To the Editor

IL6-Gene Variation in Parkinson's Disease

I have read with interest the recent report on the putative impact of chemokine polymorphisms in Parkinson's Disease[1]. Based on a meta-analysis of case-control investigations for *IL-6* and several other candidate genes, the authors concluded protective effects of an *IL-6* promoter variant, rs1800795 or IL-6 G[-174]C. However, key issues appear to have been overlooked. Firstly, the study by Infante et al[2] used a TaqMan genotyping procedure with unknown primers. It is therefore impossible to tell in retrospect whether the transcribed or the antiparallel DNA strand served for allele calling and whether the risk allele was "G", or "C". As rs1800795 stands for a canonical substitution that can be read as "G" or as "C" depending on the template, strand information is essential to define genetic exposure. A second study[3] used sequence-specific oligo probes that do not differentiate between "G" and "C" but rather call only the "C" allele on the transcribed strand. A third study[4] genotyped the non-transcribed strand as can be verified by consulting the original pyrosequencing protocol. Chu et al failed to correct for the alternate strand and have mistaken "G" for "C". In other words, two of the three studies in question are non-informative and the third gives results that were misinterpreted. Finally, the authors have muddled IL-6 studies in Table 2 and have omitted additional studies[5].

The confusion of risk and protective alleles emphasizes further the need for strand-sensitive meta-analyses of G:C and A:T transversions. It is unfortunate that this procedure is not routinely implemented in PDGene (URL: http://www.pdgene.org), a database that was consulted by the authors and that also offers meta-analyses of case-control investigations. Having reviewed all PDGene entries for rs1800795, I note that as of September 2012, data from multiple studies[2-4] have been misassigned to rs13447446, a G:T substitution 63bp downstream from rs1800795. Other studies that did not investigate rs1800795 are included in PDGene's meta-analysis of this variant. While Chu et al must be given credit for identifying these errors, the information available is insufficient to support a protective role of rs1800795 in Parkinson's disease.

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To the Editor

A Case of Collet–Sicard Syndrome Caused by Necrotizing Otitis Externa

Collet–Sicard syndrome (CSS), palsy of cranial nerves nine, ten, eleven, and twelve, can be caused by a diverse set of disorders. Collet–Sicard syndrome is distinguished from Villaret syndrome by the lack of sympathetic nerve fibre involvement. The most common cause of CSS is otologic tumour[1]. Other causes include non-otologic neoplasia (primary or secondary): parotid tumours, skull base tumours, prostate metastases, kidney metastases, breast metastases, and melanoma metastases. Multiple myeloma and schwannomas of the hypoglossal nerve, and Hodgkin's disease have been reported as causes. Vascular lesions including carotid aneurysms and jugular vein phlebitis can cause CSS. Other rare causes of CSS have been reported[1].

Herewith, we report a patient with Collet–Sicard syndrome resulting from malignant otitis externa (OE) and subsequent abscess formation. To the best of our knowledge, this is only the second reported case of infectious CSS.

Case Report

A 67-year-old man presented with a three week history of progressive dysphagia to solids and liquids accompanied by episodic regurgitation and emesis of partially digested food. His past history was significant for type 2 diabetes mellitus, hypertension, erectile dysfunction, obesity, osteoarthritis, and hypothyroidism. He had been diagnosed with left sensorineural hearing loss and left OE five months prior. Ear culture was positive for *Pseudomonas aeruginosa*. Despite an aggressive antibiotic regimen and frequent debridement and microcleaning, the OE had persisted.

A swallowing assessment prior to neurologic consultation suggested severely impaired oral and pharyngeal phases of swallowing with a high risk of aspiration on all textures. This necessitated a G-tube placement. The patient was admitted to hospital. Examination by a neurologist showed a deviated tongue to the left, failure of the left soft palate to rise, severe left sternocleidomastoid (SCM) and upper trapezius weakness and atrophy, and mild dysarthria. The initial differential diagnosis included bulbar-onset amyotrophic lateral sclerosis (ALS). Subsequent examination 3.5 months later revealed persistent

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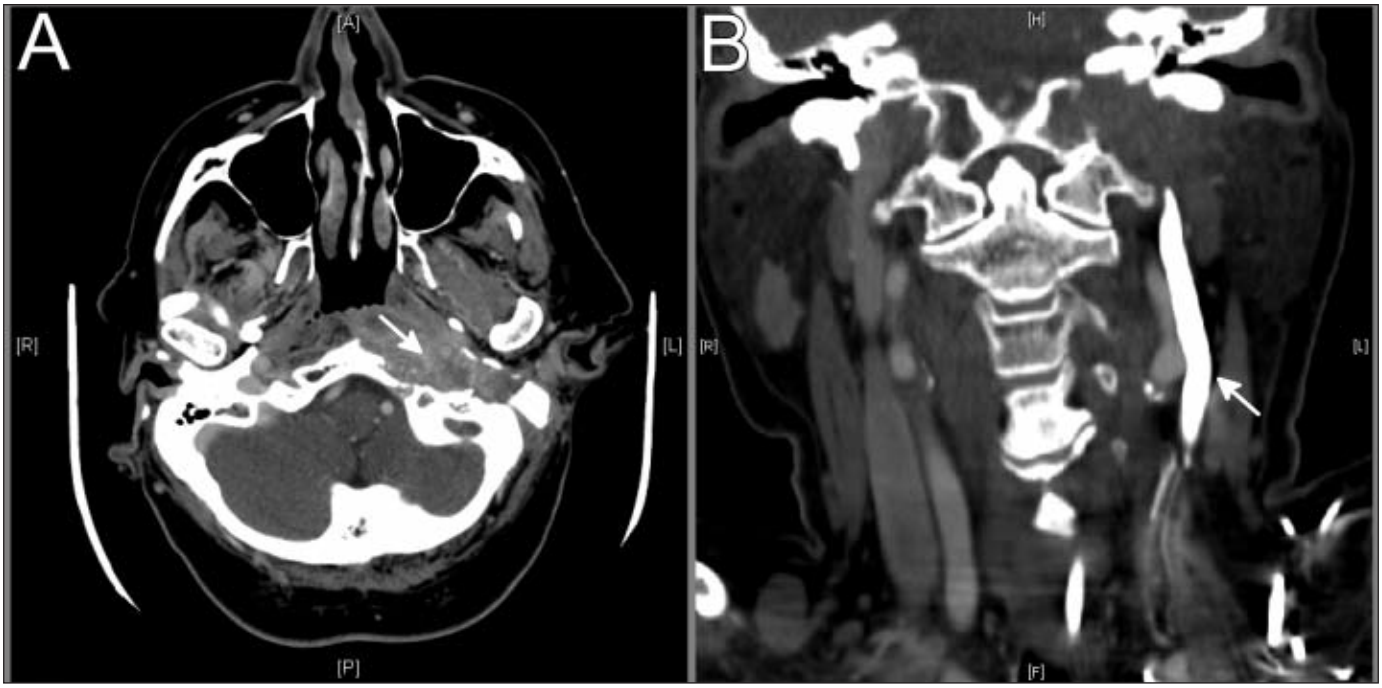

Figure: *CT head with contrast taken shortly after the onset of cranial nerve IX, X, XI, and XII palsy. A) Contrast-enhanced axial CT shows ill-marginated soft tissue (arrow) in the left carotid space that completely surrounds the distal cervical internal artery. B) Contrast-enhanced coronal CT shows erosion of the left clivus and temporal styloid process with deep venous sinus thrombosis (arrow).*

dysarthria, dysphagia, tongue deviation to left with mild atrophy, and significant atrophy and weakness of the left SCM and upper trapezius. Infrequent fasiculations were noted in the left hemi-tongue and left trapezius.

Magnetic resonance imaging suggested a left nasopharyngeal carotid space mass with osseous involvement of the left clivus. This mass impinged on cranial nerves IX, X, XI, and XII exiting the brainstem. Contrast computed tomogram (CT) of the neck revealed bony erosion of the left skull base including the left side of the clivus, bony walls of the foramen lacerum, the jugular foramen, and the inferomedial portion of the petrous temporal bone adjacent to the petrooccipital fissure. Additionally, there was a venous sinus thrombosis in the left transverse and sigmoid sinuses (Figure).

The patient was treated with heparin for the venous thrombosis. He subsequently developed a lower gastrointestinal bleed that necessitated discontinuation of anticoagulation. The infection was treated with intravenous meropenem and oral ciprofloxacin for four months. His symptoms gradually improved. Follow-up CT scans, two months after the initial presentation, showed a persistent skull-base mass, an unchanged venous sinus thrombosis, and slight improvement to the left mastoid air cells.

Four months after presentation, the patient's deficits had partially, but not fully, resolved. He was back on a normal diet and had had his G-tube removed. There was less weakness of the SCM, trapezius, and swallowing musculature. Further nerve conduction studies were performed. The left spinal accessory nerve compound motor action potential was 0.7 mV compared with the right side at 2.3 mV. There was denervation with chronically-remodelled polyphasic motor unit potentials in the left SCM and trapezius muscles.

Discussion

Cranial nerves IX, X, and XI all pass through the jugular foramen. The jugular foramen pars nervosa contains the glossopharyngeal nerve and the jugular foramen pars vascularis contains the vagus and spinal accessory nerves. Cranial nerve twelve passes through the hypoglossal canal, and exits near the jugular foramen. An inflammatory process located in the posterior lacerocondylar space can cause CSS[1].

This patient developed otitis externa (OE) likely as a result of his poorly-controlled type 2 diabetes mellitus. This OE was subsequently complicated by skull-base abscess, which caused CSS. *Pseudomonas aeruginosa* is a common cause of OE in diabetic patients. Despite local and systemic antibiotic therapy for the OE, the infection spread from the mastoid air cells to the skull base whence it caused cranial nerve palsies. In this patient's case, it is unlikely that the venous sinus thrombosis caused the cranial nerve palsies. The palsies improved when the infection was resolved despite the thrombosis remaining. There have been several reports of CSS caused by venous thrombosis[1]. In all of these cases, the thrombosis was in the jugular vein; in this patient's case, the thrombosis was in the transverse and sigmoid sinuses.

In a review of the literature, we found one case report in which there was an infectious cause of CSS[2]. A 56-year-old man

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with a history of type 2 diabetes mellitus and prior cerebrovascular accident (CVA) developed skull-based osteomyelitis and subsequent CSS plus unilateral facial nerve palsy. In his case, the presenting symptoms included dysphagia to solids and liquids, hoarseness, facial palsy, and neck pain. These symptoms were mistaken for a CVA. Eventually, oseomyelitis was recognized, he underwent surgical debridement, and he had a course of intravenous antibiotics. His condition soon drastically improved.

There were several reports of syndromes similar to CSS caused by infection. In these cases, the syndromes involved palsies of some, but not all of cranial nerves IX, X, XI, and XII, with or without sympathetic nerve fibre involvement. Lee et al[3] described a case of osteomyelitis causing cranial nerves IX, X, and XII palsy. An infectious cause of Villaret's syndrome was reported by Huang and Lu[4] and by Goldstein et al[5]. The case reported by Goldstein et al[5] is very similar to the case reported herewith. In that case, a 72-year-old man with prior history of type 2 diabetes mellitus and treatment-resistant OE presented with generalized weakness, confusion, otorrhea, otalgia, progressive hoarseness, and weight loss. He soon developed all of the signs of Villaret's syndrome. He responded well to aggressive surgical debridement.

We conclude that infection is a rare cause of Collet-Sicard syndrome. Skull-base infection should be on the differential diagnosis of a patient presenting with swallowing difficulties and focal cranial nerve palsies. Index-of-suspicion should be especially high when a chronic, treatment-resistant course of OE precedes the nerve palsies.

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