

Brain Hemorrhages in Jacobsen Syndrome: A Retrospective Review of Six Cases and Clinical Recommendations

Paul Grossfeld*

Division of Cardiology, Department of Pediatrics, UCSD School of Medicine, San Diego, California

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Jacobsen syndrome is a rare chromosomal disorder caused by distal deletions in the long arm of chromosome 11. All patients with Jacobsen syndrome have Paris–Trousseau syndrome, a bleeding disorder that causes neonatal thrombocytopenia, and persistent platelet dysfunction. Despite that, to date there are no reported cases of hemorrhagic strokes occurring in patients with Jacobsen syndrome. In the last 6 years at least six cases of brain hemorrhages in patients with Jacobsen syndrome have occurred. In this report, we perform a retrospective review of these six cases. The analysis indicates that the etiology of brain hemorrhages in Jacobsen syndrome is likely multifactorial. A likely cause (or causes) was identified in three of the cases, and additional potential risk factors were identified. Based on these findings, clinical recommendations are provided that should aid in the identification of those individuals with Jacobsen syndrome that are at increased risk for brain hemorrhages, and will hopefully decrease the occurrence of this devastating complication in people with Jacobsen syndrome. © 2016 Wiley Periodicals, Inc.

Key words: Jacobsen syndrome; Paris–Trousseau syndrome; hemorrhagic stroke

INTRODUCTION

Jacobsen syndrome (JBS; MIM 147791) is a rare chromosomal disorder caused by deletions in distal 11q [Jacobsen et al., 1973; Grossfeld et al., 2004; Mattina et al., 2009]. Previous genotype/phenotype studies [Favier et al., 2015] have identified multiple disease-causing genes for the spectrum of clinical disorders that characterize the syndrome, including congenital heart disease [Ye et al., 2010], intellectual disability [Coldren et al., 2009], behavioral problems [Akshoomoff et al., 2015; Nakamura et al., 2016], Paris–Trousseau bleeding disorder [Favier et al., 1993; Raslova et al., 2004], structural kidney defects Ye M. Unpublished data (2016), and immunodeficiency [Dalm et al., 2015a].

At the time of our first conference for patients and their families through the 11q Research and Resource Group in August, 1998, in San Diego, there was one known, unpublished case of a child with Jacobsen syndrome who had suffered a brain hemorrhage. The cause was unclear and 15 years later she succumbed to complications from

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congenital heart disease. No subsequent cases of brain hemorrhages in people with Jacobsen syndrome were known until recently, and to date there are no reports in the medical literature of brain aneurysms or hemorrhagic stroke occurring in Jacobsen syndrome. Since 2010, six more cases of brain hemorrhages in people with Jacobsen syndrome have been identified.

Patients with Jacobsen syndrome are likely at increased potential risk for suffering brain hemorrhages from multiple factors. First, all patients have Paris–Trousseau syndrome, a platelet disorder characterized by thrombocytopenia, and persistent platelet dysfunction. Second, at least two previous genetic linkage studies have identified an association between distal 11q and aneurysms of the brain or aorta [Vaughan et al., 2001; Ozturk et al., 2006].

In this report, six recent cases of brain hemorrhages in people with Jacobsen syndrome are reviewed retrospectively, potential risk factors are identified, and based on these observations clinical recommendations, and guidelines for future management are provided.

METHODS

Patients were identified through direct contact from the patients' families by their initiative by e-mail and/or social media, specifically through the European Chromosome 11

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*Correspondence to:

Paul Grossfeld, M.D., Professor of Pediatrics, Division of Cardiology, Department of Pediatrics, UCSD School of Medicine, 3020 Children's Way, MC 5004, San Diego, CA 92123.

E-mail: pgrossfeld@ucsd.edu

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support group (www.chromosome11.org), 11q Spain (11qes.org), and the 11q Research and Resource support group (www.11qusa.org).

CLINICAL REPORTS

Patient 1

A previously healthy 15-year-old female became acutely ill and was diagnosed with a hemorrhagic stroke. At the time of admission her blood pressure was 230/190. Her platelet count was 184, her PT was 10.4, (INR = 0.94), and her PTT was 24. Platelet function studies were abnormal, demonstrating a prolonged bleeding time (greater than 15 min), and abnormal PFA 100 (CEPI 275 sec, normal 70–167, CADP 211 sec, normal 60–130 sec). Brain imaging studies did not reveal an aneurysm. Since her stroke she has had persistent systemic hypertension for which she is being treated medically. She has made a nearly full neurologic recovery but does have some residual lower extremity weakness.

Patient 2

A 12-year-old female had an acute-onset severe headache and fainted. She was diagnosed with a brain hemorrhage. Brain imaging studies revealed a 3 cm ruptured aneurysm. Her platelet count was 54 K, her PT and PTT were normal (INR = 0.88, aPTT ratio 0.8). She underwent surgery, which left her in a coma, and she died shortly after.

Patient 3

A 24-year-old female had been suffering headaches for a few months, and subsequently became acutely ill. She was found to have an 8 cm hemorrhage in her right frontal cortex, but without any evidence for an aneurysm. Her platelet count was 305 K, PT was 14.8 (INR 1.25), and her PTT was 37.8 (ratio 1.15). She had a partial neurologic recovery but a month later she suffered a second hemorrhage near her brain stem and did not survive. An autopsy was performed, and there was no evidence for aneurysm or vasculitis. The patient had been taking oral contraceptive pills and was found to have very low serum iron levels.

Patient 4

A 21-year-old previously healthy female was diagnosed with pneumonia and perimyocarditis. She subsequently developed atrial fibrillation and suffered a hemorrhagic stroke, confirmed by CT of the brain. The study demonstrated evidence of a previous small stroke. The patient was found to have a familial Factor V Leiden mutation, which was carried by her maternal grandfather who suffered a stroke at age 38. She was also found to have increased factor VIII levels (250% of normal). She had been taking oral contraceptive pills for 2 years prior to the event. At the time of her stroke, her INR was 1.0, PTT was 27, and platelet count was 200 K. She has made a partial recovery with residual right hand weakness, difficulty ambulating, and slight speech impairment.

Patient 5

A 23-year-old previously well male suffered a massive cerebral hemorrhage, for which he underwent surgery to evacuate a hematoma. A CT angiogram revealed no brain aneurysms or AV malformations. At the time of admission his platelet count was 75 K, PT 13.9/INR 1.2, and his PTT was 28 sec. He has since made a partial neurologic recovery.

Patient 6

A 4-month-old female with hypoplastic left heart syndrome underwent a stage I Norwood procedure. Throughout her hospital course she had platelet counts of 30–60 K. After her heart surgery she was started on Lovenox to prevent thrombus formation in the shunt. She subsequently developed a hemothorax. After this event she was transfused with platelets to maintain a platelet count of >75 K, and the lovenox dose was decreased to keep an anti-factor X level goal range of 0.3–0.5. A week later she suffered a massive brain hemorrhage. At that time the platelet count was 144 K, PT 14 (INR 1.08), PTT 49.6. Medical support was withdrawn and she expired shortly after.

DISCUSSION

To date, there have been no reports in the medical literature of brain hemorrhages in patients with Jacobsen syndrome. Since 2010, we have identified six cases of people with Jacobsen syndrome suffering brain hemorrhages. All patients with Jacobsen syndrome have the Paris–Trousseau platelet disorder, which is characterized by thrombocytopenia of the newborn, and persistent platelet dysfunction. Consequently, all people with JS are at risk for bleeding.

As shown in Table I, the ages ranged from 4 months to 25 years, and five of the six patients were at least 12 years old. Although newborns with JS typically have severe thrombocytopenia, platelet counts tend to normalize by school age, suggesting that the severe thrombocytopenia in infancy may not pose a higher risk for brain hemorrhages at that age in the absence of other contributing factors. There were five females and one male, consistent with our previous report of a 2:1 female to male ratio in Jacobsen syndrome. Of these six cases, one was found to have a brain aneurysm. Three of the cases (Patients 1, 2, and 5) had been previously well without any preceding symptoms until the time of the event. In one case, the patient had complained of headaches for months preceding the event. Two of the cases had been severely ill, one (Patient 4) with pneumonia and pancarditis, and one (Patient 6) had recently undergone complex congenital heart surgery, specifically a stage 1 Norwood procedure. Patient 4 also had a familial mutation in the Leiden Factor V clotting factor and had atrial fibrillation preceding her stroke. One case (Patient 1) was likely due to previously undiagnosed systemic hypertension. Three of the subjects had thrombocytopenia at the time of the hemorrhage, and only one patient (Patient 6), who had been on lovenox, had a prolonged PTT. INRs were normal in all six subjects.

At least one of the patients likely suffered a brain hemorrhage secondary to an embolic stroke (Patient 4). Two of the five females (Patients 3 and 4) had been taking oral contraceptive pills (OCPs)

TABLE I. Clinical Data

Subject	Sex	Age	Deletion*	Risk factors/etiology	Outcome	Miscellaneous
1	F	15	10.58 Mb	None; no aneurysm; Plt = 184 K; PT = 10.4 (INR = 0.94); PTT = 24	Nearly full recovery after event	Dx'd with hypertension
2	F	12	11q24.1-ter	3 cm brain aneurysm; plts = 54 K; INR and PTT normal	Died	Had acute onset headache
3	F	24	11q24-ter	On OCPs; no aneurysm; Plt = 305 K; PT 14.8 (INR 1.25); PTT = 37.8 (ratio 1.15)	Died	Had low iron levels had persistent chronic headaches preceding event
4	F	21	14.3 Mb	Factor V mutation increased factor VIII level Pneumonia, atrial fibrillation Pancarditis; on OCPs; no aneurysm; INR = 1; PTT = 27; Plts = 200 K	Partial recovery	Had evidence for a previous embolic stroke on CT
5	M	23	11q24.1-ter	No aneurysm; Plt count 75 K, PT 13.9/INR 1.2; PTT 28 sec	Partial recovery	
6	F	4 m	9.5 Mb	HLHS, s/p stage 1 Norwood; was on Lovenox (anti-factor Xa levels 0.3–0.5); no aneurysm immunodeficiency, h/o NEC Plt counts 30–60 K	died	

*All patients were diagnosed with Jacobsen syndrome by either karyotype analysis and/or arraycomparative genomic hybridization, have a terminal deletion in 11q, and are assumed to have Paris–Trousseau platelet disorder.

at the time of their stroke, suggesting that OCPs might be a risk factor for causing an embolic stroke in these patients. Patient 6 developed an acute hemorrhagic stroke after being started on lovenox in order to prevent thrombosis of her cardiac shunt. This raises the possibility that pharmacologic inhibition of clotting factors in Jacobsen syndrome patients that already have abnormal platelets may significantly increase the risk for bleeding.

The reason for the increase in the number of cases identified over the last six years is unclear. Based on the potential etiologies identified, the most likely explanation is increased awareness and reporting, rather than an actual increase in frequency of the events. It is likely that there are additional cases that have occurred that have not been reported.

SUMMARY AND CLINICAL RECOMMENDATIONS

There has been an increased number of patients with Jacobsen syndrome suffering hemorrhagic strokes, with three of the cases in this report dying, and the three survivors were left with significant neurologic impairment. The etiologies are likely multifactorial and based on this retrospective review of six cases, Table II lists current recommendations and guidelines. Baseline non-invasive brain imaging, specifically an MRA without contrast should be performed as a screen to identify a brain aneurysm. Neurosurgical consultation should be obtained as indicated. At this time, it is unclear whether serial studies should be performed in patients who have a normal baseline study. Medications that affect platelet function or inhibit clotting factors (e.g., coumadin, lovenox, or heparin) should be avoided or used only under extraordinary circumstances, for example, if there is documented evidence for thrombus formation. In that case, intravenous heparin should be used with extreme caution, and with aggressive monitoring of PTT. Oral contraceptives, which are

used to minimize blood loss from menses, should be prescribed in low doses to minimize the risk for thrombus formation. All patients with Jacobsen syndrome should have frequent monitoring of their blood pressure. Identifiable causes, including coarctation of the aorta and structural kidney defects, both of which occur at increased frequencies in Jacobsen syndrome compared to the general population, need to be ruled out. Hypertension should be treated aggressively. Infections should also be treated aggressively. Recent evidence implicates that most, if not all patients with Jacobsen syndrome have varying degrees of immune deficiency, and some patients might require antibiotic prophylaxis and/or intravenous immunoglobulin [Dalm et al., 2015b]. Measures should be taken to minimize head trauma when possible. Lastly, new-onset, severe or unusual headaches should be heeded, with a low threshold for performing brain imaging.

Clearly more information is needed to better identify the apparently small subset of patients with Jacobsen syndrome that are at increased risk, beyond that caused by Paris–Trousseau syndrome, and over time these guidelines may change. These recommendations may also be useful for the management of at-risk patients with other genetic syndromes.

LIMITATIONS

Patients were identified through a combination of contacts with families and treating physicians, as well as through social media. Medical information for each case was obtained directly from families of the affected patients and/or from the treating physicians. Consequently, some of the information obtained was not by direct review of the medical records and although unlikely, could be either inaccurate or lacking additional information. As stated above, there are likely additional cases that have not been identified.

TABLE II. Clinical Recommendations and Guidelines

- Non-invasive imaging (MRA and MRI if possible) for baseline, and potentially serial followup as needed
- Neurosurgery consultation as indicated
- Avoid medications that can worsen platelet function, or inhibit clotting pathways
- Judicious use of medications that can cause increased clotting (e.g., OCPs)
- Avoid head trauma
- Treat hypertension aggressively and rule out underlying causes (cardiac, renal)
- Treat infections aggressively, and assume people with JS are immunocompromised
- Consider brain imaging studies for new-onset severe or persistent headaches

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