Neurological manifestations of pediatric achondroplasia

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The neurological and neuroradiological manifestations of pediatric achondroplasia are analyzed on the basis of 10 cases. In addition to the classical symptomatology of an enlarging head, with or without increased intracranial pressure, several patients presented symptoms related to a small foramen magnum. Respiratory problems and quadriparesis were also observed in these patients. Six patients who were treated by foramen magnum decompression showed remarkable improvement. Neuroradiological evaluation revealed a significant number of patients with dilated cortical sulci and basal cisterns, and mild dilatation of the ventricles on computerized tomography (CT) and/or ventriculography. Two patients showed signs of obstruction at the fourth ventricle outlets. Some exhibited anomalous dilatation of cerebral veins and dural sinuses, narrowing of the sinuses at the jugular foramen, and enlarged emissary veins. Ventriculoperitoneal or ventriculoatrial shunts were placed in three patients. In the other children with a large head and dilated ventricles, head growth curves paralleled the normal slope, and there was no significant clinical evidence of increased intracranial pressure or enlarging ventricles on follow-up CT scan.

KEY WORDS: achondroplasia, foramen magnum stenosis, quadriparesis, hydrocephalus, venous sinus, jugular foramen

ACHONDROPLASIA is the most common and best known form of infantile dwarfism. The usual neurological manifestations of achondroplasia have been reported to be macrocrania and cauda equina compression due to a narrow spinal canal. Head enlargement has been considered to be caused by true megalencephaly or hydrocephalus. The occurrence of a symptomatic narrow lumbar canal is rare in pediatric patients, but the presence of medulla or cord compression in a small foramen magnum seems to be rather frequent.

We have treated 10 infants and children with achondroplasia who developed progressive head enlargement. Six infants presented with respiratory problems and quadriparesis related to a small foramen magnum. The neurological and neuroradiological manifestations of pediatric achondroplasia are analyzed on the basis of the 10 cases (Table 1).

Clinical Material and Methods

Radiological Studies

Cerebral Angiography and Venography. Cerebral angiography was performed on nine patients. The vertebrobasilar arterial system and the termination of the basilar artery were located at a high level because of a small posterior fossa and short clivus. In extreme cases, the choroidal point of the posterior inferior cerebellar artery was above Twining’s line (Fig. 1). In seven cases, there was a significant cortical avascular area in the lateral view. Such areas were compatible with the wide cortical subarachnoid spaces seen on pneumoencephalography or computerized tomography (CT).

Characteristically, cortical veins were dilated and cortical anastomotic venous channels were well devel-
TABLE 1

Summary of 10 cases of achondroplasia*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age</th>
<th>H.C. (cm)</th>
<th>Neuroradiological Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ventricle Dilatation</td>
<td>Subarachnoid Dilatation</td>
</tr>
<tr>
<td>1</td>
<td>M, 4 mos</td>
<td>46.5</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>F, 3.5 mos</td>
<td>46.1</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>M, 1 yr 3 mos</td>
<td>51.5</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M, 1 yr</td>
<td>50.0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>F, 1 yr 9 mos</td>
<td>51.5</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>M, 4 mos</td>
<td>44.5</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>F, 8 mos</td>
<td>46.0</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>8</td>
<td>F, 1 yr</td>
<td>50.4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>F, 1 yr 1 mo</td>
<td>46.2</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>10</td>
<td>F, 6.5 mos</td>
<td>46.2</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

*H.C. = head circumference; VP = ventriculoperitoneal shunt; VA = ventriculoatrial shunt; +++ = marked; - = none.

Pneumoencephalography. Pneumoencephalography was performed on eight patients. There was no obstruction of cerebrospinal fluid (CSF) in six of them. In two patients, air was not seen in the ventricular system, and subsequent Conray ventriculography showed a complete block at the outlets of the fourth ventricle (Fig. 6). In almost all patients, enlarged cortical subarachnoid spaces and basal cisterns were observed, but the cisterna magna was extremely small or not observable (Fig. 7). The aqueduct of Sylvius, fourth ventricle, and other posterior fossa structures were found at a relatively high level.

Computerized Tomography. Computerized tomography was performed on six patients. The findings usually included a mild or moderate degree of lateral ventricular dilatation, enlarged cortical sulci and basal cisterns, and a narrow foramen magnum (Figs. 8 and 9). Because of the underdeveloped petrous bone and small posterior fossa, the fourth ventricle was not visualized at the petrous bone level with the usual scanning angle. The partial-volume effect would have had some influence on the size of the foramen magnum obtained by CT, but it was possible to visualize the size of the bone and soft tissue by changing the window levels and width (Fig. 9).

Radioisotope and Metrizamide CT Cisternography. The CSF dynamics were studied by radioisotope cisternography in six patients (Fig. 10) and by metrizamide (Amipaque) CT cisternography in four (Fig. 11). There were no CSF blocks in the subarachnoid spaces, even at the level of the narrow foramen magnum. Definite ventricular reflux was not observed. In three patients, the radioactivity concentrated near the parasagittal region, and persisted for over 72 hours.

Myelography. Myelography was performed on nine patients. Pantopaque was used in one patient and metrizamide in another two patients as a contrast medium. The remainder were investigated by gas (air

FIG. 1. Case 1. Lateral view of the right transbrachial cerebral angiogram of a 4-month-old baby boy, showing an unusually high position of the basilar artery and posterior inferior cerebellar artery. Unrolling of the anterior cerebral artery is also observed.
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Fig. 2. Case 2. Anteroposterior (left) and lateral (right) views of the left carotid angiogram, venous phase, in a 3½-month-old baby girl. The transverse sinus and torcular Herophili are lower than normal. The occipital and marginal sinuses are dilated and have a spectacle-like appearance (left). The great vein of Galen is elongated and terminated high. The straight sinus is also elongated and located posteriorly.

Fig. 3. Case 7. Anteroposterior view of the right carotid angiogram, venous phase, in a 3-month-old baby girl. Abnormally dilated posterior and marginal sinuses are seen.

Fig. 4. Case 2. Lateral view of the jugular phlebogram of the craniovertebral region of a 3½-month-old baby girl. The dural sinus is narrow at the jugular foramen (curved arrow). Emissary mastoid veins are seen draining into the extracranial venous plexuses (straight arrow). The dilated marginal and occipital sinus are again seen.
or O₂) myelography. In eight patients, myelography showed that the foramen magnum was encroached upon by a bulbous odontoid process and the thickened posterior edge of the foramen magnum, both of which obviously compressed the lower medulla. However, no complete block was observed at this level, and the gas or positive contrast material passed to the basal cisterns without difficulty (Fig. 12). Dorsal and lumbar myelography was performed in two cases in which metrizamide was used as a contrast medium. The films revealed a generally narrow spinal canal without definite cord or cauda equina compression.

Clinical Studies

Narrow Foramen Magnum. A narrow foramen magnum was observed in eight patients, and decompressive suboccipital craniectomy was performed in six of them. It was not attempted with the other two because their symptoms were less severe or too advanced. The symptoms presented were respiratory difficulty, cyanosis attacks after crying, quadriparesis, and poor head control. The deep tendon reflexes were not increased in infants.

Operations were performed with the patients in the prone position, and the thickened rim of the posterior foramen magnum was removed as far laterally as possible. In one case, the dura mater was incised because of an abnormally high level of posterior inferior cerebellar artery on angiography, but there was no mass lesion in the posterior fossa; an extremely dilated marginal sinus was observed. In the remaining five cases, the dura mater was not opened. Remarkable improvement of symptoms was observed postoperatively, respiratory difficulty improved immediately after surgery, and the paresis of the extremities disappeared gradually. However, the tendency for the head circumference to increase remained unchanged.

Hydrocephalus. In most patients with achondroplasia, there are no CSF blocks in the ventricles or in the subarachnoid spaces. Usually the ventricular dilation is not severe, and clinical signs of hydrocephalus are not as severe as in other types of congenital hydrocephalus. It has also been observed that hydrocephalus in achondroplasia is easily arrested. Shunting procedures are not indicated in most cases, unless the head circumference is abnormally enlarged or the neurological deficits become more definite. In some cases of communicating hydrocephalus, however, a coexisting obstruction of the outlets of the fourth ventricle may be present. We observed this noncommunicating hydrocephalus in two patients who showed...
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Signs of more severe increased intracranial pressure (ICP), such as bulging fontanels and enlarged lateral ventricles. Shunting procedures may be indicated in this type of hydrocephalus.

Shunt operations were performed on three patients. One patient (Case 1) has been followed for 4.5 years, and at present he is still shunt-dependent. His was a noncommunicating hydrocephalus (Fig. 6), and decompressive posterior fossa craniectomy was also carried out. In the second patient (Case 9) a ventriculoperitoneal shunt was inserted. Four years later the shunt is apparently not functioning, but the patient is now asymptomatic, and hydrocephalus is thought from CT evidence to be arrested (Fig. 7). The third patient (Case 10) was diagnosed by air studies as having noncommunicating hydrocephalus at 6.5 months old, and a ventriculoatrial shunt was performed, but the follow-up period has not been adequate for comment. Now 15 years old, this patient is severely physically handicapped, totally blind, and has gait disturbance; CT scans show moderately dilated lateral ventricles. The other seven cases showed communicating hydrocephalus, and they have been followed by periodic CT studies without surgery for 2 to 8 years. Their hydrocephalus has not been active or is apparently arrested, and their head growth is now proceeding at a normal rate.

Discussion

Narrow Foramen Magnum

The mortality in the first year of life in achondroplasia is surprisingly high. The exact cause of fetal achondroplasia is unknown, but it has been reported that a small foramen magnum due to osseous hypertrophy may cause a serious compression of the cord and caudal medulla in achondroplastic dwarfs. This has been recognized from autopsied cases, but only a

FIG. 7. Case 9. Upper: Lateral view of brow-up pneumoencephalogram of a baby girl aged 1 year 1 month, showing enlargement of the lateral ventricle and distension of basal cisterns and enlarged cortical subarachnoid spaces. A ventriculoperitoneal shunt was placed. Lower: Computerized tomography of the patient at 5 years 6 months old. The shunt was apparently not functioning, but there were no signs of increased intracranial pressure. The scan shows minimal dilatation of lateral ventricles, but the cortical subarachnoid spaces are not significantly dilated.

FIG. 8. Case 3. Computerized tomography of a baby boy aged 1 year 3 months, showing moderately dilated lateral ventricles and enlarged cortical sulci.
few cases have been reported in which the compression was radiologically documented or surgically relieved. Luyendijk, et al.,20 reported a 15-year-old girl who presented with a high level of medullary compression resulting in basilar impression, and a narrow foramen magnum and C-1 arch. Her post-operative recovery from progressive quadriplegia was remarkable.

We have observed a rather high incidence of symptomatic narrow foramen magnum. The symptoms presented were attributed to direct compression of the medulla oblongata. The infants usually had feeding problems, poor head control, inability to sit without support, quadriplegia, and cyanosis attacks after exercise or crying.

In achondroplasia, the foramen magnum has been reported to be encroached upon by the thickened posterior edge of the foramen magnum, the hypoplasia of the clivus, and a narrow high cervical spinal canal.20 However, the bulbous changes of the odontoid process appeared to play an important role in compressing the medulla anteriorly, as usually observed on myelo-igraphy. The diameters from the posterior aspect of the dens to the posterior margin of the foramen magnum are different in myelograms and plain x-ray films; the former show much less space because of the cartilagenous overgrowth of the odontoid process, which is not usually demonstrated on plain x-ray films. Our surgical results have been dramatic; respiratory difficulty and cyanosis attacks disappeared soon after operation. It may be impossible to perform the operation in cases of terminal achondroplasia or thanatophoric dwarfism, but we believe that many patients might benefit from decompression of the foramen magnum.

Enlargement of the Head

Head enlargement has been considered to be a result of true megalencephaly or hydrocephaly. Dennis, et al.,7 studied five cases of autopsied achondroplastic dwarfs and reported that the enlargement of the head was due to megalencephaly rather than dilatation of the ventricle. However, most of these patients died of increased ICP and respiratory and/or cardiac failure. The increase in brain weight may be due to brain edema, and the diagnosis of the megalencephaly from autopsy is rather difficult to evaluate.

Many neuroradiological studies have proposed that the cause of the large head is hydrocephalus, a condition with ventricular dilatation. Cohen, et al.,3 reported air encephalography in eight of 15 achondroplastic children. All their patients showed some degree of ventricular dilatation without increased ICP or any other evidence of progressive hydrocephalus, and a shunting procedure was indicated in only two cases. The cortical mantle remained thick in all patients. Mueller, et al.,22 studied nine achondroplastic dwarfs with CT, and found that all had large ventricles that ranged from the upper limits of normal to severe hydrocephalus. In our series, the lateral ventricles were dilated to a mild to moderate degree in all cases. Our findings indicate that the large head of achondroplastic dwarfs is the result of a hydrocephalic rather than a megalencephalic process.
Pathogenesis of Hydrocephalus

The pathogenesis of hydrocephalus in achondroplastic dwarfs is still the subject of controversy. The skeletal abnormalities (achondroplastic shortness of the base of the skull and upper cervical spine) were once thought to be the cause of obstruction of the fourth ventricle outlets.\(^{1,18}\) Wise, et al.,\(^{34}\) reported two achondroplastic children with hydrocephalus, one with an obstruction between the ventricular system and the subarachnoid space, and the other with no obvious CSF obstruction. In our two cases of obstruction, the block was found at the fourth ventricle outlets. In one of them, however, posterior fossa decompression was performed without any lessening of the tendency to enlarged head circumference and increased ICP. Thus, shunting procedures were eventually necessary. Findings suggest that a coexisting obstruction of the extraventricular spaces is frequently present in achondroplasia.

The majority of the evidence available seems to indicate that there exists a communicating type of hydrocephalus in achondroplasia. James, et al.,\(^{18}\) demonstrated communicating hydrocephalus in two achondroplastic children with radioisotope cisternography. Depresseux, et al.,\(^{8}\) also performed radioisotope cisternography on achondroplastic dwarfs. These authors reported entirely normal CSF flow, and no dynamic disorder of the CSF was observed. Depresseux, et al.,\(^{8}\) concluded that the ventricular dilatation in achondroplasia is the result of a morphogenetic expansion of the telencephalic ependymal cavities in moderate hydrocephalus or an atrophic process. However, these authors failed to repeat radioisotope cisternography after 24 hours. In three of six patients in our study, the radioactivity concentrated near the parasagittal region, and continued for over 72 hours. These findings suggest that there is failure of CSF absorption at this level. Those patients with parasagittal stasis will presumably benefit from CSF diversionary shunts. However, the CSF absorption seems to be gradually compensated for with age, so the shunting procedure may not be necessary in most cases. The degree of ventricular dilation in achondroplastic children is usually mild or moderate. Dandy\(^{5}\) observed that the progression of the hydrocephalus in achondroplasia ceases at puberty, because growth of the base of the skull after birth probably leads to some relief of the hydrocephalus. Mild or moderate dilatation of the lateral ventricle was seen in all patients in this series, but a shunting procedure was necessary in only two, both of whom had a noncommunicating type of hydrocephalus. The other cases were followed by periodic CT studies.

Enlarged cortical sulci in achondroplastic dwarfs have been reported by several authors.\(^{23,34}\) The basal cisterns are also enlarged, but the cisterna magna is small or absent. Mueller, et al.,\(^{20}\) noted the association of enlarged cortical sulci and hydrocephalus in three of nine patients, and stated that this combination would be primarily the result of cortical atrophy, or secondary to a compensated hydrocephalic state with CSF over the sulci when the pressure is relieved.

The present authors encountered enlarged cortical sulci more frequently. The main difference between Mueller's series and ours is that our patients were much younger and had more marked neurological...
problems. It is unlikely that the large sulci are due to primary cortical atrophy. Most of these patients show good physical and mental development. The signs of increased ICP, such as large head, bulging fontanel, and increased intraventricular pressure, tend to suggest that the large cortical sulci indicate communicating hydrocephalus. Moreover, a follow-up review of seven patients by means of CT scans revealed that the dilated cortical subarachnoid space seems to decrease with advancing age or after shunting procedures. The association of enlarged cortical sulci and ventricle dilatation has been reported by several authors in hydrocephalic infants, as well as achondroplastic dwarfs. Most of these cases of hydrocephalus are due to factors such as venous pressure elevation, sinus occlusion, and superior vena cava obstruction.\textsuperscript{14,30}

Radioisotope cisternography and venography findings suggest that stenosis of the jugular foramen causes elevation of venous sinus pressure and the development of anastomotic venous channels. The ventricular and cortical sulci dilatation may be produced by a disturbance of CSF absorption as a result of increased venous retrograde pressure. This mechanism was originally proposed by Welter\textsuperscript{33} in 1936, and the development of the emissary veins lends support to it.

It is known that the elevation of superior sagittal sinus pressure will decrease CSF flow across the arachnoid villi, resulting in a greater CSF volume.\textsuperscript{25} It is not widely accepted, however, that increased intracranial venous pressure will produce hydrocephalus. It has not been possible to induce hydrocephalus in experimental animals by occluding the cerebral venous sinuses, and thrombosis of the dural sinuses can produce increased ICP without ventricular dilatation. On the other hand, ventricular dilatation following elevation of intracranial venous pressure has been demonstrated by other investigators. Bering and Salibi\textsuperscript{2} occluded the accessible pathway of intracranial venous outflow, obtaining sustained periods of intracranial venous hypertension and producing ventriculomegaly in 74\% of dogs. A number of investigators have reported pediatric cases linking venous factors with hydrocephalus.\textsuperscript{6,8,12,14,34,50,51,57,68,80} Kinal\textsuperscript{7} reported four infants with hydrocephalus who had
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abnormalities of the lateral sinuses and jugular bulbs. There are several reports of superior vena cava occlusion, which produced communicating hydrocephalus.14,14,30

The reported cases of dural sinus hypertension can be divided into two groups. Patients in the first group develop hydrocephalus and those in the second group develop pseudotumor cerebri. Haar and Miller14 and Rosman and Shands27 suggested that the difference in outcome is related to age; when an increase in intracranial venous pressure occurs in children aged less than 18 months, hydrocephalus results, whereas in persons 3 years of age or over, pseudotumor cerebri is caused. The difference depends on whether the cranial sutures are patent or closed. Since achondroplasia is a developmental anomaly, the skeletal changes and the enlargement of the head develop during intrauterine life, and increased venous pressure may lead to hydrocephalus. With the development of the alternative routes of venous drainage and growth of the base of the skull after birth, ICP will be relieved and the majority of head circumference curves will parallel the normal slope.

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