HUMANITIES

Dr. Charles Miller Fisher: Important contributions to ophthalmology

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Introduction

One of the most accomplished Canadian physicians and researchers of his time, Dr. Charles Miller Fisher (CMF) is perhaps best known for his contributions to neurology and stroke medicine. By the end of his career, he had earned an impressive collection of honours and awards and left a legacy of contributions to his field of neurology as well as to ophthalmology. Some of his most famous discoveries include the thrombo-embolic theory of ischemic stroke, carotid artery disease as a cause of stroke, atrial fibrillation as a stroke substrate, lacunar infarcts, transient ischemic attacks (TIAs), and features of thalamic and cerebellar hemorrhage[1]. His dedication to clinicopathological correlation and careful observation were what led to the many discoveries he made over his lifetime and although CMF was a neurologist, he made an important mark in the field of ophthalmology. This paper explores and summarizes some of the key discoveries and contributions CMF made to the field of ophthalmology over the course of his career.

Biography

CMF was born in Waterloo, Ontario, and earned his Medical Degree from the University of Toronto in 1938 before continuing to train at Henry Ford Hospital in Detroit until 1939[2]. Shortly after completing his intern year, he joined the British Royal Navy. While participating in World War 2, CMF was imprisoned in a German Prisoner of War Camp from 1941-1944[1,2]. During his capture, he reportedly learned German, Italian, Spanish, mathematics, navigation, and music theory. After his release, he returned to medicine and continued training as a neuropathologist in Boston, Massachusetts, before returning to Montreal General Hospital. In Montreal, he developed a Neuropathology service and began to study and describe a constellation of symptoms which he later coined "TIAs." This discovery paved the way to our modern understanding of stroke as a thromboembolic phenomenon, and marked the beginning of a long and fruitful career for CMF. Even at the age of 96, he remained actively involved in research.

As a clinician, CMF was intensely curious and meticulous. This is made clear in his very detailed, and often peculiar observations. He is said to have categorized patient symptoms based on features like "patients who wrote off the paper," "mumblers," "irascible patients," and "topplers." Observations as nuanced as "the right sole was more ticklish than the left" can be found in his published work[1,3]. In addition to his role as a clinician, he left a bold mark on each of his students. One such student went on to write a paper entitled "Fisher's Rules," which highlights—among other things—the importance of closely studying one's patient at the bedside[4].

Contributions to Ophthalmology

TIA (Transient Ischemic Attack)

In 1951, CMF published the pivotal "Occlusion of the Internal Carotid Artery," where he first explores the role of the internal carotid artery in cardiovascular disease and its role in cerebral ischemic stroke[3]. The observation of a predictable collection of "premontory fleeting symptoms" affecting patients who would later go on to develop an ischemic cerebral stroke was his first and arguably most famous clinical observation. These symptoms included paresthesia, aphasia, and monocular blindness. The link between ischemic stroke and carotid artery disease challenged the then-popular "vasospasm theory," and later led to the widespread acceptance of the thrombo-embolic theory of ischemic stroke.

TIA and TMB (Transient Monocular Blindness)

The visual disturbances involved in TIAs are classically monocular and occur ipsilateral to the stenotic carotid artery. Their onset is abrupt lasting usually about one minute, which some patients describe as "like a blind pulling down" in the affected eye. In one case, a patient who developed hemiplegia famously remarked: "isn't it funny that I went blind in my wrong eye? My paralysis was on the left and my right eye went blind." The patient was initially thought to have hemianopsia, but it was later realized that these visual symptoms were likely due to carotid artery occlusion.

From the idea that ipsilateral visual disturbances can be caused by fleeting ischemia caused by ipsilateral carotid artery occlusion, the term "transient monocular blindness (TMB)" emerged[5]. As the visual features of

TMB closely resemble hemianopsia, CMF coined TMB to distinguish it from the broader "amaurosis fugax"—an all-encompassing term for all types of visual loss, whether monocular, binocular, and regardless of the etiology. In fact, in 1989, CMF declared that he still preferred the term TMB over amaurosis fugax[6].

Observations of the Fundus Oculi in TMB

In 1959, CMF carefully outlined changes in retinal circulation in two instances of TMB (Figure 1)[7]. This was important in establishing the connection between TIAs and their corresponding vascular events, and ultimately lent further support for thromboembolic phenomena as the underlying cause of TIA. Throughout the paper, CMF entertains the alternative hypotheses that the observations could be explained by vasospasm and local areas of collapsed or constricted vessel. However, he describes features that make the presence of intravascular embolic material the most likely explanation.

Firstly, the junction between the white segment and the blood-filled arteries was always square or transverse, with no mixing of red and white segments. The diameter of these segments was always equal, further supporting the presence of an intravascular material versus a segment of arterial constriction or collapse. As the white segments moved distally along the retinal arteries as if an intravascular material was being pushed along by the column of blood proximal to it, the white segment appeared to stop momentarily at bifurcations. At one point, erythrocytes were seen passing distally across the white segment, but did so only at the outer edge. If the white segment represented an area of locally constricted vessel, the erythrocytes would be expected to pass through the center.

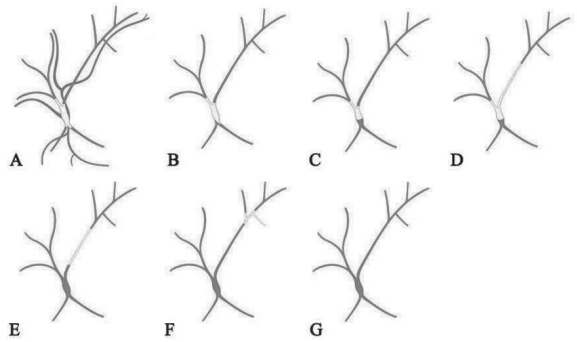

Figure 1. Changes in retinal circulation at 6 different time points in one case of TMB. This attack of monocular blindness occurred in 3 quadrants of visual field in the left eye and lasted a total of 60 minutes.

Miller-Fisher Syndrome

In 1956, CMF described a variant of Guillain-Barre Syndrome that now bears his name[8]. Miller-Fisher Syndrome was first recognized by CMF as a triad of neurological complaints that appeared to be linked to a preceding respiratory illness. Classically, ophthalmoplegia, ataxia, and areflexia characterize this condition. It therefore somewhat resembles several other diagnoses with similar presentations including vascular disease, Wernicke's Encephalopathy, and brainstem tumors.

In "An unusual variant of acute idiopathic polyneuritis," CMF describes 3 cases of stereotyped, transient neurological symptoms that were all preceded by a respiratory complaint. Within 3-4 days of onset of neurological symptoms, 2 of these patients developed external ophthalmoplegia with the eyes fixed in primary gaze. In all cases, pupils were equal and mid-dilated reacting slowly to light, and moderate ptosis was seen in 2 cases. The orbicularis oculi functioned normally, and neither visual fields, acuity, nor fundi were abnormal during the episodes. Remarkably, CMF noted restoration of ocular movements a few days after the peak of symptoms and near-full recovery after 8-12 weeks with no intervention.

CMF concluded that vascular disease was likely not the cause of these transient neurological symptoms. Although basilar artery thrombosis can cause ataxia and extensive ophthalmoplegia, it would almost certainly also damage the reticular formation and therefore have severe effects on regulation of consciousness. Another reasonable explanation for this syndrome was Wernicke's encephalopathy, which also commonly includes ataxia and ophthalmoplegia. Unlike Wernicke's Encephalopathy, however, there was no evidence of malnutrition and consciousness was never affected in these patients.

The link to polyneuritis was made after CMF recognized a rise in CSF protein in one of these cases. Furthermore, the loss of reflexes coupled with paresthesias suggested involvement of the peripheral nerves. Previously, some cases of polyneuritis were found to show a similar type of ophthalmoplegia, making CMF reason that this syndrome—now known as Miller-Fisher syndrome— was a variant of acute idiopathic polyneuritis in which involvement of the limbs is minimal and is instead characterized by ophthalmoplegia in addition to ataxia and areflexia.

One-and-a-Half Syndrome due to Ocular-Pontine Deficit

One-and-a-half syndrome was one of many important neuro-ophthalmological discoveries made

by CMF in his 1967 paper "Some Neuro-Ophthalmological Observations"[9]. One-and-a-half syndrome is a combination of a horizontal conjugate gaze palsy in one direction, and an internuclear ophthalmoplegia causing paralysis of adduction in one eye in the opposite direction. Most commonly, horizontal abduction of one eye is impaired, and complete horizontal paralysis is seen in the other[10].

CMF attributed this phenomenon to a lesion located near the pontine conjugate lateral gaze center causing the conjugate gaze palsy in the contralateral eye. This also affects the nearby MFL fibers, causing internuclear ophthalmoplegia in the ipsilateral eye (Figure 2). This discovery was anatomically important as it indicated the MLF must cross caudally in the pons near the level of the paramedian pontine reticular formation (PPRF) and Abducens nucleus, before reaching the oculomotor nucleus in the midbrain.

This condition is usually caused by a stroke or demyelinating disease such as Multiple Sclerosis affecting this area of the caudal pons, and is quite rare[10]. In particularly rare cases, such a lesion could be caused by tumors, arteriovenous malformation, and basilar artery aneurysm.

Wrong-Way Eyes

Supratentorial hemorrhage usually produces a contralateral hemiplegia and deviation of the eyes toward the side of the lesion, opposite to the paralyzed side of the body[9]. However, in "Some Neuro-Ophthalmological Observations," CMF describes cases of supratentorial hemorrhages resulting in deviation of the eyes toward the side of hemiparesis, prompting him to examine 3 cases in detail and to perform pathological correlation[9]. In each of these cases, CMF found hemorrhage in the medial thalamus on one side, ipsilateral to the direction of eye deviation, and a large pooling of blood in the third ventricle.

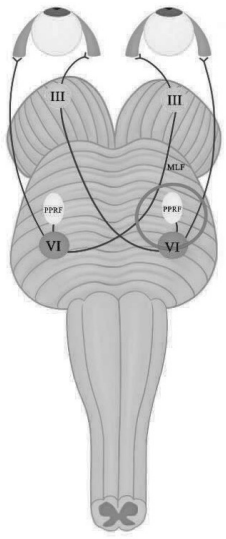

Figure 2. Brainstem schematic of one-and-a-half syndrome due to ocular-pontine deficit.

While the precise etiology of wrong-way eyes is unclear, some proposed mechanisms include compression of the mesencephalon affecting descending oculomotor pathways originating in the contralateral hemisphere[11]. The compression of the mesencephalon from hemorrhage and cerebral edema at this level are thought to involve the descending oculomotor fibers as they decussate[12].

Prognostically, the finding of wrong-way eyes in the context of prethalamic hemorrhage is typically a marker of poor outcome, as it usually indicates compression of the brainstem[12]. This clinical sign should prompt urgent surgical decompression.

Preservation of Pupillary Reflex in Miosis due to Pontine Injury

Prior to "Some Neuro-Ophthalmological Observations," intrapontine hemorrhage and devastating pontine infarcts were often diagnosed clinically as miotic pupils that were unreactive to light[9]. The strongly miotic pupils could be explained by insults to the descending sympathetic pathways involving pupillary dilation, but how these lesions impaired their inability to react to light was still unclear.

Hoping to explain this phenomenon, CMF examined 6 patients with extreme miosis: 2 of which suffered pontine infarction, and the other 4 pontine hemorrhage. In each of these patients, their pupillary response to light was measured and recorded using a hand lens for magnification. In all patients, a small reaction to light was observed. CMF concluded that the degree of miosis seen in such lesions likely made any reaction to light exceedingly difficult to observe.

Localizing Value of Scintillations and Vertical Nystagmus

Scintillations

Visual scintillations may be experienced by patients with ocular migraines but can also be caused by cerebral ischemia or hemorrhage[9]. While cerebral lesions were thought to probably involve cortical areas responsible for vision, it was unclear where precisely lesions producing scintillations arose. Three cases of scintillations were observed showing thrombosis of the vertebral arteries, basilar arteries, and PCA. Ischemia was present in the pons and occipital lobes. In all cases, injury to the MCA or temporal lobes was not observed.

Based upon the pattern of vascular involvement and cerebral injury, CMF concluded that scintillations

caused by hemorrhage or infarct may indicate damage to the calcarine sulcus or primary visual cortex, and the optic radiations are probably not involved.

Vertical nystagmus

Before 1967, it was widely held that vertical nystagmus is an indication of lesion involving either the upper or lower portions of the brainstem[9]. In the case of upper brainstem lesions, the thought was that vertical nystagmus may represent weakness of vertical gaze. However, in "Some Neuro-Ophthalmological Observations," CMF remarked having never encountered vertical nystagmus in patients who experienced thalamic-subthalamic hemorrhage involving paresis of conjugate vertical gaze. Examination of other cases of upper brainstem lesions also failed to detect any cases of vertical nystagmus. However, in cases of brainstem lesions involving the lower pons or upper medulla, vertical nystagmus was often found. While not entirely clear what the mechanism was, CMF concluded that vertical nystagmus may be an indication of brainstem damage of the pontomedullary junction, and not the upper brainstem.

Ocular Bobbing in Pontine Lesions

Ocular bobbing (OB) is a clinical sign characterized by rapid conjugate downward movement of the eyes, followed by a slow, conjugate return to primary gaze[13]. This sign is commonly seen in cases of extensive pontine damage by hemorrhage or infarction and is therefore a poor prognostic indicator.

In "Ocular Bobbing" (1954), CMF explores 3 cases of unresponsive patients who showed signs of OB and were later determined to have suffered pontine infarction or hemorrhage. Typical cases of OB were described as rapid, conjugate downward movement of the eyes to a range 1/4 to 1/3 total voluntary range, followed by a slower upward return to primary gaze. This pattern of ocular movements did not appear to be related to breathing or blinking, and the underlying mechanism was not known. However, due to the absence of horizontal eye movements, CMF postulated that OB is merely roving of the eyes without the horizontal component, making the vertical movements more obvious.

Indeed, OB is currently thought to be the result of damage to the paramedian pontine reticular formation which is responsible for eye movement along the horizontal plane, while sparing the vertical gaze center[14]. This mechanism is further supported by the observation that pupils remain equal and reactive to light, which suggests that the midbrain is not involved in the pathophysiology of the clinical sign. Ultimately, OB may be a clinically useful sign in the unresponsive patient as it indicates serious pontine disease and signifies a poor prognosis.

Oval Pupils

In 1980, CMF described a form of irregularly shaped pupils that previously had not been well-characterized. While square, slit, and pear-shaped pupillary deformations had previously been described, as well as pupillary irregularities seen in neurosyphilis, oval shaped pupils had not[15].

In "Oval Pupils," CMF describes 17 cases of oval pupils and their associated neurological pathologies. In 16 of all 17 cases, patients had suffered severe cerebrovascular events, including hypertensive cerebral hemorrhage, ruptured saccular aneurysm, epidural hemorrhage, bilateral cerebral infarction, brainstem stroke, and cerebral anoxia. The 17th patient did not have any vascular disease but was found to have an isolated acute oculomotor palsy.

Given the number of cases related to disastrous cerebral hemorrhage or ischemia, oval pupils seemed to be associated with acute intracranial vascular events. In all cases, damage to the oculomotor nerve nucleus was present, suggesting midbrain involvement as the underlying pathology in oval pupils. CMF proposed damage to the oculomotor and pupillomotor nerve as a possible mechanism, causing paralysis of the pupillary sphincter along one axis and thereby producing an elliptical pupil. Direction of the axis was varied across cases and did not appear to be related to the pathological process or mechanism of damage.

In most cases, oval pupils were a transient stage preceded by an acute pathological process, and complete restoration of round pupils was seen in all cases. CMF concluded that an oval pupil represents a temporary stage leading to oculomotor nerve paralysis, or in rarer cases, recovery to full symmetrical nerve function.

Conclusion

Looking at all the discoveries and contributions made by CMF over the course of his career, it is difficult to fathom that they were all made by one man in one lifetime. Beyond his excellence in academia and research, he was a memorable teacher and an incredibly interesting individual. Although CMF dedicated his life to neurology and played an important role in our modern understanding of stroke medicine, to limit his achievements there would be to sell them short. The discoveries made by CMF in both neurology and ophthalmology strengthened the connection between these two fields, and ultimately led to a more complete understanding of neuro-ophthalmology. Dr. Charles

Miller Fisher is undeniably a giant in neurology, but the impact he made on the field of ophthalmology is perhaps a better kept secret that deserves to be uncovered.

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