencephaly was assumed when documentation of an enlarged head in a close relative (by measurement or history, see results) was obtained. Prematurity was described as a gestational age < 37 weeks. Perinatal problems were defined by any neonatal distress necessitating reanimation.

Literature studies of IEH report children younger than 3 or 4 years old without complex morphoneurological abnormalities. To answer our first question and for comparison purposes, a subgroup was drawn from the total group including all infants with pericerebral space evaluation before the age of 3 and excluding those with mental retardation associated with complex dysmorphic features.

Statistical comparisons between subgroups and analysis of variables correlation were based on Fisher's exact test and chi-squared test.

Illustrative case reports

Case 1

This female child was delivered normally at full-term, the result of a normal pregnancy. Birth OFC is not known. The father is macrocephalic. At 5 months, she was referred because of macrocephaly, frontal bossing, an "eye-popping" phenomenon and suspected hydrocephalus. Neurodevelopmental assessment was normal. A cerebral CT scan revealed slight ventricular dilation and pericerebral space enlargement (Fig. 1). Lumbar cerebrospinal fluid (CSF) was normal. A repeat cerebral CT scan at 9 months showed no change. Diagnostic puncture of enlarged pericerebral space revealed normal CSF under normal pressure and excluded a subdural collection. At 21 months, a 3rd cerebral CT scan (Fig. 1) revealed definite decrease of both subarachnoid and ventricular dilation. The eye-popping phenomenon had disappeared. At 48 months she is developing normally.

Case 2

This male child was delivered after a normal pregnancy. Birth OFC is not known. Both parents are normocephalic. He was admitted at hospital at 18 weeks because of sudden onset of persistent crying, loss of consciousness and hypotonia. He presented signs of increased intracranial pressure. His OFC was between the 90th and 97th percentile. Radioisotopic cisternography revealed right parietal and left frontal collections. Repetitive aspiration of the former drained a chronic subdural effusion and aspiration of the latter diagnosed an acute subdural haematoma. Complete skeletal survey and repeated parent questioning did not suggest a battered child syndrome. Recovery was complete. However, OFC growth was too rapid and crossed the 97th percentile at 6 months. The child is now 9.5 years old, macrocephalic and normal.

Case 3

This female child was delivered by a caesarean section because of materno-fetal disproportion after a normal pregnancy. Birth OFC is not known. Both parents are normocephalic. At 4 months OFC was already above the 97th percentile but the child's development and skull transillumination were normal. At 5 months the child was admitted to hospital because of excessive crying, irritability, vomiting and fever that appeared after an apparently benign fall from a height of 40 cm. A CT scan revealed bilateral subdural collections. Chronic subdural fronto-parietal haematomas were drained bilaterally. Repeated parent questioning and enquiry at home did not suggest a battered child syndrome. Recovery was complete. The child remained macrocephalic and normal. Control cerebral CT scan at 8 months revealed only slight pericerebral SAS dilation and increased ventricular size. At 14 months, a 2nd control cerebral CT scan showed decrease of ventricular and subarachnoid dilation. The child is now 7 years old, macrocephalic and normal.

Case 4

This is a non-battered megalencephalic child with radiologically documented pericerebral SAS enlargement at 1 and 6 months of age who spontaneously developed a subdural hygroma at the age of 9 months.

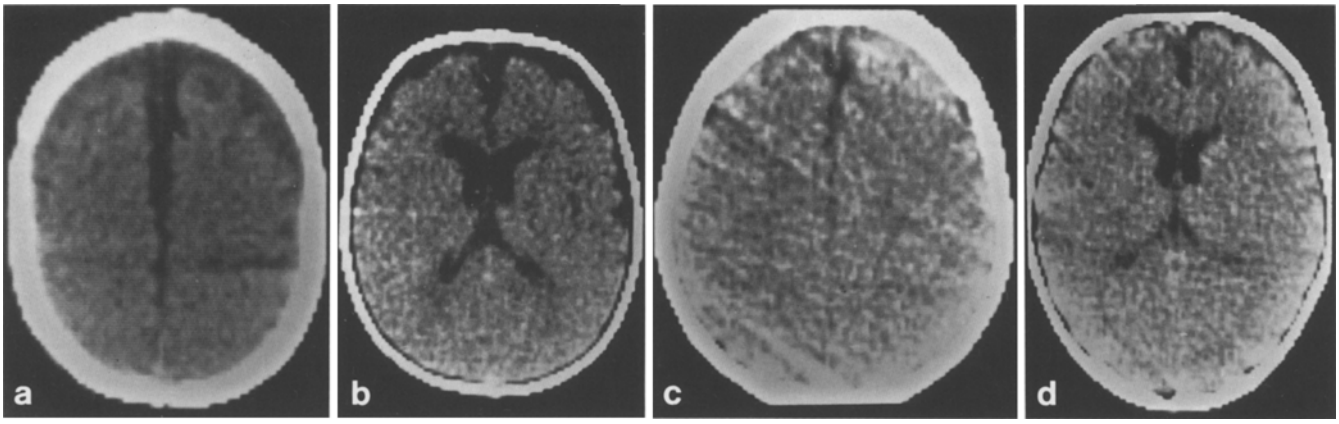

Fig. 1a–d. Cerebral CT scans of case 1. **a, b** Age 5 months: reveals diffuse enlargement of pericerebral SAS, wide interhemispheric fissure and slightly dilated lateral ventricles; **c, d** age 21 months: reveals definite decrease of pericerebral SAS, interhemispheric fissure and ventricular dilation

Results

Population characteristics are shown in Table 1. The male preponderance (sex ratio M/F = 50/24) is not understood but corresponds to literature findings [5]. 68 children (92%) were older than 36 months at follow up. Family history was available in 71 cases. There was a familial history of megalencephaly in 50 (70%) cases which could be assessed by OFC measurement in 36/50 cases, and found in first degree relatives in 44/50 cases. Outcomes of children with familial and nonfamilial megalencephaly were compared. Both groups had a similar perinatal history. We found no statistically significant difference for the occurrence of DD ($P > 0.5$) or mental retardation ($P = 0.33$) and for school outcome ($P > 0.5$). However, 21 children had not reached school age at follow up and conclusions concerning school outcome are tentative. Mental retardation was more frequent in nonfamilial megalencephaly than in familial cases though the difference was not significant. No significant association between perinatal history and the occurrence of either DD ($P > 0.5$) or mental retardation ($P > 0.5$) was found. Of 62 known birth OFC, 31 (50%) were already above the 90th percentile and 31 (50%) were between the 10th and the 90th percentile. Of 28 normocephalic children at birth with OFC measures before 24 months of age, rapid head growth with crossing of the 97th percentile occurred within 12 months for 19 and between 12 and 24 months for 9. Figures 2 and 3 show a smoothed representation of all OFC values of boys and girls showing percentile crossing from birth to 24 months and further OFC growth paralleling 3 and 4 standard deviation for boys and girls, respectively[1]. Wave aspect is due to smoothing and to incomplete follow up OFC values. Megalencephalic infants at birth had more frequent DD than birth normocephalic infants but the comparison was not quite significant ($P = 0.06$). Mental retardation and school prognosis were similar in both birth normocephalic and megalencephalic infants.

Two children were giants, a mentally retarded boy and a normal girl, with heights constantly above the 97th percentile. Neither showed features of Sotos syndrome [6]. Of 74 children, 7 (9.5%) had complex dysmorphic features.

Developmental assessment, neurological findings and school outcome (Fig. 4)

All 74 children underwent developmental and neurological assessment. Typical motor delays were hypotonia, head lag or late acquisition of gross motor skills for infants or clumsiness

Table 1. Population characteristics

Number of patients	74
Sex ratio (M/F)	50/24
Mean follow up (range)	8 years 10 months (15 m – 21 y)
Familial megalencephaly	50/71
Birth OFC > 90th percentile	31/62
Complex dysmorphic features	7/74

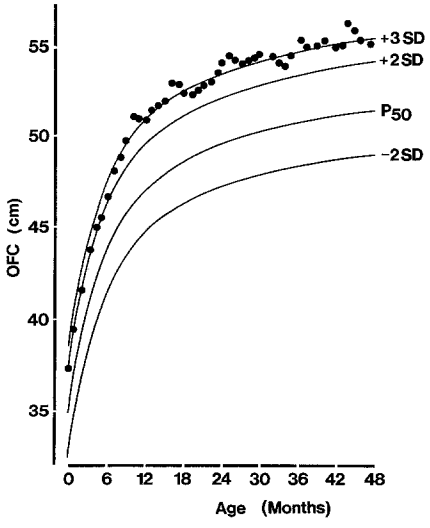

Fig. 2. Smoothed representation of OFC growth in boys

[1] $SmOFC(t)$ = smoothed OFC at time $t = OFC_{P50}(t) + \frac{1}{9}(Z_{t-2} + 2Z_{t-1} + 3Z_t + 2Z_{t+1} + Z_{t+2})$ where Z_t = mean OFC deviation from percentile 50 (P50) at time $t = \frac{1}{N}\sum (OFC(t) - OFC_{P50}(t))$. Obtained results are similar when expressing OFC in standard deviations: $2(OFC(t) - OFC_{P50}(t))/(OFC_{P97}(t) - OFC_{P50}(t))$

for children and teenagers. Language delay consisted in late and difficult acquisition of normal language. Of the 17 developmentally delayed at follow up, 12 were 6 years or older. As follow up evaluations were often made many years after the initial examination and therefore DD could have disappeared at any time between the two evaluations, at what age DD disappeared cannot be ascertained. Eight children (11%) were mentally retarded, three of whom have complex dysmorphic features. A significant association ($P = 0.02$) between complex dysmorphic features and mental retardation was found. Three children presented with a subdural haematoma/effusion.

Mean age at school evaluation was 11 years 1 month; 47 (90%) were older than 7 years. Of the nine "delayed" children who attended regular school normally, eight had remained clumsy and one had language difficulties. Of the ten children attending a special school, seven were mentally retarded and three combined developmental delay with psychological problems for two and complex dysmorphic features for one. These findings indicate that an isolated DD probably does not prevent a normal school attendance.

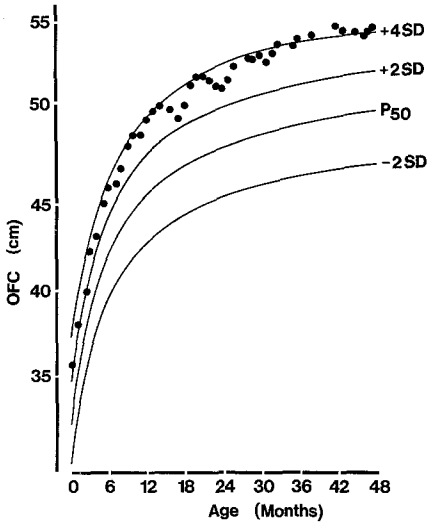

Fig. 3. Smoothed representation of OFC growth in girls

Comparison of megalencephalic children with normal or enlarged pericerebral SAS (Table 2)

Forty-four children met the selection criteria (see patients and methods). Pericerebral SAS were evaluated by 24 CT scans, 4 cerebral echographies, 4 air pneumoencephalographies and 12 transilluminations. Twenty-two infants with normal pericerebral SAS (18/22 24 months or younger at evaluation) were compared with 22 infants with enlarged pericerebral SAS (21/22 24 months or younger at evaluation). None of the children had a subdural collection. The differences are not statistically significant.

Neuro-imaging findings

A total of 49 cerebral CT scans, 8 cerebral echographies and 6 air pneumoencephalographies were done. Ventricular size evaluation of 43 children revealed minimal or mild dilation in 20 cases (46.5%). Nine children had more than one CT scan. Ventricular size remained stationary ($n = 6$) or spontaneously decreased ($n = 3$). Pericerebral space width was stationary ($n = 5$), spontaneously decreased ($n = 2$) or increased in one. Cerebral CT scans in two children revealed diffuse abnormal white matter hypodensity. They both are developing normally at 5 and 9 years old. Robinson [13] reported a similar case, though with more important hypodensities, for whom a temporary diagnosis of Alexander disease was made but which the clinical course did not confirm. Infants with PMG can therefore show unusual white matter hypodensity on cerebral CT scan but may this not be pathological.

Discussion

PMG exhibits a wide spectrum of probably heterogenous conditions. Use of standard OFC growth curves introduces the

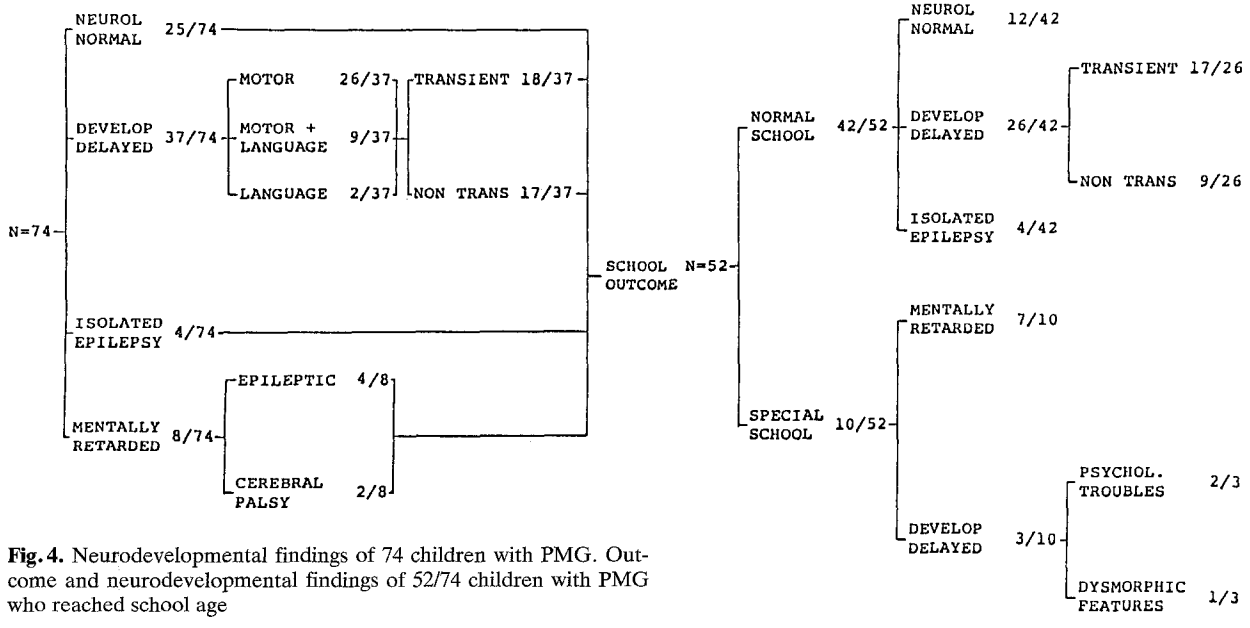

Fig. 4. Neurodevelopmental findings of 74 children with PMG. Outcome and neurodevelopmental findings of 52/74 children with PMG who reached school age

Table 2. Comparison of megalencephalic children with normal (NSAS) or dilated (DSAS) pericerebral subarachnoid space

	NSAS ($n = 22$)	DSAS ($n = 22$)	P
Male	14/22	12/22	>0.5
Normal delivery	8/19	10/22	>0.5
Prematurity	2/19	3/20	>0.5
Perinatal problems	3/21	6/22	0.5
Birth megalencephaly	10/20	12/21	>0.5
Developmental delay	13/22	12/22	>0.5
Mental retardation	2/22	1/22	>0.5
Normal school outcome	11/15	11/12	>0.5
Signs of increased intracranial pressure	3/22	7/22	0.3
Enlarged ventricles	7/18	10/15	0.17
Frontal bossing	11/21	17/21	0.1

first bias by selecting 1%–5% of the normal population. The neurodevelopmentally normal children of our study could therefore belong to the normal population. This could also apply to patients with "benign familial megalencephaly" [1].

Our results indicate that megalencephalic children with normal or enlarged pericerebral SAS do not differ significantly with regard to perinatal, familial, morphological, neurodevelopmental and school histories, and we postulate that enlargement of pericerebral SAS – or idiopathic external hydrocephalus – is but a variant of PMG with transient alteration in CSF dynamics. It has been shown [10, 12] that excessive head growth progresses even though pericerebral SAS enlargement disappears. In our study, children with idiopathic external hydrocephalus showed more frontal bossing, ventricular dilation and minor signs of increased intracranial tension than megalencephalic children without enlarged pericerebral SAS although the difference is not significant. In these cases, a genetic defect affecting the development of the arachnoid villi and/or CSF absorption has been suspected [2].

Two facts indeed seem to support the view of an alteration of CSF dynamics: Chazal et al. [4] demonstrated a resistance to CSF absorption in two children with pericerebral SAS enlargement. Portnoy and Croissant [10] studied seven megalencephalic children with high opening pressure of the arachnoid villi and/or high sagittal sinus pressure, similar to that seen in adult benign intracranial hypertension.

We found a great variability in the head growth dynamics of children with PMG, half of them being megalencephalic at birth, the other half becoming megalencephalic and crossing the percentiles at different ages within the first 24 months. It is not clear why OFC in girls is in term of standard deviation greater than in boys.

Minor developmental delays in megalencephalic children are being reported with increasing frequency. We found no statistically significant relationship between either megalencephaly at birth and the occurrence of perinatal problems or between delivery mode, prematurity or perinatal problems and the occurrence of DD or mental retardation. Further, no perinatal history was suggestive of a cerebral lesion. This indicates that neurological and developmental findings in our children under study can be attributed to megalencephaly. A large proportion of our population (37/74) was found to be developmentally delayed, though 18/37 only transiently. Alvarez et al. [2] think that megalencephaly-associated DD generally disappears before the age of 2 years. However 12/29 of our study children who once showed DD were still found to be clumsy (12) or delayed in language (3) at school age follow up. This suggests either that the population of Alvarez et al. should be re-evaluated at school age in search of minor motor abnormalities or that there are three subsets of PMG: one with entirely normal neurological development whose distinction from the normal population can be problematic, a second with minimal short-lived DD and a third with more important motor or language acquisition problems.

We found many minor head shape anomalies, mainly frontal bossing which is certainly due to the impressive brain growth and, in some cases, to the ventricular dilation. Seven children showed complex dysmorphic features which were significantly associated to mental retardation, reflecting the severe end of the PMG spectrum. However, we could describe no new megalencephalic syndrome.

Deleterious consequences of pericerebral SAS enlargement seem very rare but a predisposition to non-traumatic subdural collection was suggested by Kapila et al. [7]. Our case reports (2–4) indicate that a subdural effusion can occur spontaneously or only after minor trauma in megalencephalic children. One of them (case 4, whose pericerebral SAS was known to be enlarged before the development of the subdural hygroma) supports actual views of increased tearing susceptibility of the bridging subarachnoid veins [7]. We are fairly confident that our three described infants with spontaneous subdural collection were not battered children. The latter condition is very difficult to exclude, it should however not be wrongly suspected in case of idiopathic subdural collection.

Neuroradiological studies revealed ventricular dilation in 20/43 cases which is a common phenomenon in megalencephaly and in IEH [1, 2, 4, 9, 10, 12] and is probably a consequence of the same suspected alteration of CSF absorption in both conditions.

Further research is obviously needed to fully delineate PMG, its relationship to IEH and to understand why some brains do become so large. An insight to the last question was proposed by Schoenle et al. [14] who reported a case with extreme megalencephaly and elevated insulin growth factor II in CSF and brain and proposed a causative relationship between insulin growth factor II and megalencephaly. Further, only prospective studies could reveal differences in the occurrence of DD in familial/non familial cases of PMG, to better assess the relationship between PMG and IEH and to define which megalencephalic children belong to the normal population.

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