Skeletal Radiol. 1, 25–28 (1976)

Skeletal Radiology

Macrocranium and Macrencephaly in Neurofibromatosis*

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Abstract. Data were collected on 52 patients (30 males and 22 females) with neurofibromatosis. Using the volumetric method of Gordon, it was found that 44% of the patients had cranial capacities above the 95th percentile (70% were above the 50th percentile). The presence of intracranial tumors and/or hydrocephalus did not influence skull size. Four patients above the 95th percentile had normal pneumoencephalograms and cerebral angiograms, indicating that the cause of the macrocranium, in some instances at least, is macrencephaly. Volumetric measurement of the sella turcica in 27 of the 52 patients gave results which strongly suggest that idiopathic enlargement of the sella in neurofibromatosis is uncommon, if not rare. Skull films of 26 patients with tuberous sclerosis did not show an increase in cranial capacity similar to that found in neurofibromatosis.

Key words: Neurofibromatosis – Skull abnormality – Sella turcica enlargement – Macrencephaly – Macrocranium.

In 1973, Weichert et al. [12] published the first systematic evaluation of head size in neurofibromatosis. Their study was prompted by the clinical suspicion of macrocranium in two patients with neurofibromatosis from the practice of one pediatrician. They found that of 24 children with von Recklinghausen's disease who had satisfactory roentgenograms of the skull, 75% had macrocranium. As we had not recognized this finding in our practice and had not been able to find it listed in any of the standard texts dealing with neurofibromatosis, we were somewhat skeptical of this high figure but, nevertheless, set out to evaluate our own material, We were aware of the fact during 1972 Norman [6] had reported a family of 10 members with neurofibromatosis, 6 of whom had large heads, and that, in the same year, DeMyer [2], in his excellent paper on megalencephaly in children, had included neurofibromatosis as one of the possible causes. As no references to previous reports of such abnormalities were given, it was assumed that these were isolated, incidental observations.

Case Material and Method of Measurement

In this retrospective study we were able to find in our files 50 patients with neurofibromatosis (28 males and 22 females) who had skull films satisfactory for measurement. These patients ranged in age from 4 months to 62 years with the majority being in the pediatric age group. Cranial capacity was calculated from 68 skull examinations obtained on these patients, using the well known method of Gordon [4]. This approach, which measures the inner capacity of the skull, is in contrast to the study by Weichert, et al. [12] in which outer size of the skull was measured by the method of Haas [5]. Gordon's method was chosen because we wanted to get some idea of cranial content size and because it embodies percentiles rather than the statistically less acceptable "range" inherent in the Haas procedure. Furthermore, it seemed reasonable to assume that confirmation of macrocephaly in neurofibromatosis by a different mode would be even more convincing. Incidentally, Bray et al. [1] have reported a close correla-

* Presented, in part, at the First Annual Meeting of the International Skeletal Society, Washington, D.C., March 23–27, 1974, and at the Eleventh Annual Meeting of the European Society of Pediatric Radiology, Helsinki, Finland, May 29-June 1, 1974

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tion between Gordon's figures and the widely used clinical measurement of occipito-frontal circumference.

Patients with known intracranial tumors and/or hydrocephalus were included in the initial study.

Results

The results are shown in Figure 1. As can be seen, 80% of the boys' skulls and 75% of the Girls' skulls had cranial capacities greater than the 50th percentile. Of greater significance is the figure obtained for the abnormally large heads. No less than 46% of the 50 patients had cranial capacities above the 95th percentile.

Later, when our total number of patients had grown to 52, we used a somewhat more uniform approach, selecting only the initial skull examination for each patient. In this analysis the total number of patients with cranial capacities above the 50th percentile dropped to 70% but the more important

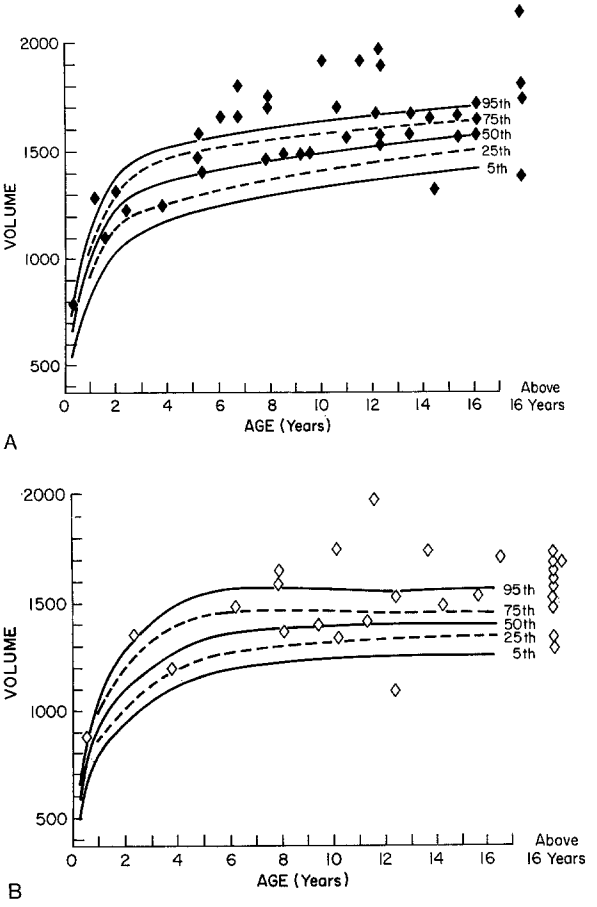

Fig. 1. A Cranial capacity measurements in males with neurofibromatosis. **B** Cranial capacity measurements in females with neurofibromatosis

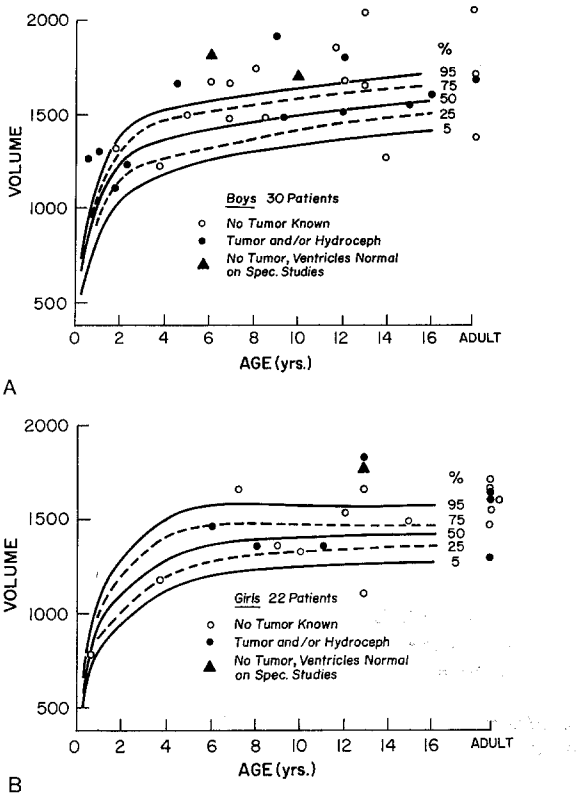

Fig. 2 A and B. Cranial capacity of neurofibromatosis patients with and without known intracranial pathology. Increased intracranial volume was seen equally as often in patients with and without known intracranial tumors or hydrocephalus

group, those patients with cranial capacities above the 95th percentile, remained almost constant at 44%.

We again chose to include those neurofibromatosis patients with known intracranial tumors and/or hydrocephalus in our analysis. In this group there were six optic nerve gliomas, three pontine gliomas, two patients with aqueduct stenosis and one each with acoustic neuroma, cerebellar astrocytoma and communicating hydrocephalus. One older patient, originally though to have hydrocephalus, was subsequently shown to have cerebral atrophy. Although these patients with known intracranial lesions were included, they were identified in such a way on the graphs that one could determine if their presence in any way influenced the overall results as far as cranial capacity was concerned. That they did not is clearly shown in Figure 2. It is evident that in patients with known intracranial pathology, 70% are above the 50th percentile and 44% are above the 95th percentile, indicating no difference whatsoever from the previous determinations.

Among the neurofibromatosis patients who had special neuroradiologic procedures such as angiograpy and pneumoencephalography, there were four who had cranial capacities above the 95th percentile

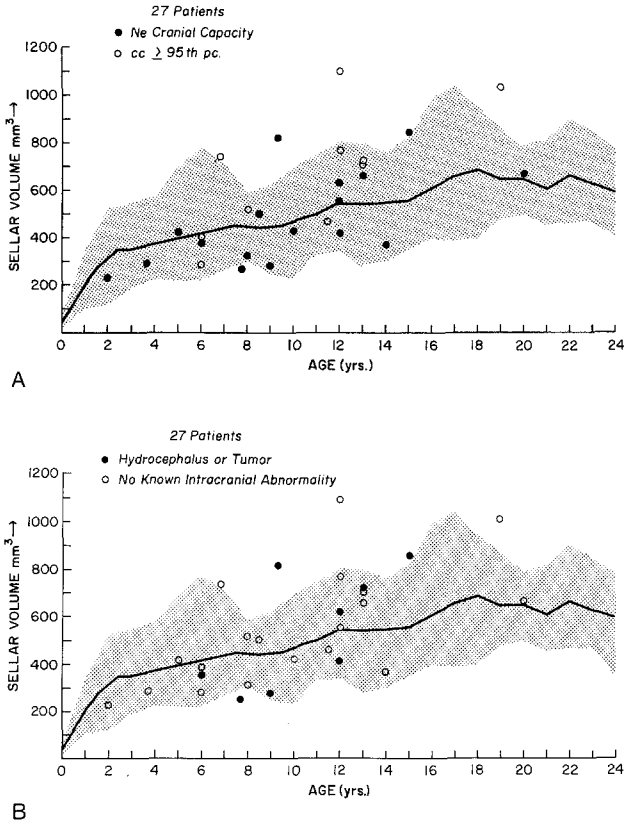

Fig. 3. A Sellar volume of patients with neurofibromatosis as determined by the method of DiChiro and Nelson [3] is compared with intracranial volume. Almost all patients had sellar volumes within the normal range (shaded area). **B** Sellar volume compared to known intracranial pathology in these same patients. Sellar size was increased as often in patients with and without known intracranial abnormality

but whose ventricles were felt to be normal in size without evidence of an intracranial mass. Although the number of patients is too small to permit convincing conclusions, the macrocranium (increased skull size) which obviously occurs quite commonly in neurofibromatosis, may well be due in fact to macrencephaly (increased brain size). Interestingly, four of the patients reported by Weichert et al. [12] had an admitting diagnosis of macrencephaly but the manner in which this was determined is not stated.

Size of Sella Turcica

Whereas macrocranium has been ignored as a sign of neurofibromatosis, enlargement of the sella turcica in this disorder has ben reported on numerous occasions. This may be associated with dysplasia of the sphenoid bone or due to erosion by optic nerve gliomas, acoustic neuromas or pituitary adenomas, all of which appear to have a higher incidence in neurofibromatosis than in the general population. Rarely, it is idiopathic. With this in mind, we thought that it might be worthwhile to compare the volume of the sella turcica with cranial capacity on the one hand, and with the presence of known intracranial pathology on the other. Skull films of 27 different patients in whom the critical width of the sella could be measured were collected and volumetric determinations were made using the method of DiChiro and Nelson [3]. These showed no correlation between sellar volume and cranial capacity in neurofibromatosis patients with or without known intracranial disease (Fig. 3). Eighty-five per cent of the sella turcicas were within the normal range regardless of cranial capacity or the presence of known intracranial tumor or hydrocephalus. Of the three cases clearly above the limits of normal size, one was an obvious example of sphenoid bone dysplasia and another was the result of erosion by an optic nerve glioma. Only one was truly idiopathic and this was the one closest to the normal range. Admittedly, there are more sella volumes above the 50th percentile in subjects with abnormally large cranial capacities, but this is not statistically significant ($p=0.2$). These findings lead us to seriously question the importance of idiopathic sellar enlargement in neurofibromatosis. If it is found a diligent search should be made for the specific cause.

Other Neurocutaneous Syndromes

Having confirmed beyond reasonable doubt that macrocranium occurs in a highly significant number of individuals with neurofibromatosis, we were curious to determine if the same held true for other neurocutaneous syndromes. Skull films of twenty-six patients with tuberous sclerosis were obtained from our files and measured for cranial capacity by the Gordon method (Fig. 4). There were 16 girls and 10 boys ranging in age from 7 months to 14 years. When multiple examinations of the same patient were present, the initial one was selected for measurement. None of these individuals had a known intracranial tumor or hydrocephalus but one harbored a huge aneurysm arising from the cavernous portion of the right internal carotid artery. Incidentally, his cranial capacity was at the 10th percentile.

It is clearly evident that patients with tuberous sclerosis do not have a significant degree of macrocranium, less than 4% of the patients being above the 95th percentile and less than 50% being at or above the 50th percentile.

We were unable to find enough examples of the Sturge-Weber syndrome or the von Hippel-Lindau syndrome to warrant analysis of their cranial capacities. Because of the unilateral or bilateral cortical

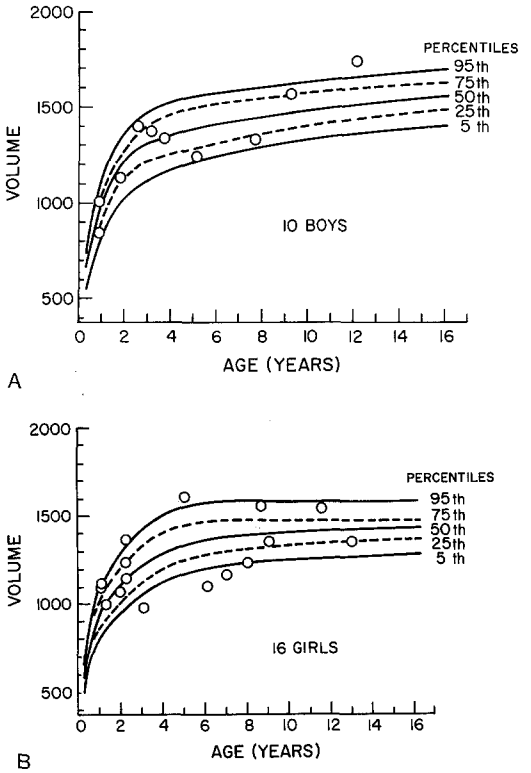

Fig. 4A and B. Cranial capacity in 26 patients with tuberous sclerosis. Almost all had intracranial volumes at or below the 95th percentile, in contrast to the neurofibromatosis patients

atrophy inherent in the Sturge-Weber disorder it appears likely that the intracranial volume would be diminished in most instances. The von Hippel-Lindau syndrome is so rare that measurement of the cranial capacities of the very few patients with this disorder who might be seen in any one medical center seems rather pointless. Neurofibromatosis, therefore, emerges as the only one of the neurocutaneous syndromes in which detection of a large head has any practical importance.

Comment

More than two thousand articles have been written on the subject of neurofibromatosis since von Recklinghausen's [11] classic description in 1882. As previously mentioned, there are a few isolated references to macrocranium as a manifestation of the disorder; in fact it was the most prominent feature in the so-called "elephant man", one of the earliest documented, albeit originally unrecognized, neurofibromatosis patients in medical history. On numerous occasions, Sir Frederick Treves [7–10] called attention to his celebrated patient's huge and misshapened head. Incredibly, these observations were not applied to subsequent patients with neurofibromatosis and, perhaps because the changes were more subtle, nearly a century passed before it was shown that macrocranium constitutes a frequent, significant skeletal manifestation of the disease. Further studies including computed tomography may well show that macrencephaly is an equally important finding in this disorder.

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