Megalencephaly

A Clinical Study with Chromosomal Analysis*

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Through the ages people have been curious about big heads. Various attributes have been assigned those who possessed them. An example is the childhood jingle:

Little head, little wit.
Big head, big wit.

Or, varying usually with the size of the head of the speaker:

Little head, little wit.
Big head, not a bit.

The weights of brains of various group of laborers, tradesmen and professional groups were tabulated. The largest brains, as expected, belonged to the group of professional people. Canavan and Eisenhardt studied the brains of 50 insane criminals and found that 36 had a brain weighing 1400 gm. or more. We might conclude that these were “professional” criminals. “Elite” brains were weighed. Lord Byron at 1807 gm., Bismarck at 1790 gm., and Thackeray at 1600 gm., seemed to have established a trend favoring braininess until the brain of Anatole France, the novelist, was weighed in at 1017 gm. The last weight is that of the brain of a 2-year-old child.

To the neurosurgeon, however, a large head, and especially an enlarging head in a child, represents hydrocephalus. The following case presents these stigmata.

Case Report

The patient was 25 mos. old when first seen at the Yale-New Haven Medical Center, referred by Dr. Merrill Baratz, the family pediatrician. The chief complaint was of vomiting 1 or 2 times daily for 6 or 8 weeks. During this time he would frequently rest his head on the floor or upon his mother’s lap. He also resumed taking a noon-day nap, a practice he had discarded previously. The patient was delivered at 8 mos. gestation by Caesarean section. The indication for the Caesarean section was previous sections for cephalopelvic disproportion, the fetuses’ heads being large. At birth this child’s head was not enlarged. It measured 36 cm., the 60th percentile. His weight at birth was 3380 gm. He had a heart murmur which was attributed to incomplete closure of the ductus arteriosus or foramen ovale. The patient had moderate respiratory difficulty with a tachypnea of 60 per min. during the 1st week of life. A small pedunculated nodule of the skin with a narrow stalk in the “pilonidal region” was removed by ligation. The patient was moderately icteric at the time of discharge on the 10th day. At 10 mos. the circumference of his head was 50 cm. and had been enlarging steadily since that time. The patient’s motor development was retarded; he began to walk at 21 mos. of age.

Three siblings have minimally enlarged heads. An older brother had roentgenograms of the skull at 30 mos. of age because of concern about the size of his head, 53.5 cm. in circumference. These were reported as showing an increased size of the cranial vault in relation to the facial bones. One sister had an obstructive uropathy requiring resection of the neck of the bladder. The mother’s head is enlarged and measures 62 cm. Both parents are of normal intelligence.

Examination. The child was an obese, white male, alternately crying and dozing. The circumference of the head was 58 cm. and uniformly enlarged (Fig. 1). The expected average at 2 yrs. is 49 cm. and at 3 years is 50 cm. The fontanelles were closed. Examination of the fundus in a struggling child revealed an abnormality of the optic disc that was interpreted as papilledema on the left. Subsequent attempts to photograph the fundus have been unsuccessful. The heart murmur was not heard. The patient had normal male genitalia and the testes were in the scrotum.

Fig. 1. Patient at 40 mos. of age showing uniform enlargement of head without frontal bossing. Circumference of head is 59.5 cm.
Diagnosis. The child was admitted with the diagnosis of hydrocephalus. In the operating room a right frontal burr hole was placed. The surgeon, after some difficulty in catheterizing the lateral ventricle, introduced 20 cc. of air. The ventricular system was not enlarged. The mantle of the brain was thickened, and the convolutional pattern appeared to have a moderate increase in complexity (Fig. 2). We were left with the diagnosis of megalencephaly.

2nd Admission. The patient was re-admitted for further evaluation at 40 mos. of age.

Examination. The circumference of his head was 59.5 cm. His weight was 20 kg. The fundus revealed a glial nodule of the left optic nerve head. The vomiting had not been relieved by tonsillectomy and adenoidectomy. Physical and neurological findings were unchanged from the previous admission.

Psychological testing revealed an unusual pattern of performance. He read numbers but could not name pictures of objects. (The patient was able to count to 30.) He communicated almost exclusively by utilizing a combination of gestures and vocal signals. He used a few words (especially no-no-no) and would repeat sentences said to him. Often he used something like jargon which was very expressive but unintelligible. His conception of simple cause-and-effect relationship and danger was rudimentary.

Various other studies were carried out and the results are listed in Table 1. The values of the studies on blood, urine and cerebrospinal fluid are within normal limits with two exceptions: The level of serum cortisol (hydrocortisone) is slightly low. The urinary 17-ketogenic steroid value is elevated since the value recorded is for approximately one-half of the total 24-hr. urinary volume. The other half of the urinary output was distributed by the patient. The serum cortisol and the 17-ketogenic steroids were determinations of the same group of adrenal cortical hormones. As the determination of serum cortisol is a more reliable test, the adrenal cortical function, as measured, is probably within normal limits.

The chromosomal complement of a leucocytic preparation was determined (Fig. 3). This revealed a diploid karyotype. A secondary constriction was seen in 1 of the 6-12 group of chromosomes but this was not a constant finding and thus of doubtful significance.

History of the Disease

Megalencephaly refers to a large, abnomal brain. The condition has been known for some time. The case of a 1-yr.-old male with clinical hydrocephalus was reported by Schupman in 1888. The child died during a convulsion and at autopsy the brain weighed over 2½ lbs. (1130 gm.). The lateral ventricles were small and contained a very insignificant quantity of fluid. The convolutions were enlarged and developed remarkably. Fletcher, at the suggestion of Andrews, apparently was the first to use the term megalencephaly. Vircow referred to this condition as cephaloma. Canavan described a case under the title of Schilder's encephalitis periaxialis diffusa; the brain weighed 1890 gm. (after 3 days in formaldehyde). The description resembles that

Table 1

<table>
<thead>
<tr>
<th>Laboratory data</th>
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<tbody>
<tr>
<td>Blood</td>
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<tr>
<td>Hematocrit 36%</td>
</tr>
<tr>
<td>Count of white blood cells 7800</td>
</tr>
<tr>
<td>Fasting blood sugar 65 mg.%</td>
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<tr>
<td>Blood urea nitrogen 10 mg.%</td>
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<tr>
<td>Sodium 142 mEq./l.</td>
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<tr>
<td>Potassium 4.6 mEq./l.</td>
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<tr>
<td>Chloride 103 mEq./l.</td>
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<tr>
<td>Bicarbonate 20.8 mEq./l.</td>
</tr>
<tr>
<td>Protein-bound iodine 5.8 μg.%</td>
</tr>
<tr>
<td>Cortisol 10.0 μg.%</td>
</tr>
<tr>
<td>Urine (Incomplete specimen)</td>
</tr>
<tr>
<td>17 ketosteroids 0.5 mg./24 hrs.</td>
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<tr>
<td>17 ketogenic steroids 1.8 mg./24 hrs.</td>
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<tr>
<td>Creatine 117 mg./24 hrs.</td>
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<tr>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>Cells—None</td>
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<tr>
<td>Protein 11 mg.%</td>
</tr>
<tr>
<td>Other studies</td>
</tr>
<tr>
<td>Electroencephalogram. Within normal limits</td>
</tr>
<tr>
<td>Roentgenogram of skull. Sella turcica markedly widened in anteroposterior diameter</td>
</tr>
<tr>
<td>Skeletal survey for age of bone. Consistent with chronological age</td>
</tr>
<tr>
<td>Upper gastrointestinal series. No apparent visceromegaly</td>
</tr>
<tr>
<td>Electrocardiogram. Sinus tachycardia</td>
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* Courtesy of Dr. Herbert A. Lubs, Jr., Genetic Disease Research Laboratory, Department of Medicine, Yale University School of Medicine, New Haven, Conn.
given by earlier writers as being characteristic of megalencephaly. Wilson\(^2\) chose megalencephaly as the topic for his Presidential Address to the Section of Neurology, Royal Society of Medicine in 1883. Since that time there have been scattered reports of autopsied cases.

The incidence is difficult to tabulate. Campbell\(^1\) reported 15 brains that weighed over 1700 gm. in 1146 autopsies at an asylum, about 1.3 per cent of the population in an asylum. Korbin\(^17\) found 1 case in 50,000 autopsies at the Los Angeles County Hospital. Matson\(^19\) has indicated that he occasionally has seen children with large heads who on study turned out to have normal-sized ventricles with no evidence of obstruction to spinal-fluid circulation. In 1 case\(^17\) the characteristic pattern was demonstrated by ventriculography yet the patient retained the diagnosis of congenital hydrocephalus until death.

Other findings are common in this disease. There is marked predilection for males. All but 1 of Campbell’s 15 patients were males. We found only 3 cases involving females.\(^1,12\) Mental retardation of varying degree is the rule, although Korbin’s patient is listed as having normal development and died at 42 mos. following a tonsillectomy. McGrath\(^13\) reported the case of an idiot savant, with a head 70 cm. in circumference, who had an exceptional ability to calculate dates. When asked, “What day of the week was April 1, 1893?,” the patient gave the correct answer, Thursday, in 7 sec. Epilepsy is common; Ford\(^13\) stated that 50 per cent of the patients are epileptic and 5 of Campbell’s 15 patients had seizures.

The life expectancy is short, with many children dying with intercurrent infection or with convulsions. The cases of Benda\(^6\) (40 and 64 years), Wiglesworth and Watson\(^24\) (37 years), and Campbell\(^9\) (29 years) lived to adulthood with a severe degree of dementia.

There are no specific pathological changes in megalencephaly and various reports tend to be confusing and contradictory. Norman\(^14\) believed megalencephaly should be reserved for heavy brains having additional structural anomalies and listed 3 varieties:

1. Diffuse overgrowth of protoplasmic macroglia (astrocytes), some with malignant transfiguration.
2. Uniform enlargement without neuroglial preponderance.
3. Incidental feature of other anomalies, e.g., tuberose sclerosis, amaurotic familial idiocy, metachromatic leuco-encephalopathy and hemihypertrophy.

We shall not discuss this 3rd class although it would seem that study with present-day techniques might result in the reassignment of many cases listed as primary megalencephaly to this group.

The above classification refers primarily to the microscopic description. Grossly, too, there are variations in appearance. The brain may show a uniform enlargement involving the cerebrum, cerebellum, brain stem\(^12,25\) and in some cases\(^3,11\) the spinal cord. The convolutional pattern is simple\(^22\) and individual gyri are large and broad with no appreciable abnormality of shape or number. The brain fills the cranial cavity to capacity. On section of the brain the ventricles are not dilated.

A second, equally common, gross pattern has the enlargement restricted to the cerebrum which has a convolutional pattern of great complexity and many secondary fissures.\(^3,13,17,24\) The primary fissures usually may be identified. The cerebellum may share in this pattern to a greater or lesser degree. There may be, in both of these gross patterns, a disproportionate increase in the gray matter or both gray and white matter may be enlarged.\(^14\)

Weij\(^23\) reported a case which is in Norman’s 1st class. He performed differential counts of the various neural elements in what he calculated to be comparable sections of normal and megalencephalic brains and concluded there was no increase in the number of neurons as the thickened cortex would seem to indicate. He felt the glial elements were increased causing the neurons to be dispersed. Others have found a proliferation of astrocytes in the cortex\(^7,13\) and white matter.\(^8\)

A well-proportioned and harmonious growth of nerve cells and fibers, without gliosis or other interstitial reaction has been described.\(^7,24,26\) The neurons show a peculiar generalized dysplasia of the ganglion cells of the different cortical layers. They also may show changes from slight chromatolysis to advanced degeneration.

Ferraro and Barrera\(^11\) noted a diffuse distribu-
tion of small round cells which they considered to be some type of biopotentential indifferent cell. Isolated groups of cells consisting of these indifferent cells, plus mature glial and neuronal elements, were found. Heterotopias of neural elements have been described. No correlation of the complexity of the convolutional pattern and the microscopical findings is found.

The etiology is unknown. Wilson proposed a neurohormonic defect similar to that causing hemihypertrophy of a limb. He added that the brain is perhaps the sole organ that is not subject to the hypertrophying influence of disordered pituitary function and referred to Atkinson's report in which only 3 of 265 brains in acromegalics were enlarged. Cushing and Davidoff listed a brain weighing 1525 gm. in their report of acromegaly. The weights of the other 3 brains are not recorded. In his pituitary monograph, Cushing reported the case of the giant Turner (Case XXXII) who was 8 ft., 3 in. tall and died at the age of 36. His brain weighed 1884 gm. and the convolutions were normal and unusually well formed. The body had been embalmed 3 days prior to the autopsy. He also referred to the brains of the giants Wilkins and Hessler which weighed 1540 and 1465 gm., respectively. Korbin, too, postulated a nonspecified hormonal abnormality. Dennis et al., recorded 5 cases of megalecephaly in achondroplastic dwarfs and suggested that excess growth hormone which cannot be utilized by the abnormal long bones was diverted to the brain. No report of the determination of hormonal levels has been found. The present authors are impressed with the frequency of neonatal asphyxia in the present and other recorded cases. Whether this is etiologic or symptomatic is problematic.

Summary

A case of megalecephaly is presented. The patient had the apparent stigmata of hydrocephalus with a progressively enlarging head, vomiting, listlessness and what was thought to be papilledema. Ventriculography revealed the correct diagnosis. A descriptive review of megalecephaly is given. No case in which the diagnosis of megalecephaly was made or suggested prior to ventriculography was found. The neurosurgeon is thus most likely to make this diagnosis. Various endocrinologic parameters and chromosomal analysis were found to be normal in this case.

References