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Branchial Anomalies in Idiopathic Hypoparathyroidism: Branchial Dysembryogenesis

Michael J. Miller, M.D.,* Boy Frame, M.D.,* Andrew K. Poznanski, M.D.,** C.E. Jackson, M.D.,* and Gustave Bermudez, M.D.*

Four of 13 patients with idiopathic hypoparathyroidism had associated congenital anomalies of branchial origin. Three had characteristic hypernasal speech. One of these patients exhibited a cleft palate and the other two had functional and anatomic anomalies of the velo-pharyngeal musculature which explained the speech disturbance. The fourth patient represents the twenty-second recorded case of the III and IV pharyngeal pouch (DiGeorge’s) syndrome, manifested by absent parathyroids and thymus glands associated with unusual facial features and cardiovascular anomalies. Our four patients exhibited a total of 15 congenital anomalies of branchial origin. By including our patients with those reviewed from the literature, 156 patients with idiopathic hypoparathyroidism had a total of 40 different kinds of anomalies of branchial or primitive pharyngeal origin, including absence of the parathyroids. These anomalies of branchial origin may occur alone or in combination. We recommend that the term branchial dysembryogenesis be employed to broaden the III and IV branchial pouch syndrome by including multiple defects of branchial origin whether or not the parathyroids are included. Parathyroid insufficiency should be considered in patients with single or multiple congenital anomalies derived from the branchial arches and pouches.

In patients with idiopathic hypoparathyroidism, the parathyroid glands are usually congenitally absent or replaced by fatty and fibrous tissue. An absence of the thymus, associated with immunologic deficiencies, has also been described by DiGeorge in this variety of parathyroid insufficiency. Because of a common embryologic origin, the combined defect has been designated by Taitz as the III and IV branchial pouch syndrome. In reviewing the case records of 13 patients diagnosed at the Henry Ford Hospital as having idiopathic hypoparathyroidism, congenital anomalies of branchial arch origin were noted in four. Based on our experience and a review of published case reports, patients with idiopathic hypoparathyroidism have increased occurrences of congenital defects in tissues arising from all the branchial pouches and arches. We recommend that the III and IV branchial pouch syndrome be broadened to include multiple congenital defects at all the branchial levels. The term “branchial dysembryogenesis” is suggested, whether or not the parathyroids are included.

Case Reports

Patient One was a baby girl, the product of a full term, normal pregnancy with a birth weight of seven pounds. At one month of age cyanosis and a systolic heart murmur were noted. Radiologic films of the chest showed cardiomegaly and cardiac catheteri-
zation documented the presence of a patent ductus arteriosus and a small interventricular septal defect. She underwent a successful ligation of the patent ductus.

At 12 years of age she was admitted to the hospital for evaluation of seizures and mental retardation. A marked hypernasal quality of speech had been present since early childhood and was unchanged after removal of the tonsils and adenoids. Her speech was high-pitched and hypernasal in quality. Examination also showed that the patient had a round face with hypertelorism and malformed, low-set ears. Papilledema, a 4+ Chvostek, dental hypoplasia, a high-arched palate, and a pansystolic cardiac murmur were also noted. There were no skeletal stigmata of pseudohypoparathyroidism.

The biochemical data supported a diagnosis of hypoparathyroidism. (Table I) Injection of 200 units of parathyroid extract (Lilly) brought a prompt 8-fold phosphaturic response.

Treatment with 75,000 units of Vitamin D daily resulted in the serum calcium levels returning to normal and disappearance of the seizures and papilledema.

The hypernasal speech has persisted. Cinefluorography of the palate and upper pharynx demonstrated marked velo-pharyngeal incompetence. (Figure 1 a-b) The pharynx was deeper than normal and movement of the soft palate during phonation was reduced.

Serum calcium levels obtained from the mother and siblings were normal. Chromosomal analysis of peripheral blood leukocytes showed a normal female karyotype 46XX.

Comment: A 12-year old girl with idiopathic hypoparathyroidism had a patent ductus arteriosus and an interventricular septal defect. She had a round face, hypertelorism, a high arched palate, and low-set, malformed ears. Hypernasal speech was present from early childhood. Cinefluoroscopy of the pharynx demonstrated an abnormality of the soft palate and pharynx.

Patient Two was a 12-year-old boy referred because of maladjustment at school. The child's birth weight was 7½ pounds and the mother had had a threatened abortion during the pregnancy. A cleft palate, present at birth, was repaired at two years of age. When seen here, a diagnosis of mild mental deficiency was made, without electroencephalographic or other evidence of brain damage. Nasal intonation of the voice was ascribed to the cleft palate. The next year, the patient experienced several grand mal seizures. Bilateral papilledema and persistent bilateral Babinski signs were noted, but no clinical features of pseudohypopara-
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Figure 1-a
Normal closure of velopharyngeal musculature, showing sharp angulation of soft palate or "knee action" during phonation.

Figure 1-b
View showing poor angulation of the palate with marked velopharyngeal incompetence which persisted throughout phonation at fluoroscopy. (Patient One)
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The mandible was excessively prominent and was associated with marked dental malocclusion. Hypocalcemia and hyperphosphatemia were present. (Table I) There was a normal phosphaturic response after the injection of 200 units of parathyroid extract. Treatment with 100,000 units of Vitamin D daily corrected the hypocalcemia. The papilledema subsided and there was no recurrence of seizure activity. The hypernasal voice persisted. Cinefluoroscopy during speech and swallowing showed a normal palatal motion without any evidence of venopharyngeal incompetence. Serum calcium levels in the mother and siblings were normal. Chromosomal analysis demonstrated a normal male karotype, 46XY.

Comment: A 12-year old boy with idiopathic

<table>
<thead>
<tr>
<th>Brachial Level</th>
<th>Pouch</th>
<th>Arch</th>
<th>Groove</th>
<th>Associated Pharyngeal Primordia</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Middle ear cavity Eustachian tube</td>
<td>Aortic Arch I involutes Mandible Auricle of ext. ear Tympanic membrane Incus and malleus</td>
<td>Muscles mastication ant, diagastric tensor palatini tensor tympani</td>
<td>External auditory meatus</td>
</tr>
<tr>
<td>II</td>
<td>Tonsillar fossa</td>
<td>Aortic arch II involutes Auricle of ext. ear Parts of hyoid bone Styloid process Stapes Muscles: facial expression post diagastric stylohyoid stapedius</td>
<td></td>
<td>Thyroid</td>
</tr>
<tr>
<td>III</td>
<td>Parathyroid Thymus</td>
<td>Aortic Arch III: common carotid art. prox. internal carotid art., ext. carotid art. Right base of aortic arches III &amp; IV: innominate art. Parts of hyoid bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV, V</td>
<td>Ultimobranchial Body</td>
<td>Aortic arch V: involutes Muscles: Laryngeal, inf. pharyngeal Constrictors: Striated m. of esophagus</td>
<td></td>
<td>Cardiac primordia laryngotracheal bud</td>
</tr>
<tr>
<td>VI</td>
<td>Aortic Arch VI: ductus arteriosus pulmonary arteries</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Miller, Frame, Poznanski, Jackson and Bermudez

hypoparathyroidism had a congenital cleft palate with hypernasal speech and an enlarged mandible with dental malocclusion.

Patient Three was a 53-year-old man admitted to the hospital with pneumonia. His past history indicated recurrent convulsions from early childhood, controlled with Dilantin® and phenobarbital. Mental retardation and a speech defect had been noted early in life.

Examination showed a mentally-retarded individual with a twanging hypernasal quality to his speech. There was a high arched palate, the nasal septum was markedly deviated to the right, and the velo-pharyngeal opening was much wider than normal. There were no physical features of pseudo-hypoparathyroidism.

The serum calcium was decreased and serum inorganic phosphorus was increased. (Table I) A five-fold phosphaturic response was obtained after infusion intravenously of 200 units of parathyroid hormone.

Cine speech study (Figure 1-c) showed the soft palate to have a distorted muscular contracture associated with an unusual configuration and rounded contour, instead of the acute angulation normally observed. There was outpouching of the posterior nasopharynx with adequate development of Passavant's ridge to complete velopharyngeal closure.

The patient had experienced several episodes of pneumonitis, which responded to treatment with antibiotics. Serum immunoglobulins were present in normal concentrations. A normal serum calcium has been maintained with 90,000 units of Vitamin D administered daily. Chromosome analysis revealed a normal male karyotype of 46 XY.

Comment: A 53-year-old male with idiopathic hypoparathyroidism had hypernasal speech from early childhood. Cinefluoroscopy revealed the velopharyngeal opening was much wider than normal and the soft palate exhibited an abnormal muscular contracture and a rounded bulge at the point of the usual normal triangulation.

Patient Four was the product of a normal full-term pregnancy with a birth weight of 7 pounds. Soon after birth he began to convulse.

On physical examination it was noted that the ears were low-set and the pinnae folded. The mandible was receded but otherwise not deformed. There was a precordial systolic murmur. No thymic shadow was seen on study of the chest x-ray films.

The serum calcium was 5.4 mg/100 ml and increased promptly to 12.8 mg/100 ml after 200 units of intravenously administered parathyroid extract (Lilly). Increasing cyanosis, due to congestive heart failure, did not respond to treatment and resulted in death at the age of three weeks. Serum calcium levels in the mother and siblings were normal.

The findings at autopsy included cardiomegaly due to tetralogy of Fallot. Dissection and multiple sections of the cervical and upper mediastinal tissues removed en bloc failed to demonstrate thymic or parathyroid tissue. Lymph follicles and spleen were lacking in germinal centers.

Comment: A newborn infant with convulsions due to idiopathic hypoparathyroidism died from congestive heart failure secondary to tetralogy of Fallot. Low-set malformed ears and mandibular recession were present. Neither thymus nor parathyroids could be identified at autopsy.

Patient Data

The available older literature and detailed case reports during the past five years of patients with idiopathic hypoparathyroidism were reviewed for evidence of associated congenital anomalies of branchial origin. Table II and Figure 2a-c list the anatomic structures that are derived from the primitive branchial arches, grooves, pouches and contiguous pharyngeal areas. A total of 143 cases was reviewed from the literature. Table III lists the numbers and types of congenital anomalies found in these and in our 13 patients. In the total of 156 cases of idiopathic hypoparathyroidism, 33 patients had associated branchial anomalies, with 99 separate instances of 40 different types of anomalies, in addition to parathyroid insufficiency.

Discussion

Our attention was initially attracted by a similar and characteristic hypernasal speech in three of thirteen
patients with idiopathic hypoparathyroidism. In patient One velo-pharyngeal incompetence was noted by cinefluoroscopy. In patient Two a cleft palate was the likely explanation for the hypernasal speech. Cinefluoroscopy of patient Three demonstrated an abnormal soft palatal contraction and configuration during phonation. We thought this explained the speech impairment.

Speech disturbance related to palatal anomalies and malfunction, as described here, has not been emphasized previously as a clinical feature of idiopathic hypoparathyroidism. An intermittent and dysarthric speech of a distinctly different nature and laryngeal stridor secondary to hypocalcemia has been reported. Hypernasal speech was mentioned briefly in one case report in the literature; however, further comment or investigation was not instituted. Since the abnormal speech was first noted early in life in our patients, a congenital origin for the defect is likely. Restoration of the serum calcium to normal did not cor-

Figure 1-c

View showing poor angulation of soft palate, forming a rounded and blunted contour rather than the sharp angle normally present during phonation. (Patient Three)
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Figure 2-a

Midsagittal section of pharynx and oronasal cavities in cross-hatched areas are derived from the stomadeum. Stippled areas posterior to the stomadeum are derived from the primitive pharynx. Roman numerals indicate the site of evagination of the corresponding branchial pouch.


The altered speech in any of the patients.

All three of our patients with hypernasal speech exhibited anatomic or functional defects of the velo-pharyngeal musculature or palate. We suggest the defects observed in patients Three and One indicate a defective or disorganized differentiation of branchiomeric musculature, leading to an anatomic and muscular malfunction in the adult derivatives. Figure 3 illustrates the palatal and pharyngeal muscles, listed in Table II, which are derived from the branchial arches and form the embryologic basis for the observed palatal anomalies and hypernasal speech.

We noted in our patients additional congenital anomalies that arise from dysembryogenesis of the primitive pharyngeal region during the fourth and fifth week of fetal life. The embryology of the pharyngeal transformation is a complex process and many isolated or combined congenital anomalies have been described originating from branchial structures and the primitive
Figures b and c demonstrate aortic arches and derivatives at approximately 33 days. An oblique view of the aortic arches and aorta with segments normally lost darkened.


Pharyngeal wall, as well as the contiguous cardiac primordia. With altered embryologic development, it is not difficult to visualize diminished or altered structure and function of glandular or other tissues derived from the branchial anlage. Table III depicts the numbers and kinds of congenital defects analyzed in 156 patients.

In patient One, both a patent ductus arteriosus and an intraventricular septal defect were observed, in addition
### TABLE III—BRANCHIAL ANOMALIES IN IDIOPATHIC HYPOPARATHYROIDISM ANALAGNE

<table>
<thead>
<tr>
<th>Arch</th>
<th>Branchial Level</th>
<th>Associated Pharyngeal Derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6) lowset malformed ears</td>
<td>(4) hypertelorism</td>
</tr>
<tr>
<td></td>
<td>(2) short lip philtrum</td>
<td>(4) micrognathia</td>
</tr>
<tr>
<td></td>
<td>(3) bifid uvula</td>
<td>(2) prognathism</td>
</tr>
<tr>
<td></td>
<td>(2) cleft palate</td>
<td>(1) small pre-maxilla</td>
</tr>
<tr>
<td></td>
<td>(1) cleft nose</td>
<td>(1) large maxillary arch</td>
</tr>
<tr>
<td></td>
<td>(1) indented nose</td>
<td>(4) widely separated teeth</td>
</tr>
<tr>
<td></td>
<td>(3) high arched palate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) anomalous middle ear</td>
<td>(1) branchiogenic cyst</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1), (2), (3)</td>
<td>(156) parathyroid dysgenesis</td>
</tr>
<tr>
<td></td>
<td>(2) anomalous speech musculature</td>
<td>(22) absent thymus</td>
</tr>
<tr>
<td></td>
<td>(1) aberrant left subclavian art.</td>
<td>(4) aberrant or ectopic thymus</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) aortic atresia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) double aortic arch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) right aortic arches</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) coarctation of descending aorta</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) tetralogy of Fallot</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) complete transposition of great vessels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) vascular ring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV, V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2) esophageal atresia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) patent ductus arteriosus</td>
<td>(5) I.V.S.D.</td>
</tr>
<tr>
<td></td>
<td>(1) hypoplastic pulmonary valve</td>
<td>(2) persistent truncus arteriosus</td>
</tr>
<tr>
<td></td>
<td>(1) &quot;large&quot; pulmonary artery</td>
<td>(1) hemicardiac</td>
</tr>
</tbody>
</table>

( ) = No. of patients

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The unusual facial features of hypertelorism and low-set, malformed ears. The mandible was excessively prominent in patient Two and was associated with marked dental malocclusion. In patient Four postmortem examination confirmed the absence of parathyroid and thymus glands associated with the tetralogy of Fallot. This patient also exhibited an unusual countenance with micrognathia and low-set, malformed ears.

Recent literature concerning idiopathic hypoparathyroidism notes an increased awareness of associated congenital anomalies of branchial origin. Congenital absence of the thymus with attendant immunologic deficiencies was reported by DiGeorge. An awareness of associated cardiovascular anomalies of the branchial arches has also received attention. However, multiple anomalies of other branchial and primitive pharyngeal derivatives in patients with idiopathic hypoparathyroidism have not been emphasized previously. It appears that embryologic defects at the first and second branchial levels are associated as frequently with idiopathic hypoparathyroidism as...
those anatomic defects derived from the third and fourth branchial levels.

Patient Four represents the twenty-second reported instance of the III and IV branchial pouch syndrome, although an immunologic deficiency was not identified. This syndrome usually consists of absent parathyroid and thymus glands, cardiovascular anomalies and an immunologic deficiency. Almost uniformly, these cases have had a fatal outcome, the patient dying either of an infectious process or a cardiovascular death.²

Hypoparathyroidism need not always be present in patients with branchial dysembryogenesis. Cameron reported¹¹ four patients with thymic aplasia occurring with a spectrum of grave cardiovascular defects but without parathyroid insufficiency. Our patient One may represent another incomplete variant of the III and IV pharyngeal pouch syndrome manifested by unusual facial features, cardiovascular anomalies and parathyroid hypofunction but without an absence of the thymus gland or immunologic deficiencies.

Our search for the cause of a hypernasal speech in three of our patients led to palatal and velo-pharyngeal anomalies associated with parathyroid insufficiency. Four of our 13 patients with diagnosed idiopathic hypoparathyroidism exhibited a total of 15 anomalies of the primitive pharyngeal anlage. Analysis of an additional 143 case reports of idiopathic hypoparathyroidism in the literature revealed a
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total of 99 instances of 40 different kinds of branchial anomalies, including the 16 instances in our patients. We believe that this degree of association is beyond coincidence, although statistical analysis is not possible since the total population group from which these cases were drawn is not known.

Previous investigators may have overlooked speech defects and various congenital anomalies of branchial origin in patients with idiopathic hypoparathyroidism. We predict that in the future a large constellation of anomalies of branchial anlage will be found associated with absence of the parathyroids. Such congenital defects from the branchial region obviously may occur as isolated phenomena or in other combinations, with or without an absence of the parathyroid or thymus glands. Since increased occurrence of similar congenital anomalies of branchial anlage has not been described in pseudohypoparathyroidism, further significance is added to this association in idiopathic hypoparathyroidism. The etiology of this syndrome remains speculative. The published case reports of idiopathic hypoparathyroidism and associated branchial anomalies have been of the sporadic (non-familial) form, and evidence of a genetic defect has not been present. Medications and infections, including rubella in the mother during the first few weeks of fetal life, cannot be ruled out as a cause for the defects observed. Since various forms of congenital heart disease have been reported to occur in association with maternal rubella in the first trimester, other related branchial anomalies may have a similar basis of origin.

In consideration of the wide spectrum of embryologic defects found associated with idiopathic hypoparathyroidism, including many derived from the branchial and pharyngeal anlage other than the III and IV pharyngeal pouches, we recommend the term branchial dysembryogenesis as a more complete description of the disease spectrum being considered in this paper. Patients with any combination of the branchial defects described should be screened for possible parathyroid insufficiency.

REFERENCES

Miller, Frame, Poznanski, Jackson and Bermudez


