Author’s response to reviews

Title: Isolated hypoglossal nerve palsy from internal carotid artery dissection related to PKD-1 gene mutation

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Author’s response to reviews:

RE: Isolated Hypoglossal Nerve Palsy due to Internal Carotid Artery Dissection - a Case Report
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Dear Editors,

Thank you for the timely processing of our manuscript.

As you suggested, we studied comments carefully and made corresponding changes to the manuscript, which were highlighted. A list of responses to reviewers was attached for your reference.
Please extend our thankfulness to the reviewers, with whose suggestions make the improvements of this manuscript became possible.

With regards,

Minghua Wu

Responds to the Reviewer’s Comments

Peter Appelros, MD PhD (Reviewer 1)

There have been quite a few reports on the association between carotid artery dissection and hypoglossus nerve palsy through the years.

The most interesting feature in this case is the possible association between the PKD1-gene and carotid artery dissection. I think that this should be pointed out and discussed more. The title could, for example, contain a reference to the mutation in question.

Response: Thank you for this helpful suggestion. We now revised the Title: “Isolated hypoglossal nerve palsy from internal carotid artery dissection related to PKD-1 gene mutation”. We also made more description about this feature (See the following).

Why was a genetic investigation initiated in this case?

Response: We understand your concern. This is a young patient, he was previously healthy, has no common risk factors for atherosclerosis, has no history of trauma during the onset, and did not find some factors that may cause vascular diseases such as infection and immunodeficiency. So we arranged a screening of cerebrovascular gene mutation to find the potential mechanism of the weakness of the vascular wall.
I think that more text in the Discussion should be devoted to the association between connective tissue diseases and carotid dissection. Is the first time an association between carotid dissection and the PKD1-gene has been shown?

Response: Thank you for this helpful suggestion. We now add more text in the Discussion:

“Previous studies have supposed that ICAD patients could have a constitutional, at least to some extent, genetically determined weakness of the vessel wall. More than half of patients with carotid artery dissection were found to have skin connective tissue abnormality, including composite fibrils within mid-dermal collagen bundles and enlarged fibrils[12]. The previous study also found that concomitant arterial abnormality such as tortuosity, kinking or coiling ICA was common[13], and our patient also had tortuous basilar artery. In addition, heritable connective tissue disorders such as Ehlers–Danlos syndrome, Marfan’s syndrome, are associated with an increased risk of spontaneous ICAD[3]. ADPKD has also been rarely described correlating with dissection of the cerebral arteries[14-16].” (page 7, line 8).

Also, as this manuscript is written for neurologists, somewhat more could be said on the nature of polycystic kidney disease. For example, why is there an association between autosomal dominant polycystic kidney disease and carotid dissection? Does this condition result in a weakened connective tissue structure in general?

Response: Thank you for this helpful suggestion. We have revised this section at Discussion:

“ADPKD is the most common inherited renal cystic disease, it is also associated with various extrarenal manifestations, such as polycystic liver disease[17], cardiac valvular anomalies, colonic diverticular and vascular complications. The prevalence of intracerebral aneurysms in patients with ADPKD is 8–10% and therefore more common than in the general population [1]. It is reported that more than 90% of ADPKD was attributed to the mutation of the PKD-1 or PKD-2 genes[18]. These two genes encode polycystin, a membrane glycoprotein, located in arterial smooth muscle, which deficiency may play an important pathogenic role in arterial complications[19].” (page 7, line 18).

Chih-Ping Chung (Reviewer 2)

This is an interesting case report about a patient with right 12th cranial nerve palsy and right ICA dissection.
1. Please have the manuscript English edited. There are several inappropriate wording and grammars in the text.

Response: Thank you for your careful reading and helpful suggestion. The language was now revised thoroughly. Many typos and rhetorical errors were corrected and highlighted.

2. Author presumed that right ICA dissection with vessel dilatation compressed the 12th cranial nerve and led to right 12th cranial nerve palsy. To support this postulation, a follow-up MRA showing healing and normalized of right ICA dissection and lumen associated with recovered 12th cranial nerve function is needed.

Response: Thank you for this helpful suggestion. The patient had a completely recovery at 3 months after onset (Fig 1, B). We scheduled a CTA examination 6 months later and found a completely recovery of the internal carotid lumen, with only mild residual hematoma within the vascular wall. We have added this picture as the supplemental Fig. 2.

3. Tongue muscle atrophy usually indicates a "chronic" 12th cranial nerve lesion. What is the duration of symptom onset and between symptom onset and vessel examinations? This point needs to be discussed.

Response: We understand your concern. The word “atrophy” may be a misunderstanding description. As the hypoglossal nerve palsy was found within 3 days after the onset. Local muscle contraction may occur when the lateral paralyzed tongue is protruding. We have revised the word“atrophy” to “local palsy”.

4. The finding with enlarged structure within the hypoglossal canal is interesting. Please make more clear and extensive discussion about this finding.

Thank you for this helpful suggestion. We revised at Discussion: “The hypoglossal canal is a bone passage which contains the canalicular segment of the hypoglossal nerve, a branch of the ascending pharyngeal artery, and a venous plexus known as the anterior condylar vein[5]. Visualization of the canalicular venous plexus could be important in the evaluation of hypoglossal nerve palsy because an enlarged emissary vein draining into the sigmoid sinus may be responsible for this palsy[5, 6]. Dynamic contrast-enhanced MR could be considered to compare the different enhancement timing of hypoglossal canal structures (arteries, veins, and dura) for confirmation[7]. ” (page 6, line 15).