Lindau’s Disease—in the Hudson Valley*

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The group of manifestations of a peculiar developmental defect described by Lindau\(^7,18\) includes angiomatosis of the retina, hemangioblastoma of the cerebellum, medulla, and spinal cord, visceral cysts, hypernephroma, and cutaneous hemangiomas. The term “von Hippel’s disease” has been used by ophthalmologists to refer to angiomatosis of the retina alone, although 20 per cent of these cases will show manifestations of the disease in the central nervous system.\(^17,18\)

The purpose of this paper is to present a family study in which 13 cases of Lindau’s disease and 8 cases of bilateral cataracts were found.

**Review of Literature**

The initial description of angiomatosis of the retina was made by Fuchs\(^11\) in 1882. Collins\(^6\) in 1894 reported the same condition in siblings, thus giving the first indication of the familial nature of the disease. Angiomatosis of the retina was established as a clinical entity in 1904 by von Hippel\(^13\) and has since been known by his name.

Jackson\(^14\) presented the initial description of hemangioblastoma of the cerebellum in 1872. Although Seidel\(^16\) had recognized a relationship between angiomatosis of the retina and hemangioblastoma, it remained for Lindau\(^17,18\) to correlate fully the involvement of multiple organs.\(^10\) Lindau’s report consisted of a detailed review of the literature, autopsy cases, and personal cases which clearly established this group of abnormalities as “Lindau’s disease.” He noted that while hemangioblastomas arise most commonly in the cerebellum, they may be found in the medulla and spinal cord,\(^15\) but never in the cerebrum, and that usually they were single lesions, but not uncommonly occurred as multiple cerebellar lesions or coexisted with lesions of the medulla or spinal cord.

The first pedigree to establish the transmission of the hereditary defect was that of Rochat.\(^23\) He described 6 affected members of a family in three successive generations. Möller,\(^29\) in his study of a large family, indicated that the inheritance was of a dominant autosomal type.

The inherited incidence has been reported by many observers,\(^1-3,6,7,12,16,19-22,34,37,38,39\) the most extensive pedigrees being those of Silver,\(^27\) Nicol,\(^21\) and Christoferson et al.\(^4\) Silver expressed the view that penetrance might be as high as 80–90 per cent were it not for deaths from other causes although his actual incidence was only 44 per cent. Christoferson et al. found only 12 per cent affected.

Lindau,\(^17,18\) and Cushing and Bailey\(^8,9\) emphasized the surgical treatment of cystic hemangioblastoma, recognizing that drainage of the cyst alone was not adequate and that the mural nodule must be excised for a cure. Stein et al.\(^59\) have shown that the prognosis following early and complete excision is very good and reported 1 case with a 23-year follow-up. Möller\(^29\) reported the first case in which the preoperative diagnosis of Lindau’s disease had been made and an operation deliberately carried out leading to a cure.

The treatment of the retinal lesions has not been entirely satisfactory.\(^30\) Among the treatments used have been fever therapy, roentgen ray, diathermy, vitamins, and enucleation. Recent work by Schepens\(^38\) on the surgery of retinal detachments associated
with angiomatosis of the retina has been very encouraging.

The general nature of the involvement of the central nervous system and retinal manifestations of the disease are basically the same,\textsuperscript{17,18} i.e., a benign primitive vascular tumor (hemangioblastoma) with an adjacent cyst, differing only in size in the anatomic sites of origin.

Materials and Methods

A pedigree of the involved family was constructed utilizing information from a number of sources including older family members, family Bibles, birth and death records, church and cemetery records, historical societies, and old newspaper clippings. Medical data were accumulated from family doctors, hospital records, pathological specimens, roentgenograms, and personal interviews and examinations. The data on the patients with cataracts were obtained from a local ophthalmologist who had operated on several members of the family, and from parents, children and siblings of the involved members.

Results

A family tree encompassing seven generations, 140 years, and 200 persons was established. Great difficulty was encountered in tracing the early members because there were no birth or death records kept in the up-state villages of New York State prior to 1885 and few good records prior to 1900. Factors that facilitated the study were the unusual family name and the fact that few of the family had migrated more than fifty miles from the village in the Hudson Valley where their ancestors had lived in the early 19th century.

Thirteen people in three generations had signs and/or symptoms of Lindau's disease. All living members of this group were located and examined, and the diagnosis was verified. The cause of death in the deceased was documented through hospital charts, and operative and autopsy reports. The hereditary pattern of the affected and the carriers of the trait are shown in Fig. 1.

In a parallel group stemming from the sister of the progenitor of the Lindau's group, 8 people in three generations were found with bilateral cataracts of the usual senile type which were not associated with manifestations of involvement of viscera or central nervous system seen in the other group. The exact age of onset of symptoms from the lenticular opacities could not be determined, but was estimated in all cases to be within the fourth to sixth decades of life.

The pertinent clinical and pathological data are shown in Table 1.

Eight of 18 (62 per cent) patients with Lindau's disease had angiomatosis of the retina (Table 2), three (23 per cent) with no other manifestations. Four of the 8 patients with angiomatosis of the retina (50 per cent) had retinal detachments from which 3 (38 per cent) had become blind in the affected eye. One patient was operated upon for a total retinal detachment and after 3 years had 20/30 vision in the affected eye. Of those with angiomatosis of the retina, the incidence of bilateral angiomatosis was 25 per cent, and of multiple unilateral and/or bilateral angioma, 50 per cent. Six of 10 (60 per cent) eyes with angioma had no alteration of function, 4 (40 per cent) had retinal detachments, and only 3 (30 per cent) were blind. Both the oldest patient (68 years) and the youngest patient (14 years) with angiomatosis of the retina had multiple lesions and were asymptomatic.

Five hemangioblastomas were present in the cerebellar hemispheres, 1 was in the vermis, and 1 was in the conus medullaris.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Heredity of Lindau's disease.}
\end{figure}
TABLE 1
Summary of clinical and pathological data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age*</th>
<th>Involved</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>F.M.</td>
<td>F</td>
<td>(70+)</td>
<td>?</td>
<td>Died of metastatic carcinoma; primary focus unknown</td>
</tr>
<tr>
<td>A.J.</td>
<td>F</td>
<td>64</td>
<td>yes</td>
<td>Angiomatosis of retina O.S. Five lesions seen. Vision unaffected. Otherwise in good health</td>
</tr>
<tr>
<td>G.M.</td>
<td>M</td>
<td>(20+)</td>
<td>no</td>
<td>Died from trauma. Unaffected carrier</td>
</tr>
<tr>
<td>V.D.</td>
<td>F</td>
<td>50</td>
<td>no</td>
<td>Unaffected carrier</td>
</tr>
<tr>
<td>M.S.</td>
<td>F</td>
<td>23</td>
<td>yes</td>
<td>History of nausea, vomiting, &amp; headaches intermittently for 4 mos. Negative neurologically. Normal CSF pressure &amp; protein. Discharged &amp; readmitted less than 1 wk. later in extremis. Died 12 hrs. after excision of L. cerebellar hemangioblastoma. Autopsy of head only</td>
</tr>
<tr>
<td>S.O.</td>
<td>F</td>
<td>73</td>
<td>yes</td>
<td>Six yrs. postop. Nephrectomy for hypernephroma &amp; excision of intrabdominal metastasis. No recurrence of disease</td>
</tr>
<tr>
<td>D.K.</td>
<td>F</td>
<td>(33)</td>
<td>yes</td>
<td>Onset of failing vision O.D. with headaches. Then dizziness &amp; ataxia. Angiomatosis of retina O.D. with partial detachment, papilledema &amp; cerebellar signs. Refused surgery; later accepted. Hemangioblastoma of vermis was biopsied &amp; cyst was drained. Died 10 yrs. later from recurrence</td>
</tr>
<tr>
<td>G.B.</td>
<td>M</td>
<td>53</td>
<td>no</td>
<td>Unaffected carrier</td>
</tr>
<tr>
<td>F.R.</td>
<td>F</td>
<td>(33)</td>
<td>yes</td>
<td>Headaches for 1 yr., followed by nausea, vomiting &amp; staggering. Admitted in extremis. Died several hrs. after ventricular drainage. Autopsy: hemangioblastoma of cerebellum, angioma of liver, cutaneous hemangioma of face</td>
</tr>
<tr>
<td>K.K.</td>
<td>F</td>
<td>(38)</td>
<td>yes</td>
<td>Pain in back with osteolytic lesion of spine. Later had pathological fracture of femur. Autopsy: bilateral polycystic kidneys &amp; hypernephroma with multiple widespread metastasis. Eyes normal</td>
</tr>
<tr>
<td>E.S.</td>
<td>F</td>
<td>32</td>
<td>yes</td>
<td>Headaches for 6 mos., L-sided weakness &amp; numbness, papilledema, L. cerebellar signs, angioma O.D. Hemangioblastoma removed from L. cerebellar hemisphere. Alive &amp; well 6 yrs. postop. with mild L. cerebellar signs. Vision unaffected</td>
</tr>
<tr>
<td>M. H.</td>
<td>F</td>
<td>43</td>
<td>no</td>
<td>Normal physical findings. Unaffected carrier</td>
</tr>
<tr>
<td>J.Y.</td>
<td>F</td>
<td>14</td>
<td>yes</td>
<td>Bilateral angiomatosis of retina. Normal physical findings, encephalogram &amp; pyelogram</td>
</tr>
<tr>
<td>L.V.A.</td>
<td>F</td>
<td>18</td>
<td>yes</td>
<td>Multiple cutaneous hemangiomas</td>
</tr>
<tr>
<td>M.M.</td>
<td>F</td>
<td>22</td>
<td>yes</td>
<td>Spontaneous retinal detachment (complete) with severe visual impairment. Four angioma O.D. Operation for retinal detachment. Vision now is 20/30 in involved eye, 8 yrs. postop. Otherwise well</td>
</tr>
</tbody>
</table>

* Present age, excepting figures within parentheses, which give age at death.
Each was cystic with mural nodules that ranged in size from 0.5×0.5×1.0 cm. to 7.0×7.0×5.0 cm. Two patients had cerebellar signs prior to development of papilledema although they had suffered from headache for months. In 4 patients, the hemangioblastoma was associated with angiomatosis of the retina, and in 2, the ocular symptoms preceded manifestations of involvement of the central nervous system. One patient had 2 hemangioblastomas removed from the same cerebellar hemisphere within 1 year with a good result. On the second admission, she had an ipsilateral hemisensory deficit which cleared with the cerebellar signs after removal of the tumor and cyst. The deaths can be attributed to late diagnosis with decompensation prior to operation in 2 cases, and to incomplete removal with recurrence in 1. Each patient became symptomatic for the first time during the third decade of life.

The diagnosis of hypernephroma was made in 3 patients who ranged in age from 28 to 67 years. One died of multiple widespread metastasis including brain, spine, long bones, and viscera. Two patients survived over 5 years after nephrectomy, 1 of whom had a simultaneous removal of an intra-abdominal metastasis. One patient had no signs or symptoms of hypernephroma until 5 years after the death of her daughter from hemangioblastoma of the cerebellum (and angiomatosis of the retina).

Two patients had cutaneous manifestations of their angiomatous disorder. In 1 it was the only manifestation of disease until sudden death from a cerebellar hemangioblastoma in the third decade of life, while in the other it is at present the sole evidence of disease.

Conclusions

Patients with any type of angiomatous disorder and a positive family history should be considered as having Lindau’s disease because of the tendency for multiple lesions (56 in 21 people) and for the manifestations to occur at various times in the patient’s life, even as late as the seventh decade. Those who are now listed as carriers of the hereditary trait may well become affected if followed for a sufficient period.

Angiomatous lesions of the retina have a tendency to be multiple (24 in 8 people), temporal, and peripheral. Therefore, each patient who is suspected of having Lindau’s disease should have complete retinoscopy through pupils that have been dilated. In our experience, this is done best with the indirect ophthalmoscope (Scheppens-ASO) which allows stereoscopic visualization. Although the tortuous artery and vein emerging from the disc leading to an angioma usually can be seen with direct ophthalmoscopy, the peripheral lesions, detachments, and secondary

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**TABLE 1—(Continued)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age*</th>
<th>Involved</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>F.V.A.</td>
<td>F</td>
<td>36</td>
<td>yes</td>
<td>Spontaneous retinal detachment with complete blindness at age 18 yrs. Seven yrs. later had headaches, nausea, vomiting, ataxia, dysmetria &amp; nystagmus. O.S., 7 angiomata &amp; totally blind; O.D., 1 angionia, papilledema &amp; unafflicted vision. L. cerebellar signs. L. cerebellar hemangioblastoma removed with complete clearing of cerebellar signs &amp; papilledema. One yr. later had recurrent headaches, staggering, L. cerebellar signs, L. hemihypesthesia, &amp; finally papilledema. Another distinct cystic hemangioblastoma was removed from L. cerebellar hemisphere with complete clearing of cerebellar signs, hemihypesthesia &amp; papilledema. Cutaneous hemangioma</td>
</tr>
</tbody>
</table>

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**TABLE 2**

*Angiomatosis of retina*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>6</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2</td>
</tr>
<tr>
<td>Blindness (involved eye)</td>
<td>3</td>
</tr>
<tr>
<td>Unaffected vision</td>
<td>5</td>
</tr>
<tr>
<td>Reduced vision</td>
<td>1</td>
</tr>
<tr>
<td>Retinal detachment, partial</td>
<td>2</td>
</tr>
<tr>
<td>Retinal detachment, complete</td>
<td>2</td>
</tr>
</tbody>
</table>
changes may be missed or not fully appreciated.

Although surgical excision of cerebellar hemangioblastomas is usually feasible, excision of hemangioblastomas of the spinal cord or medulla appears to be neither possible nor advisable because of the extreme vascularity and the proximity to vital structures. Bipolar cauterization of the spinal tumor can be attempted but its effectiveness has not been established. Drainage of the syrinx when it occurs alone or in combination with an hemangioblastoma appears to be at least temporarily effective.

The general morbidity from angiomatosis of the retina appears to be lower than the literature would indicate.\(^4,26\) This raises serious questions as to the advisability of treating asymptomatic cases. Retinal detachments, in selected cases (especially early cases), can be treated successfully by qualified ophthalmic surgeons.

Hypernephromas associated with Lindau’s disease have been referred to as “benign” in some reports.\(^3,26\) This is in striking contrast to 2 of 3 cases reported here which had both clinical and histological characteristics of true malignant disease. Although early diagnosis and nephrectomy are ideal, treatment is impossible with bilateral hypernephroma (as in Case K.K.) even if the diagnosis is made early.

The relationship of the Lindau’s group to the cataract group has not been established embryologically or pathologically. The lenticular opacities differ greatly from the retinal lesion in that the latter and all other angiomatous structures have their origin from mesoderm, whereas the lens is derived from ectoderm. Whether this represents an abortive form of Lindau’s disease or is a coincidence remains unanswered.

Transmission was through affected and unaffected males and females as an autosomal dominant with incomplete penetrance.

### Summary

Summaries of the lesions and their combinations are shown in Tables 3 and 4. Two hundred people of a single family were studied and 21 were found to have inherited cataracts or Lindau’s disease. Because of the systemic nature of Lindau’s disease, new lesions may develop even in successfully treated patients.

The exact incidence of Lindau’s disease in a family with a positive history may be difficult to assess because of the inadequacy of records in the past and the span of time covered by each generation.

We wish to thank Drs. W. Kite, H. Judge, H. Little, V. Tompkins, H. Salm, L. Niessen, E. Ginouves, E. Wolfe, C. Hare, W. Pickett, A. Rappaport, H. Johnson, W. Reese, B. Shortkroff, and the many others too numerous to mention who assisted us in carrying out this study. We are especially indebted to Dr. Charles E. Schepens for his assistance in the ophthalmological aspects of this study.

### References


25. Scheepens, C. Personal communication.


Discussion

Dr. Frank J. Ottenasek: Our own interest in this disease was stimulated by a remarkable family, which was encountered over a period of about 20 years at the Johns Hopkins Hospital.

[Slide] The individual members of the family who were proven to have the disease histologically are shown in black. The stippled circles indicate members of the family who died with symptoms of the disease, unproved pathologically. Those who apparently were free from the disease are uncolored. The small figures indicate inadequate data or represent children who were presumed to be too young to have acquired symptoms of the disease. Every living member of the family was examined with the exception of 1.

It is possible to make several interesting observations from our study of this family. First of all, the patient is usually an adult when his symptoms begin. Only 1 patient in our series was under 20, the oldest 68. The earliest lesion in the individual is usually an angioma of the retina, resulting in progressive loss of vision. The average age incidence of this was about 25 years, whereas the incidence of cerebellar or cord hemangioma was later by 5 to 10 years. This is an important consideration, because it is readily seen that the disease
Lindau’s Disease—in the Hudson Valley

does not appear until after children have been born to the person carrying the disease.

In general, the life expectancy is poor after symptoms have developed, but prognoses must be qualified by location of the lesion and its apparent rate of growth. For example, the presence of a verified lesion of the retina carries no apparent risk to life. It was present for 19 years in 1 of our patients, and for 9 years in another, before death resulted from other manifestations of the disease. A solitary cerebellar hemangioma, if successfully removed, is compatible with good life expectancy. One member of the family lived 16 years following such a removal, only to expire 6 months after the removal of a kidney component of the disease. Because of the late appearance of symptoms, the affected person already has produced offspring who will themselves transmit the disease. The familial character of the illness can be lost in the obscurity of accidental death, other illnesses, or whereabouts unknown.

Lindau’s original series showed no hemangiomatous tumors lying above the tentorium. None of our patients had supratentorial lesions except those of the retina.

Four of the members of our family had right parietal craniotomies performed for supposed focal sensory seizures, with arteriogram in the left hand. One of these operations was performed by Frazier, another by Coleman, 1 by Dandy, and 1 by myself. None of these 4 patients had a supratentorial lesion of any kind, and they subsequently were shown to have posterior-fossa hemangiomas of the brain stem and cerebellum. Although there is not much likelihood today that an unnecessary craniotomy would be done on such a patient, we still have no proper neurophysiological basis of explanation for the apparent seizures and loss of stereognostic sense. Case 20 in Cushing and Bailey’s book on Tumors Arising from the Blood-Vessels of the Brain had arteriogram of the left hand, and had a right parietal craniotomy done. Subsequently, a cerebellar hemangioma of cystic type was removed. It is assumed that the peculiar neurologic findings involving the left hand in this group must be caused by a selective infiltration of part of the brain stem or upper spinal cord by the hemangiomaticus tumor.

The importance of the paper this morning is in pointing up once more the remarkable familial tendency in this disease that should prompt all of us to make careful examination of all members of a family which presents one of its number with Lindau’s disease.

DR. IRWIN PERLMUTTER: In 1949 at the Lahey Clinic we went over a group of 25 verified cystic hemangioblastomas of the cerebellum and found very much what has been reported here this morning, that a great number of them had von Hippel’s disease as well.

There are certain characteristics, however, of this disease that were found in this group that should be mentioned, I believe. In the first place, in studying succeeding generations of patients with this problem, it has been found that the clinical manifestations occur earlier in succeeding generations so that parents who first manifest problems in adult life will have children who will manifest their disease earlier.

Another problem related to this disease is the relationship between the cystic hemangioblastoma of the cerebellum and the histopathology of hypernephroma and the pathogenesis of the hypernephroma—its relation to time.

It is well known that the first symptoms of hypernephroma frequently may be manifested in the central nervous system by metastasis. The original lesion in the kidney may have been present for many years. In 1 of the patients who was operated upon at Lahey Clinic in 1937, the primary lesion was a cystic hemangioblastoma of the cerebellum. The patient then returned to the Lahey Clinic with recurrent symptomatology from the posterior fossa. The opposite cerebellar hemisphere was operated upon and it was thought a similar lesion had been completely extirpated. That was in 1947.

In 1939 that patient was seen again in Miami and a hypernephroma was removed. On reviewing the slides of the second operation at the Lahey Clinic, it was found that the histology was that of metastatic hypernephroma.

DR. JACK GOODMAN: I would like to thank my co-authors for their assistance in preparing this paper, the numerous doctors and hospitals in the Hudson Valley for their cooperation in setting up clinics so that this family could be studied, and the discussers for their comments.