Treatment of pediatric intracranial dissecting aneurysm with clipping and angioplasty, and next-generation sequencing analysis: A case report and literature review

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Abstract

BACKGROUND

Large intracranial dissecting aneurysm (IDA) in the anterior cerebral circulation is rare in children. There has been no consensus on the diagnosis and treatment for IDA in children.

CASE SUMMARY

We report a 3-year-old boy with a large ruptured IDA in the right middle cerebral artery (16 mm × 14 mm). The IDA was successfully managed with clipping and angioplasty. Next-generation sequencing of the blood sample followed by bioinformatics analysis suggested that the rs78977446 variant of the ADAMTS13 gene is a risk for pediatric IDA. Three years after surgery, the boy was developmentally normal.

CONCLUSION

Clipping and angioplasty are effective treatments for ruptured IDA in the anterior cerebral circulation. ADAMTS13 rs78977446 is a risk factor for pediatric IDA.

Key Words: Intracranial dissecting aneurysm; Clipping; Pathogenic variants; ADAMTS13; Case report

Core Tip: The index case was a 3-year-old boy with a large ruptured intracranial...
Solar N et al. Pediatric intracranial dissecting aneurysm

**INTRODUCTION**

Rupture of intracranial dissecting aneurysms (IDA) is a cause of subarachnoid hemorrhage (SAH) in children. The incidence of IDA is estimated to be no more than that for cervical dissecting artery (2.6–3.0 per 100000 people per year)\(^2\). Both genetic and environmental factors contribute to the development of pediatric IDA\(^4\). At the level of pathology, ultimate formation of intramural hematoma between the intima and media consists of tear of artery and rupture of vasa vasorum\(^9\). IDA is associated with syphilis\(^4\), connective tissue diseases\(^8\), atherosclerosis\(^1\), infection\(^1\), migraine\(^4\), and alpha-1 antitrypsin deficiency\(^4\). A key event in dissecting aneurysms is the sudden widespread disruption of the internal elastic lamina and media\(^1\) in children, and particularly in the anterior cerebral circulation, has rarely been reported and represents a formidable challenge in both the diagnosis and treatment\(^14\).

We report a case of SAH caused by ruptured IDA in the anterior cerebral circulation. The patient was successfully treated with clipping and angioplasty. We also performed whole-genome sequencing to identify potential pathogenic gene polymorphisms.

**CASE PRESENTATION**

**Chief complaints**

A 3-year-old boy presented with intermittent non-projectile vomiting after a brief episode of syncope.

**History of present illness**

There was no clear triggering events for the emergence of symptoms. There was no blood in the gastric contents. Upon admission, the boy was lethargic but able to respond to command.

**History of past illness**

He had no history of trauma or surgery and no family history of cardiovascular diseases.

**Physical examination**

The Glasgow Coma Scale score was 14. Hunt-Hess grade was III. Pupil reflex was normal. The muscle strength was grade III in the left leg.

**Laboratory examinations**

With the exception of increased white blood cell count (8.58 × 10⁹/L), the laboratory test results were normal.

**Imaging examinations**

Computed tomography (CT) scan showed subarachnoid hemorrhage in the lateral
fissure cistern and a small amount of blood in the right lateral ventricle (Figure 1A). CT angiography showed ruptured aneurysm in the right middle cerebral artery (Figure 1B-D). The intracranial aneurysm (IA) was 16 mm × 14 mm, with a wide neck. The pearl-and-string sign (proximal stenosis and distal stenosis in the intracranial aneurysm) was consistent with dissecting aneurysm (Figure 1C and D), as previously reported[14].

FINAL DIAGNOSIS
Based on these features, a diagnosis of IDA was established.

TREATMENT
Surgery was conducted using a pterional approach under general anesthesia. After adequate exposure of the parent artery, an IA was apparent at the junction between M1 and M2. There was severe stenosis in the proximal part of the aneurysm. The aneurysm wall was extremely thin. The normal anatomical structure of the parent artery has been apparently destroyed. The aneurysm was opened, and the blood clot within the aneurysm and the patent artery was removed. Then the IA was clipped (Figure 2A and B). The normal anatomical structure of the parent artery was restored and the parent vessel remained patent. IDA lesion was resected and tissue specimen was sent to pathologic examination (Figure 2B and C).

OUTCOME AND FOLLOW-UP
CT angiography was conducted 2 wk later, and showed no aneurysm; the parent artery was patent (Figure 3A-C). Neurologic symptoms and signs gradually improved. At the 1 mo follow-up visit, the boy was healthy, with the exception of slight muscle weakness in the left leg (grade IV). At 3 years later, the patient had completely recovered. CT angiography revealed normal blood supply to the brain (Figure 3D).

Pathogenic variants
Whole-genome sequencing (Novogene, Beijing, China) of the blood sample followed by bioinformatics analysis according to the American College of Medical Genetics guidelines[16] revealed 13 candidate genes (Table 1). Next, we searched the PubMed database using the keyword “intracranial aneurysm” or “dissecting,” and “genes including pathogenic variation.” The literature review suggested an association between the rs78977446 variant of the ADAMTS13 gene and pediatric IDA. Briefly, ADAMTS13 participates in the inflammatory processes and vascular remodeling in IA[17,18]. Genetic variants, transcription abnormality, and methylation changes in the ADAMTS genes may be an important factor for IA[19]. In addition to IA, an autopsy study of 31 cases of aortic dissections revealed much higher frequency (0.1613) of the rs11575933 variant of the ADAMTS13 gene in aortic dissections[20] vs healthy control subjects (https://www.ncbi.nlm.nih.gov/snp/?term=rs11575933).

DISCUSSION
Treatment of ruptured IDA
IDA can be classified into two types. In type 1 IDA, the dissection is located between the elastic layer and media layer, and causes ischemic stroke. In type 2 IDA, the dissection occurs between the media and adventitia, and causes SAH[21].

Treatment options for type 2 IDA include microsurgical clipping, coiling embolization, triple stent, trapping[22], bypass[23], wrapping, and complete exclusion[24]. The choice of these treatment modalities remains controversial[25].

As an endovascular interventional therapy, clipping has been frequently used in pediatric IDA of the posterior circulation[16,17]. It does not require craniotomy and thus is associated with minimal surgical trauma. The IDA in the index case was relatively large, and was ruptured. Thus, controlling bleeding and preventing rebleeding were the primary aims of the treatment[26]. For this rare ruptured large dissecting aneurysm,
**Table 1** Pathogenic variants found by American College of Medical Genetics guidelines

| Chromosome | Position | Variation          | REF | ALT | Function     | Gene       | SIFT | Mutation taster | CADD  |
|------------|----------|--------------------|-----|-----|--------------|------------|------|----------------|-------|
| 1          | 47610522 | rs570554271        | C   | T   | Stopgain     | CYP4A22    | -    | 1, A           | 10.070978, 36 |
| 2          | 23457905 | rs45623538         | C   | T   | Missense     | UGTA1A3    | 0.0  | 1, D           | 2.458692, 19.20 |
| 8          | 154599712 | -                  | G   | A   | Missense     | FOXH1      | 0.0  | 1, D           | 6.334943, 29.3 |
| 9          | 136310917 | rs78977446         | C   | T   | Missense     | ADAMTS13   | 0.081| 1, N           | 0.962795, 10.45 |
| 11         | 17542222 | rs185040406        | C   | T   | Missense     | ABCC8      | 0.07 | 1, T           | 0.777604, N  |
| 12         | 85266484 | rs12424429         | G   | A   | Missense     | SLC6A15    | 0.295| 1, T           | 0.975276, N  |
| 13         | 800518634 | rs41281112        | C   | T   | Stopgain     | CLYBL      | -    | 1, A           | 8.514350, 35  |
| 14         | 75514138 | rs28756990         | C   | A   | Missense     | MLH3       | 0.034| 1, N           | 2.798595, 21.4 |
| 16         | 3705465  | rs77254040         | C   | G   | Missense     | DNASE1     | 0.007| 1, D           | 3.289682, 22.8 |
| 18         | 29867688 | rs3744921          | T   | C   | Missense     | GAREM1     | 0.22 | 1, T           | 0.999954, D  |
| 19         | 4157148  | rs77002741         | G   | A   | Missense     | CREB3L3    | 0.169| 1, N           | 1.858481, 15.34 |
| 19         | 39898667 | rs3746683          | C   | T   | Synonymous   | ZFP36      | -    | -              |       |
| 22         | 50525267 | rs184241799        | C   | T   | Missense     | MLC1       | 0.007| 1, N           | 3.434483, 23.0 |

CADD score > 15 means that the variation affects protein function. ALT: Mutation-type; REF: Reference. A SIFT score indicates whether the variation is likely to cause changes in protein structure or function: D: Deleterious (sift ≤ 0.05); T: Tolerated (sift > 0.05). MutationTaster represents the effect of the mutation on the protein sequence: A: Disease_causing_automatic; D: Disease_causing; N: Polymorphism; P: Polymorphism_automatic.

Microsurgery clipping and patent vessel remodeling may have a lower probability of long-term recurrence. More importantly, the lesions can be visualized during the microsurgery. Blood clot in the parent artery was cleared to establish the normal anatomy of the parent artery. IDA, which is similar to the saccular aneurysm in the same location, has the risk of rebleeding during the acute stage[30]. Also, recurrence after several years has been reported[31]. As a result, long-term monitoring is required.

**Genetic indications and precision medication**

Sequencing analysis followed by bioinformatics analysis and literature review suggested that the rs78977446 variant of the **ADAMTS13** gene is a risk for pediatric IDA. IDA is more common in children than in adults, indicating a genetic contribution, but genetic studies for pediatric IDA are rare. In a previous study, the mutational rate was significantly higher in intracranial vertebral–basilar artery dissection cases than in controls[32]. **RNF213 rs112735431 (c.14576G>A)** frequency is significantly lower in patients with intracranial vertebral artery dissection. The genetic predisposition to IDA in the index case may form the basis of future recurrence, and physicians should be aware of the unique circumstance of each patient[33].

**CONCLUSION**

In summary, clipping and angioplasty are appropriate treatments for ruptured IDA in the anterior cerebral circulation. The rs78977446 variant of the **ADAMTS13** gene is a risk factor for pediatric IDA.
Figure 1 Preoperative imaging examination. A: Subarachnoid hemorrhage caused by ruptured intracranial dissecting aneurysm (IDA); B: Computed tomography angiography shows intracranial aneurysm in the right medical council on alcohol; C and D: Pearl-and-string sign of IDAs (focal stenoses proximally and distally, which are noted by white arrows).

Figure 2 Clipping and angioplasty for intracranial dissecting aneurysms, and pathological examination. A: The aneurysm was clipped; B: The wall of the intracranial dissecting aneurysm was very thin, and a thrombus was adhered to the wall; C: The intracranial dissecting aneurysm was resected and sent for pathological examination. Pathological examination indicated irregular and malformed vascular wall structure with inflammatory infiltration.
Figure 3 Postoperative computed tomography angiography examination and follow-up. A-C: Postoperative computed tomography angiography examination indicated that the aneurysm had been resected, and the blood flow of the constructed medical council on alcohol was unobstructed; D: The 3-year follow-up showed no recurrence.

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