Abstract

Multiple endocrine neoplasia type 2A (Sipple syndrome) was first described by John H. Sipple in 1961. He encountered the index patient as a third-year medical resident, established an association between thyroid cancer and pheochromocytoma through meticulous research into the literature, and published a case report identifying a syndrome named after him.

Keywords

Sipple syndrome; Multiple endocrine neoplasia 2A; Medullary thyroid carcinoma; Pheochromocytoma; Parathyroid adenoma; Parathyroid hyperplasia; RET proto-oncogene mutation

Editors’ Note: Much of the source material for this excellent chapter came from direct interviews that Dr. Sugg held with Dr. Sipple himself.

Introduction

Multiple endocrine neoplasia type 2A (Sipple syndrome) was first described by John H. Sipple in 1961 [1]. It may be surprising to some that he was not an endocrinologist, pathologist, or surgeon, but a
pulmonologist. He encountered the index patient as a third-year medical resident, established an association between thyroid cancer and pheochromocytoma through meticulous research into the literature, and published a case report identifying a syndrome named after him.

Fig. 1 John H. Sipple, M.D. in 1956, SUNY Syracuse

Childhood

John Harrison Sipple was born on July 1, 1930, in Cleveland, OH, and grew up in Lakewood, a suburb of Cleveland. His grandparents immigrated to the USA from Germany. His father John was a banker and lawyer, and his mother Marie was a homemaker. He had an older brother Richard. Sipple attended Lakewood High School, graduating as class valedictorian. In high school, he sustained a football injury and was treated with a full-body cast for 6 weeks. This experience as a patient sparked his interest in medicine as a career. He applied and was accepted to Northwestern, Colgate, and Cornell Universities. He chose to attend Cornell because he was offered a full scholarship for 4 years.

Education, Training, and Professional Career

At Cornell University, Sipple was a zoology major, and participated in football, lacrosse, and the men’s Glee club. At the time, it was possible at Cornell to combine the last year of college and the first year of medical school, thereby obtaining both Bachelor’s and M.D. degrees in 7 years. This allowed Sipple to have his first year of medical school supported by his undergraduate scholarship, and he therefore decided to continue his studies at Cornell University Medical College.

During medical school, Sipple was especially interested in internal medicine. The required diagnostic acumen was particularly appealing. He cites Dr. David P. Barr (1897–1977), professor and chairman of the Department of Medicine at The New York Hospital–Cornell Medical Center as a role model. He vividly recalled being impressed by an interesting patient brought in for demonstration to the class by Dr. Barr. This patient had thyrotoxicosis with classical findings of Graves’ disease. He matched into a rotating internship at the State University of New York Medical Center (SUNY) in Syracuse in 1955. He was very pleased with his internship and the Department of Medicine at Syracuse and so opted to take his residency in internal medicine in Syracuse, completing it in 1959 (Fig. 1). Sipple recalls, “The residency was excellent. It stressed learning, responsibility, teaching, and research in the teaching hospital, community hospitals, and a veterans’ hospital. We were on call every other night early on and maybe one of five by the third year. The main emphasis was on being competent as a diagnostican and consultant in internal medicine but also developing skills (clinical and research) in a subspecialty was encouraged.” His experiences during residency profoundly influenced his professional life: (1) though he was interested in all the subspecialties, he was presented with opportunities to work in the pulmonary laboratory in his spare
time and he worked well with the pulmonologists; (2) he met the two men who would become his future partners; and (3) it was during his third year in residency that he encountered and decided to describe the patient in a manuscript entitled “The Association of Pheochromocyto
ma with Carcinoma of the Thyroid Gland” [1].

Having deferred his military obligation during medical school and residency, Sipple served in the US Air Force from 1959 to 1961 as chief of medicine at the 2845th USAF Hospital at Griffiss AFB in Rome, New York. This was between the Korean and Vietnam wars. At the conclusion of his military service, he accepted a 2-year National Institutes of Health (NIH)-sponsored pulmonary fellowship at Johns Hopkins Hospital, under Dr. Richard L. Riley (1911–2001), the prominent pulmonary physiologist and leader in pulmonary medicine. He was highly productive as a resident and fellow, publishing six papers on respiratory physiology and pulmonary topics. One year into the fellowship, he was offered a position as a pulmonary specialist by the two cardiologists that he had met as a resident in Syracuse, and whom he greatly respected. Faced with this choice, Sipple felt that he would derive greater satisfaction from practicing clinical medicine rather than continuing to perform research. He therefore joined the physician group Internist Associates of Central New York and began practicing internal medicine in 1962. In addition to establishing a thriving practice, he became a prominent member of the medical community in Syracuse. He developed an interest in the electronic medical record in the 1980s and designed his own system for the office. He held a number of important administrative and committee positions at Crouse Irving Memorial Hospital as well as at the University Hospital. He was active in the medical school. He was attending physician for one of the medical teams and made teaching and work rounds with the team 3 months each year. In addition, he made intensive care unit (ICU) pulmonary rounds with house staff, students, and respiratory therapists throughout the year. He also taught physical diagnosis to medical students yearly. He rose up the ladder of appointments and became a full clinical professor of medicine in 1977 at SUNY Syracuse. He was active in the Upstate New York Region of the American College of Physicians, serving as governor from 1989 to 1993. He became president of his practice group Internist Associates of Central New York from 1995 until his retirement in 2000 at age 70.

Family

Sipple married in 1955, the year he graduated from medical school. He met his wife Joy in Ohio, having attended the same high school though he graduated several years before her. She attended Kent State University, and majored in liberal arts (Fig. 2). She is an artist and avid gardener. Sipple states, “We have a great marriage. We work together to have a warm home environment and she took much of the responsibility for our home and children.” They had six children, four boys and two girls and 18 grandchildren. One son, Michael Sipple, followed in his father’s footsteps and became a practicing gastroenterologist in Syracuse, New York.

Fig. 2 John H. Sipple M.D. in 1988, at his 50th high school reunion, with his wife Joy
Description of Sipple Syndrome

In 1959, during his last year in residency, Sipple was consulted on a patient who was hypertensive after neurosurgery for an arteriovenous malformation (AVM) of the brain. The patient was a 33-year-old man, from a community near Syracuse, and had a wife and several young children. He presented to the Syracuse Veterans Administration Hospital after an onset of a severe headache, nausea, and vomiting, followed by left-sided weakness and lethargy. A lumbar puncture revealed bloody spinal fluid and elevated pressure. A large AVM was seen on a right carotid angiogram. A craniotomy was done to evacuate the hematoma. Postoperatively he developed fever, restlessness, and fluctuating blood pressure, as high as 240/120. Seventeen days later, he underwent a second craniotomy to relieve elevated intracranial pressure, another hematoma was evacuated, but the patient died 3 h later. A family history could not be obtained at the time of his hospitalization. Subsequently, a detailed family pedigree was obtained [2].

Sipple became intensely interested in this case after observing the striking findings at the patient’s autopsy. He states, “As I stood at the autopsy table, I knew I was looking at something special although I did not understand it. I doubted very much that it was a chance occurrence.” [2] The patient was found to have large adrenal tumors bilaterally, a 2-cm “pale tan mass” in the mid-portion of each thyroid lobe, and nodular enlargement of the single parathyroid gland measuring 0.9 by 0.6 cm was identified. The adrenal glands weighed 58 and 68 g and were diagnosed as pheochromocytoma by histology. Furthermore, Myron Brin, a biochemist at Syracuse, was able to measure elevated tissue epinephrine and norepinephrine levels from the adrenal tumors. The thyroid tumors were noted to be poorly differentiated and invasive, and diagnosed as follicular adenocarcinoma of the thyroid on the pathology report. Medullary carcinoma of the thyroid gland (MTC) was just described in 1959 by Hazard, Hawk, and Crile [3] from the Cleveland Clinic, and therefore the patient’s thyroid cancer was not recognized as such at the time. Subsequent pathologic analysis by Schimke confirmed the tumor from this patient to be medullary carcinoma [4] and Carney showed that it stained positive for calcitonin [5]. There were no serum calcium or phosphorus levels ordered. Since Sipple could not find any existing literature showing association of thyroid, adrenal, and parathyroid tumors, he decided that this case deserved investigation and description.

Sipple began his research into this case during residency, finishing and publishing the paper in 1961 during his Air Force service. His methodology consisted of looking up all the published cases of pheochromocytoma, specifically looking for additional cases with concomitant thyroid carcinomas. After reviewing 20 years of Index Medicus, he found 537 cases of pheochromocytoma and of those, five (in addition to his case) were associated with thyroid carcinomas. Sipple noted that the occurrence of thyroid cancer in this series of patients with pheochromocytomas was at least 14 times the expected incidence, whereas the incidence of other cancers was not increased. He hypothesized that the thyroid cancer may have been caused by fluctuating levels of epinephrine. Among the cases he reported, the earliest dated back to 1932. Four of the six cases had bilateral pheochromocytomas confirmed at autopsy, the average age of presentation in this series was 34.5 years (range 17–63), the average age at death was 39.2 years (range 24–63). He wrote up his observations and research as the only author, and the three-page case report was accepted for publication without revisions to the American Journal of Medicine (AKA the Green Journal) in 1961 [1]. Sipple noted that he received many reprint requests for this article, indicating that there was a high level of interest from the medical community. In 1962, Cushman from Rochester, New York, reported a family in which the father had pheochromocytoma, MCT, and parathyroid adenoma, the son had pheochromocytoma and MCT, and the granddaughter had MCT, and it became apparent this syndrome was genetically inherited in an autosomal dominant fashion [6]. Other cases were reported [7], and the combination of pheochromocytoma and thyroid cancer became known as Sipple syndrome [5]. After the MEN2A mutation was identified in 1993 [8], the proband’s family was studied [9], and 7 of 15 members who underwent genetic testing were found to have the C634R mutation of RET. It was proposed that the proband’s mother had the disease, since she died at age 39 of unknown causes and was thought to have hypertension. Further research by Carney into the cases described by Sipple found that one patient had a sister who died at age 28 with a “rare disorder of the sympathetic system” and a thyroidectomy. No other patient had parathyroid disease described. Carney also identified that another of the patients included by
Sipple likely had MEN 2B, having ganglioneuromatosis of the gut and enlarged lips [5]. In 1968, the term “multiple endocrine neoplasia” (MEN) was introduced by Steiner et al. to describe diseases with multiple endocrine tumors, and Sipple syndrome was designated as MEN 2. In 1974, Sizemore et al. further classified Sipple syndrome as MEN 2A, recognizing its distinction from MEN 2B [5]. Dr. Sipple kept up with work on this disease for many years, corresponding with Barry D. Nelkin, Ph.D. of Johns Hopkins, and Carl D. Malchoff, M.D. of the University of Connecticut over various projects. At the First International Workshop on MEN 2 in Ontario, Dr. Sipple gave a historical perspective [2] on his discovery of the syndrome and stated that “this workshop on MEN-2 illustrates that observations in one case can lead to the contributions of many workers in the field.”

It is interesting to note that subsequent reports have demonstrated Sipple syndrome to be present in patients described earlier in the literature, though not recognized as a syndrome. Neumann et al. [10] reported that the first case of pheochromocytoma described in the literature in 1886 by Frankel had MEN 2A. The authors hypothesized that since the patient was young (18 years old) and had bilateral disease, she had an inherited condition. The relatives of the patient were traced through historical research, and the germ-line RET mutation TGC > TGG (Cys634Trp) was found in four descendants. Sisson et al. [11] reported that investigation of the subsequent medical and family history of a proband who was initially reported in 1939 for a hyperfunctioning parathyroid adenoma revealed MEN 2A. The patient was reported by Barker and Brines [12] as an 18-year-old with osteitis fibrosa cystica who had a parathyroid tumor excised. Further investigation revealed that she underwent a thyroidectomy for probable MTC at age 29 and subsequently died of “progressive cancer” at age 70. Her children developed MTC, pheochromocytomas, and parathyroid hyperplasia. Genetic testing of her descendants revealed the RET 634 TGC > CGC mutation.

This biography of Sipple shows that a young physician’s keen sense of observation and curiosity combined with persistence in researching the literature resulted in identifying a previously unrecognized syndrome. It also illustrates the rapid medical progress over a single physician’s four-decade career; from the description of an interesting case, to definition of the syndrome and its pathology, to the identification of calcitonin as a tumor marker for MTC, to identification of the genetic mutations in MEN 2A. With the ability to diagnose affected patients before cancer develops and with the use of prophylactic surgery, the lives of MEN 2A patients are improved and extended as a result of this progress.

**Quotations**

Sipple’s inquisitiveness paid off.

(J. Aidan Carney, pathologist of Carney’s syndrome)

Eponyms are flattering, sometimes embarrassing, and certainly not descriptive…. The paper I wrote in 1959 was my only venture into endocrinology…. So much outstanding work has been done by so many investigators in this field, and my contribution was so minimal, that remembering the name MEN-2 is more meaningful to a medical student than remembering an eponym.

(John H. Sipple)

**Reflections**

*How do you feel about having a syndrome named after you?*

I got a lot of mileage out of a little case report. I don’t think any of my grandchildren would consider me famous for a case report. I don’t build it up. At the medical school, they were sure to teach about Sipple syndrome, and point me out as an example of “local man makes good”.

*How would you like to be remembered?*
As somebody who was interested in seeing what they could do with their life, plugged along, had some breaks, and had a lot of fun.

References


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