American Journal of Medical Genetics Part A

Brain hemorrhages in Jacobsen syndrome: A review of six cases and clinical recommendations

Journal:	*American Journal of Medical Genetics: Part A*
Manuscript ID	16-0774.R1
Wiley - Manuscript type:	Clinical Report
Date Submitted by the Author:	26-Sep-2016
Complete List of Authors:	Grossfeld, Paul; UCSD,
Keywords:	Jacobsen syndrome, Brain hemorrhage, Paris-Trousseau syndrome, brain aneurysm
Search Terms:	Jacobsen syndrome

TITLE: Brain hemorrhages in Jacobsen syndrome: A retrospective review of six cases and clinical recommendations

Paul Grossfeld, M.D.*

Professor of Pediatrics

Division of Cardiology

Department of Pediatrics

UCSD School of Medicine

*Corresponding author

Address:

3020 Children's Way, MC 5004

San Diego, California 92123

Phone: 858-966-5855

Telefax: 858-571-7903

E-mail: pgrossfeld@ucsd.edu

ABSTRACT

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 six 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.

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 and Nakamura, et al., 2016], Paris-Trousseau bleeding disorder [Favier, et al., 1993 and Raslova, et al., 2004], structural kidney defects Ye, et al., [unpublished data. 2016], and immunodeficiency [Dalm, et al., 2015].

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 fifteen years later she succumbed to complications from 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 and 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 support group (www.chromosome11.org) and the 11q Research and Resource support group (www.11qusa.org). Clinical information was provided by the patients' families and from treating physicians. IRB approval was not required.

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 minutes), and abnormal PFA 100 (CEPI 275 seconds, normal 70-167, CADP 211

seconds, normal 60-130 seconds). 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 3cm ruptured aneurysm. Her platelet count was 54K, 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 8cm hemorrhage in her right frontal cortex, but without any evidence for an aneurysm. Her platelet count was 305K, 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 health 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 two years prior to the event. At the time of her stroke, her INR was 1.0, PTT was 27, and platelet count was 200K. 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 75K, PT 13.9/INR 1.2, and his PTT was 28 seconds. He has since made a partial neurologic recovery.

Patient 6: A four month-old female with hypoplastic left heart syndrome underwent a stage I Norwood procedure. Throughout her hospital course she had platelet counts of 30-60K. 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 > 75K, 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 144K, 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 four months to 25 years, and five of the six patients were at least 12 years old. While 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) 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, e.g., 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, unpublished results, 2016]. 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.

ACKNOWLEDGEMENTS: The author would like to thank the families of the patients described in this report, who have voluntarily provided clinical information, as well as the treating physicians. The author would like to thank Dr. Nathaniel Chuang, Director of Pediatric Neuroradiology at Rady Children's Hospital of San Diego for his input regarding brain imaging recommendations. Dr. Grossfeld serves as the Chief Medical Advisor for the 11q Research and Resource Group (www.11qusa.org) and is on the scientific advisory board for the European Chromosome 11 support group (http://www.chromosome11.eu/) .

REFERENCES

Akshoomoff N, Mattson SN, Grossfeld PD. 2015. Evidence for autism spectrum disorder in Jacobsen syndrome: Identification of a candidate gene in distal 11q. Genet Med 17:143–148.

Coldren C, Lai Z, Grossfeld P. 2009. Comparative genomic hybridization mapping suggests a role for BSX and Neurogranin in neurocognitive and behavioral defects in the 11q terminal deletion disorder (Jacobsen syndrome). Neurogenetics 10:89–95.

Dalm VASH, Driessen GJA, Langerak AW, van Hagen PM, van der Burg M. 2015. Immunodeficiency state in the 11q terminal deletion disorder: Is it part of the syndrome? J Clin Immunol. 35(8):761-8

Favier R, Douay L, Esteva B, Portnoi MF, Gaulard P, Lecompte T, Perot C, Adam M, Lecrubier C, Van den Akker J, Lasfargues G, Najean Y, Breton-Gorius J. 1993. A novel genetic thrombocytopenia (Paris-Trousseau) associated with platelet inclusions, dysmegakaryopoiesis and chromosome deletion AT 11q23. C R Acad Sci III 316:608–701.

Favier R, Akshoomoff N, Mattson S, Grossfeld P. 2015. Jacobsen syndrome: Advances in our knowledge of phenotype and genotype. Am J Med Genet C Semin Med Genet. 169(3):239-50

Grossfeld PD, Mattina T, Lai Z, Favier R, Jones KL, Cotter F, Jones C. 2004. The terminal 11q deletion disorder: A prospective study of 110 cases. American Journal of Medical Genetics 129A:51–61.

Jacobsen P, Hauge M, Henningsen K, Hobolth N, Mikkelsen M, Philip J. 1973. An (11;21) translocation in four generations with chromosome 11 abnormalities in the offspring. Hum Hered 23:568–585.

Mattina T, Perrotta CS, Grossfeld P. 2009. Jacobsen syndrome. Orphanet J Rare Dis. 4:1172–1750.

Nakamura T, Arima-Yoshia F, Sakaue F, Nasu- Nishimura Y, Takeda Y, Matsuura K, Grossfeld P, Manabe T, Akiyama T. 2016. PX-RICS-deficient mice mimic Jacobsen syndrome-related autism spectrum disorder through impaired GABAA receptor trafficking. Nature Communications 16;7:10861

Ozturk AK, Nahed BV, Bydon M, Bilguvar K, Goksu E, Bademci G, Guclu B, Johnson MH, Amar A, Lifton RP, Gunel M. 2006. Molecular genetic analysis of two large kindreds with intracranial aneurysms demonstrates linkage to 11q24-25 and 14q23-31. Stroke. 37(4):1021-7.

Raslova H, Komura E, Le Couedic JP, Larbret F, Debili N, Feunten J, Danos O, Albagli

O, Vainchenker W, Favier R. 2004. FLI1 monoallelic expression combined with its hemizygous loss underlies Paris-Trousseau/Jacobsen thrombopenia. J Clin Invest. 114:77–84.

Vaughan CJ, Casey M, He J, Veugelers M, Henderson K, Guo D, Campagna R, Roman MJ, Milewicz DM, Devereux RB, Basson CT. 2001. Identification of a chromosome 11q23.2-q24 locus for familial aortic aneurysm disease, a genetically heterogeneous disorder. Circulation. 22;103(20):2469-7

Ye M, Coldren C, Benson W, Goldmuntz E, Ostrowski M, Watson D, Perryman B, Grossfeld P. 2010. Deletion of ETS-1, a gene in the Jacobsen syndrome critical region, causes ventricular septal defects and abnormal ventricular morphology in mice. Human Molecular Genetics. 19(4):648-56

Table I: Clinical data

Subject	Sex	Age	Deletion*	Risk factors/etiology	Outcome	Miscellaneous
1	F	15	10.58Mb	None; no aneurysm Plt=184K; PT=10.4 (INR=0.94); PTT=24	nearly full recovery after event	Dx'd with hypertension
2	F	12	11q24.1-ter	3cm brain aneurysm plts=54K; INR and PTT normal	died	Had acute onset headache
3	F	24	11q24-ter	On OCPs; no aneurysm Plt=305K; 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	14.3Mb	Factor V mutation Increased factor VIII level Pneumonia, atrial fibrillation Pancarditis; on OCPs; No aneurysm INR=1; PTT=27; Plts=200K	Partial recovery	Had evidence for a previous embolic stroke on CT

5	M	23	11q24.1-ter	No aneurysm Plt count 75K, PT 13.9/ INR 1.2; PTT 28sec	Partial recovery
6	F	4m	9.5Mb	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 30-60K	died

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

Table II: Clinical recommendations and guidelines

- Non-invasive imaging (MRA and MRI if possible) for baseline, and potentially serial follow-up 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