## Copper Deficiency Clinical Case Conference: In Defense of Checklists

Pasquale F. Finelli, MD[1] and Andrew L. McCabe[2]

In his very informative and thoughtful discussion of a patient with copper deficiency, Dr Samuels refers to the checklist concept in considering the differential diagnosis. He cites a Google search of myeloneuropathy and malnutrition as helping in suggesting the diagnosis.[1] He further notes that searching on common nonspecific neurologic signs and symptoms generates exhaustive lists that would not be helpful diagnostically. It should be noted that the use of recently introduced specialty-specific diagnostic systems can yield highly relevant checklists.[2] Using NeurologicDx in the current case study, a single-term search of "gastric bypass" or cross-referencing common terms such as "myelopathy" and "malnutrition" yields a checklist of 12 and 9 differential diagnostic considerations, respectively, both of which contain copper deficiency and other relevant disease entries. Comparatively, either of these searches in Google would give too broad a response to be helpful diagnostically.

In essence, absent the clinician coming up with the term myeloneuropathy, 1 or 2 properly chosen nonspecific signs, symptoms, or key terms used in a specialty-specific system with "smart" algorithms can provide highly relevant diagnostic checklists.

### Potential Conflicts of Interest

P.F.F. and A.L.M. are the developers of NeurologicDx.com. There are no financial disclosures, as the program is an open access resource that is Web based.

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*References*

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## Reply

Martin A. Samuels, MD

I very much appreciate the letter from Dr Finelli and Mr McCabe regarding the use of checklists generated by computer search engines. They have developed a neurological search engine at www.neurologicDx.com that is currently open to the public at no cost. I looked at the list generated by the search term "gastric bypass" and did find copper deficiency, but also on the list were B12 deficiency, benign intracranial hypertension, lactic acidemia, neuropathy, night blindness, optic neuropathy, systemic mastocytosis, Wernicke encephalopathy, and small bowel bypass. As an eminent neurologist was said to opine, "A differential diagnosis is the right diagnosis followed by a list of wrong diagnoses." The point of the clinical pathological conference is to teach others about the thinking process that underlies sophisticated clinical neurology. The effectiveness of search engines depends heavily on the search term that is chosen. As I hope the CPC demonstrated, the neurological method remains the best method to select the best search terms, in other words, to actually understand the nature of the disorder.

### Potential Conflicts of Interest

Nothing to report.

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## Gender as a Disease Modifier in Neurofibromatosis Type 1 Optic Pathway Glioma

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In the recent study by Diggs-Andrews and coworkers,[1] females with neurofibromatosis type 1 (NF1)-associated optic pathway glioma (OPG) were more likely than males to have visual decline requiring treatment, particularly when the gliomas were confined to the optic nerve(s). In a recent large, international collaborative initiative focused on visual outcomes in children with NF1-OPG following chemotherapy,[2] we also had a preponderance of females (62%) among our population of treated patients. Tumor involvement of the postchiasmatic portion of the optic pathway was the most consistent

 

**TABLE 1. Gender Distribution by Optic Pathway Glioma Location in Children Treated with Chemotherapy**

| Tumor Location (No.)[a] | Male, % (No.) | Female, % (No.) | $p$[b] |
|---|---|---|---|
| Nerve (17) | 17.6 (3) | 82.4 (14) | 0.0075 |
| Chiasm (27) | 37.0 (10) | 63.0 (17) | 0.1767 |
| Hypothalamus (16) | 37.5 (6) | 62.5 (10) | 0.3173 |
| Tract/radiations (55) | 45.5 (25) | 54.5 (30) | 0.5045 |

[a]Location is the most posteriorly involved part of the visual pathway.
[b]One sample test for proportions was performed using Stata (StataCorp, College Station, TX).

significant predictor of poor response to chemotherapy; however, gender was not prognostic for visual acuity outcome. Interestingly, on further analysis of our data, there were a disproportionate number of females with nerve-only tumors who required treatment (82.4 vs 17.6%, $p = 0.0075$; Table). The lack of an effect of gender on visual outcome may reflect the preponderance of optic tract/radiation tumors in our cohort and the strong influence of posterior tumor location on clinical outcome.

Although both clinical studies were retrospective analyses, taken together and coupled with the supporting *Nf1* genetically engineered mouse modeling results, these observations further support the hypothesis that gender may be a disease modifier for the development of clinically significant OPG in children with NF1. Future prospective studies will be required to confirm these findings and more fully elucidate the interplay of gender and other prognostic features (such as tumor location) on disease severity.

## Potential Conflicts of Interest

D.H.G.: patent relating to NF1 gene licensed to Francis Collins. R.J.P.: advisor, AstraZeneca. S.L.A.-H.: grants, Children's Tumor Foundation of Australia; personal fees, Novartis Pharmaceuticals Australia. L.J.B.: consultancy, Biogen Idec, Vaccinex, Questcor; clinical trial advisory board, Biogen Idec. G.T.L.: consultancy, Ipsen; book royalties, Elsevier.

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## Reply

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We appreciate the supportive data provided by the NF1 Optic Pathway Glioma (NF1-OPG) International Consortium study, which further strengthens the association between gender and the need for tumor treatment.[1] Dr Fisher raises several