A new hereditary PROS1 mutation caused isolated cortical venous thrombosis: a case report and literature review

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Case Report

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Abstract

Background: Protein S Deficiency is a rare inherited disease. We report a disease process that a young man with a new *PROS1*(OMIM:176880) mutation suddenly occurred Isolated cortical vein thrombosis(ICoVT).

Case presentation: The patient suffered from headaches and Paroxysmal convulsion without obvious inducement. Physical examination, coagulation function test were generally normal. The activity of protein S was 21.2%, which was significantly lower than the normal value. MRI (magnetic resonance imaging) showed right parietal cerebral hemorrhage, right parietal cortex vein thickening, cord-like. When we reviewed the patient's family history, we found that his father had successively suffered from mesenteric venous thrombosis, Portal venous thrombosis, and cerebral venous sinus thrombosis. Genetic analysis revealed a new *PROS1* mutation in the patient and his father. In addition, there is a duplication about 403.6Kb in the patient's chromosome 3q26.32-33. And we summarized the characteristics of cases with PROS1 LG2 subunit mutation.

Conclusions: This is a novel case report that a new *PROS1* gene missense mutation caused ICoVT. It provides information for us to understand the functional information of PROS1. When come to unexplained ICoVT, we need to consider the possibility of *PROS1* gene mutation.

Background

ICoVT is defined as thrombosis in one or more cerebral cortical veins without cerebral venous sinus and deep vein. It's too rare that only have a few case reports and small cohort reports[1-4]. Protein S deficiency is the major genetic risk factor for in the Asian population which increases the risk of venous thromboembolism(VTE) by 10 times[5]. The published reports are focusing on the deep vein, pulmonary vein [6, 7], mesenteric vein thrombosis[8, 9], and cerebral venous thrombosis is rarely reported[10]. What is more, ICoVT in patients with protein S deficiency has not yet been reported. Herein, we reported a Chinese young man with THPH5 (thrombophilia due to protein s deficiency, autosomal dominant, OMIM:612336) caused by a missense mutation in pros1(NM_000313.3:c.1912G>T p.Gly638Cys)and analyzed it in combination with literature.

Case Presentation

Clinical Features and pedigree establishment: A 31-year-old man was admitted to our hospital due to repeated headache for 7 days, paroxysmal and disturbance of consciousness convulsion for 4 days. 5 days ago , his MRI and MRV(MR venography) didn't report obvious abnormalities. When he came to our outpatient department 4 days ago, he suddenly felt weakness of both lower limbs, fall to the ground with limb convulsions and disturbance of consciousness. He finally awake after 30 minutes, but he can't remember the process. After that, he has experienced left limb convulsions with clear consciousness several times and lasts for 2-3 minutes each time. Generally, there is no special physical examination and obvious positive signs in the nervous system.

His father has experienced thrombosis three times including mesenteric venous thrombosis in 2004.07, portal venous thrombosis in 2010.11 and cerebral venous sinus (bilateral transverse sinus and sigmoid sinus) thrombosis in 2010.12.His mother and other family members had no thrombosis history(Figure 1). His paternal grandfather(I-1) died of esophageal cancer and his maternal grandfather died naturally.

Laboratory examination: The coagulation test is generally normal (Table 1). Thrombus screening test (Table 2) showed an abnormal result that protein S activity(PS:C) is 21.2%(reference range: 63.5-149%). Anti-SS-B antibody was positive, while the rest were negative in ANA+ANA antibody spectrum. Cranial pressure was 140mmH_2O. The number of nucleated cells in cerebrospinal fluid (CSF) was 10 × 10 ^ 6. CSF biochemistryanalysis revealed trace total protein 490mg / L. Herpes simplex virus type 1 and 2 antibody, autoimmune encephalitis antibody and pathogen high-throughput gene detection was negative and IgG index was 0.50.

Imagine features: During hospitalization, his MRI(Figure 2.A)showed a right parietal lobe intracerebral hemorrhage and cortical vein thickening like a strip. Susceptibility weighting imaging(SWI) showed a bleeding sign in the same position. No abnormality was found in MRV and computed tomography angiography (CTA) of head. MRI was reexamined 4 months after discharge (Figure2.B).

Gene analysis: NM_ 000313.3: c.1912 G > T is a missense mutation which results in *PROS1* Gly638Cys. The mutation was not found in the exon database. The pathogenicity classification of this mutation is unclear according to the ACMG variation classification guide. The Pathogenic variation criteria are PM2+PP3.

This mutation site is highly conserved between species. It's important for the structure and function of protein S. We have discovered that the patient's gene mutation was inherited from his father according to the Sanger sequencing result(Figure 1). The symptoms of the patient and his father were consistent with the clinical characteristics of THPH5. We believe that this mutation is the pathogenic variation of the patient and his father.

In addition, the patient has a repeats mutation about 403.6kb in chromosome 3q26.32-33(chr3.178919076-179322714 X3).

Therapy: Low molecular weight heparin (LMWH) 5000iu q12h anticoagulant treatment was given during hospitalization. After discharge, the patient took dabigatran ester capsule (150mg bid) and levetiracetam tablets (0.5g bid) regularly. He has not suffered from cerebral infarction again.

Discussion And Conclusions

PROS1 is a vitamin K-dependent plasma protein that plays a pivotal role in anticoagulants. It inhibits blood clotting by activating protein C(APC) [11]and tissue factor pathway inhibitor(TFPI) [12]serving as a cofactor. It also directs inhibition of prothrombin complex(FXa/FVA) production of thrombin[13]. Starting from the N-terminal, RROS1 contains a vitamin K-dependent domain, named "Gla domain", is sensitive to thrombin. Then, there are four consecutive epidermal

growth factor(EGF) like domains with high-affinity calcium-binding ability. In the C-terminal, PROS1 has a homologous plasma sex hormone-binding globulin(SHBG) which has two Laminin G-like structures(LG1, LG2).In PROS1, the SHBG-like domain is used to interact with C4BPA[14, 15].

LG1(Amino acids 299-475)and LG2(amino acids 484-666) are arranged continuously like a V-shape. It may be adverse to protein stability in some cases.So they all have disulfide bonds between subunits to stabilize LG pairs [16]. Cys448,475 in PROS1 LG1subunit and Cys639,666 in LG2 subunit are the key amino acids to form disulfide bonds.

Some disulfide bonds between domains or subunits are indispensable for the effective secretion of proteins. Free cysteine thiol groups can prolong the residence time of proteins in the endoplasmic reticulum[17]. *Pros1* Tyr444Cys is located near the key samino acids and the PROS1 secretion is greatly affected[18]. In another report, *pros1* Arg474Cys reduced the secretion of protein S by 8-fold, which was due to the impaired secretion and intracellular degradation[19]. Many results suggest that the mutation in the SHBG-like domain, especially in LG2, does not affect the mRNA transcription and PROS1 synthesis but the protein secretion[20-23].In summary, the mutation of *pros1* Gly638Cys introduces a new sulfhydryl group which impairs PROS1 secretion by affecting the disulfide bonds.

We collected the case information which mutated in the PROS1 LG2 subunit (Table 3). According to this table, we can find that the average onset age is 34.8 years old, the minimum age is 16 years old and the maximum age is 69 years old. About 76.92% of the patient are 21-50 years old when they experience primary VTE. Female (f): male (m) = 11:20. Most of the initial symptoms were DVT, followed by PE. DVT is particularly common in male patients, but less in females. Females have a considerable part of PE. PROS1 related test results vary greatly among individuals and lack follow-up test results. Only misuk Ji [24] provided FPS test results at multiple time points in patients with mesenteric venous thrombosis after total colectomy (Table 4). Therefore, we may need a more standardized standard or a more stable and accurate detection scheme.

The risk factors of cerebral venous thrombosis include dehydration, coagulation disorder, low intracranial pressure, etc [25, 26]. Arteriovenous malformation and head trauma are special factors that increase the risk of intracranial venous thrombosis[27].This patient has *pros1* Gly638Cys that is considered as its etiology. In addition, the patient's chromosome 3q26.32, q26.33 repeat amplified area include *PIK3CA*, which can lead to venous malformation[28]. It may be the another pathogeny for ICoVT.

The most common symptoms of ICoVT are headache (71%), epilepsy (58%) and focal neurological dysfunction (62%). In imaging, about 84% of patients showed brain parenchymal lesions,46% of them were presented hemorrhagic lesions,37% of them would be local edema [29].The suggestive sign of intracranial venous thrombosis is called "spinal cord sign" in CT[30] and "high-intensity venous sign and Dot sign" in MRI [31].In this paper,we can see them in MRI(Figure 2). Moreover, MRV may not give a clear suggestion due to the size and anatomical variation of cortical veins[32]. At this time, GRE sequences are needed for auxiliary diagnosis [33]. About half of the patients have a low apparent diffusion coefficient (ADC) in diffusion-weighted magnetic resonance (DWI), who is more likely to have parenchymal sequelae[34]. Although magnetic SWI is the most sensitive in diagnosing ICoVT, the changes of SWI and echo gradient may exist several years after the onset, so that we cannot distinguish whether the thrombus new or old[1]. If there is no better choice, DSA can be used to exclude other vascular diseases, such as arteriovenous malformations and fistulas [35].

In terms of treatment, the existing research results suggest that individuals with hereditary thrombotic tendency have an increased risk of primary VTE[36]. It can be seen from the table that many patients will have recurrent thrombosis within 10 years. At this time, we should pay attention to the choice of drugs. The efficacy and safety of patients using direct oral anticoagulants (DOACs) (such as dabigatran, rivaroxaban and apixaban) are similar to LMWH and vitamin K antagonist (VKA). The recurrence rate, massive bleeding rate and mortality of VTE in patients using DOACs in non-recommended dose or regimen are significantly higher [37], Therefore, taking DOACs correctly is an important part of effective treatment.

This case report and literature review provides information for us to understand the functional information of PROS1. When come to unexplained isolated cortical venous thrombosis, we need to consider the possibility of PROS1 gene mutation. We summarized the characteristics of cases with PROS1 LG2 subunit mutation which may does not affect the mRNA transcription and PROS1 synthesis but the protein secretion.

Abbreviations

ICoVT：Isolated cortical vein thrombosis; CTA：Computed tomography angiography. MRI：Imagnetic resonance imaging; MRV：MRI venography;VTE：Venous thromboembolism;THPH5 ：Thrombophilia due to protein s deficiency, autosomal dominant; DWI：Diffusion-weighted magnetic resonance;SWI：Susceptibility weighting imaging; ADC：Apparent diffusion coefficient;CSF：Cerebrospinal fluid; APC：Activating protein C;TFPI：Tissue factor pathway inhibitor;EGF：Epidermal growth factor;SHBG：Sex hormone-binding globulin;LG：Laminin G-like;VKA：Vitamin K antagonist;DOACs：Direct oral anticoagulants;LMWH：Low molecular weight heparin.

Declarations

Ethics approval and consent to participate: Verbal informed consent from the patient's relatives was obtained. The study was approved by the Ethics Committee of Fujian Medical University Union Hospital, and written informed consent was obtained from the patient and his family members. All the experiments were performed under relevant guidelines and regulations.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare that they have no competing interests.

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Author's contributions:

1. Conception and design of the study: Xiaochun Chen, Qinyong Ye, Ying Chen.
2. Provision of study materials or patients: Bin Sun, Yuqi Zeng, Erhan Yu, Xiaochun Chen.
3. Collection and assembly of data: Yuqi Zeng, Jieming Huang, Jiawei Xing.
4. Data analysis and interpretation: Jieming Huang, Erhan Yu, Jiawei Xing.
5. Manuscript writing: All authors.

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Tables

Table 1. Blood coagulation test results during hospitalization.

Days after onset	PT(second)	INR	Prothrombin activity (%)	APTT（se cond）	APTT ratio	FIB（g/L）	TT（second）	D-DI（ug/ml）
7	12.8	0.97	106.0	38.5	1.13	3.14	16.6	1.12
9	12.6	0.95	110.0	38.3	1.13	3.92	16.6	0.68
Ref value	11.0-15.0s		70.0-150.0%	28.0-42.0s		2.00-4.00	14.0-21.0	0.00-0.50

PT：Prothrombin time；INR：International normalized ratio；APTT: Activated partial thromboplastin time ；FIB：fibrinogen；TT：Thrombin time；D-DI：D-dimer.

Table 2. Thrombus screening test results during hospitalization.

iterm	Result（%）	Reference value（%）
Protein C activity	87%	60-140
Protein S activity	21.2	63.5-149
Antithrombin III	103	83-128

Table 3 Case information of patients with PROS1 LG2 mutation

Project (Area)	Mutation	Sex	Thrombotic episodes (onset age)	Test time	Drug	TPS: Ag (%)	FPS: Ag (%)	PS: A (%)	Type	Coagulation
Ewa Wypasek (Polish)[38]	p.Gly489Arg □/□	F	Stroke(45)	1y	Sus	68%	35%	-	III	Norm
Ikkei Ohashi (Japan)[39]	p.Ala491Asp □/□	M	DVT(57)	1d	No	-	38%	15%	-	d-d□1.1mg/dL
ZHAO-HUI WANG (China)[22]	p.Asp496* □AD□	F	CVT(52)	-	-	58%	52%	41%	I	Norm
		F	No(24)	-	-	40%	43%	39%	I	Norm
		M	CVT(50)	-	-	46%	50%	37%	I	Norm
		M	No(25)	-	-	50%	35%	32%	I	Norm
Ewa Wypasek (Polish)[38]	p. Ser501Pro Heerlen g.99785T>C □/□	M	DVT(38)	12y	Sus	111%	53%	-	III	Norm
		M	DVT+MI+Stroke(42)	3y	Sus	82%	38%	-	III	Norm
Ewa Wypasek (Polish)[40]	p. Ser501Pro Heerlen g.99785T>C □/□	M	DVT(38) SUVT(49)	1y	No	110.5%	52.8/55.8%	-	-	Norm
Jingyi Zhou (China)[41]	p.Thr518Argfs*39 □AD□	F	No(58)	No	-	66.49%± 0.84%	37.63%± 2.16%	40%	-	-
	p.Thr518Argfs*39 p.Arg561Trp □AD□	M	DVT(21) PE(27)	1y	Sus	13.47%± 2.97%	3.53%± 0.45%	1.8%	I	Norm
Lei Li (China)[6]	p.Thr518Argfs*41 □AD□	M	R-LE-DVT(38) R-LE-SUVT(38)	>12w	Sus	65.5%	39.8%	36.6%	III	-
Fumina Taniguchi (Japan) [42]	p.Ala525Val	F	DVT(44)	-	-	52%	25%	15%	I	-
Lei Li (China)[6]	p.Tyr560*	M	R-LE-DVT(27)	>12w	Sus	64.1%	35%	47%	I	-
		M	MVT(24) L-LE-DVT(26)	3y	Sus	55.3%	40.7%	42.6%	I PCD	-
		F	LE-DVT+PE(31) LE-DVT(36) L-UE-DVT(42)	5y	Sus	49%	33.6%	31%	I	-
		M	L-LE-DVT(18)	4y	Sus	44%	33.6%	31%	I	-
	p.Arg561Trp	F	R-LE-DVT(17) L-LE-DVT(25)	3y	Sus	57.2%	48.2%	31.7%	I	-
		M	PVT(19)	1y	Sus	70.5%	54%	50.7%	III	-
Jingyi Zhou (China)[41]	p.Arg561Trp	M	No(60)	-	-	63.32%± 0.87%	53.40%± 3.31%	59%	-	-
Lei Li (China)[6]	p.Glu598*	M	PE(32)	2y	Sus	44.3%	32.3%	32.7%	I	-
Xiaojie Huang (China)[7]	p.Glu598*	M	DVT+ PE (31□32)	-	>1m	-	-	22%	-	Hypercoagula
Fumina Taniguchi	p.Asp599Thrfs*13 p.Ala139Val	F	DVT+PE(14)	-	-	30%	8%	<10%	I	-

(Japan) [42]										
Yan-ping Zhang (China)[23]	PROS1 p.Leu607Ser SERPINC1 p.Val295Met	F	DVT(16)	-	No	67mg/L	19mg/L	<16%	I	Norm
		F	DVT(39) PE(41)	1y	Conti	85mg/L	22 mg/L	<16%	I	Norm
	p.Leu607Ser	M	No(13)	No	No	71 mg/L	23mg/L	16.7%	I	Norm
Jun Yamanouchi (Japan)[20]	p.Thr617Ala	M	DVT(69)	-	No	49.0%	26.7%	10.0%	I	Norm
SuelyM.Rezende (UK)[21]	p. His623Pro family	-	-	-	No	14.1±1.8 nmol/L	220.7±57.2nmol/L	-	I(1) III (3)	-
Lei Li (China)[6]	c.1871−2A>G	M	PE(28)	3y	Sus	58.7%	46.9%	36.9%	I	-
Misuk Ji (Korea)[24]	p.Tyr636Cys	M	MVT(45)	2-138-177d	No	-	35%-11%-23%	-	-	PT: 10.4s
Lei Li (China)[6]	p.Cys639Gly	M	L-LE-DVT(27)	3y	Sus	-	-	45.9%	-	-
	p.His664Pro	F	LE-DVT(43)	2y	Sus	-	-	56.1%	-	-

Reference range:TPS:Ag 65~135%;FPS:Ag 60~150% ;PS: A 60~150% Man:77-143%.<12w:The specific detection time after onset is unknown;sus: Suspend VK antagonist for more than 10 days and new oral anticoagulant for more than 24 hours.Conti:taking medicine at the time of sampling;Norm=normal.L,left;R,right;UE, upper extremity;LE,lower extremity;PE,Pulmonary embolism;CVT,cerebral venous thrombosis;SUVT, superficial vein thrombosis;DVT,deep vein thrombosis ;MI,miocardial infarction.PVT, portal venous thrombosis which could involving the superior-mesenteric vein thrombosis (MVT) and/or the splenic vein thrombosis (SVT) or not.Hypercoagulable:Blood routine showed that the patient's hemoglobin was 15.9g/dL, platelet count was 280*109/L, and the hematology coagulation test showed that his prothrombin time (PT) was 12.1 s, activated partial thromboplastin time (APTT) was 37.9 s, fibrinogen was 5.25g/L, factor Xa activity was 115%, and antithrombin III (AT III) activity was 92%.

Table 4 FPS:A in a patient with postoperative mesenteric venous thrombosis

postoperative day	2	131	138	145	175	177
FPS□%□	35	18	11	18	43	23

Figures

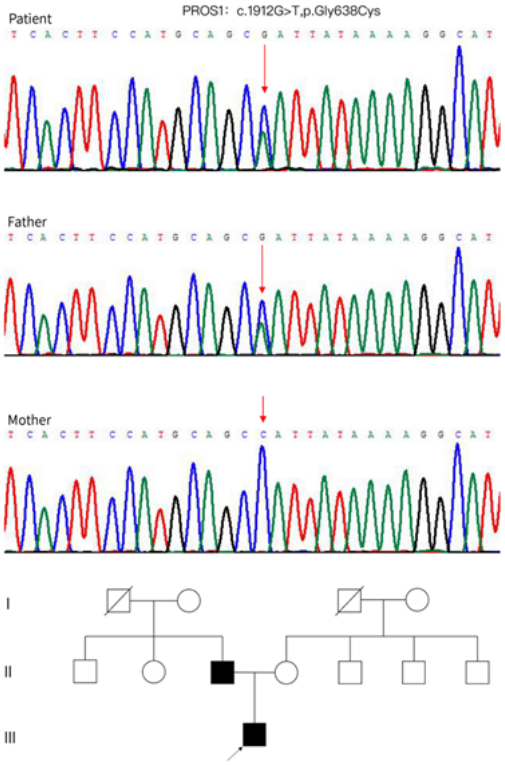

Figure 1

pedigree chart

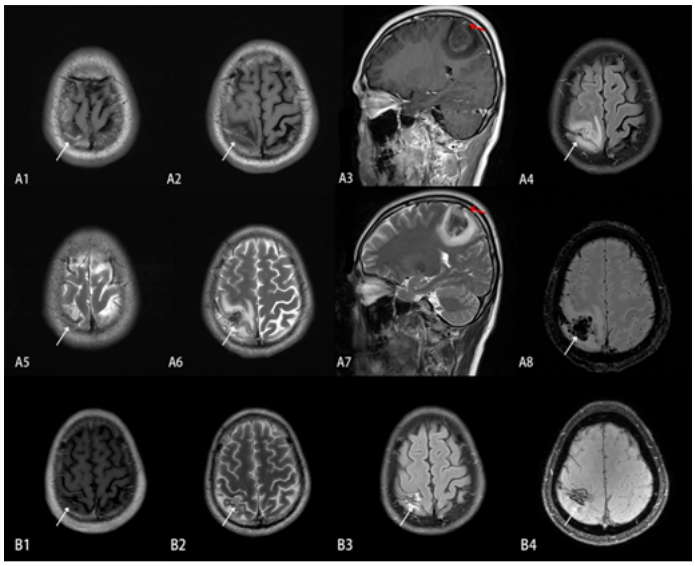

Figure 2

At onset A1: T1 coronal, A2: T1 coronal, A3: T1 sagittal, A4: Flair, A5: T2 coronal, A6: T2 coronal, A7: T2 sagittal, A8: SWI. Four months after onset, B1: T1 coronal, B2: T2 coronal, B3: Flair, B4: SWI.(spinal cord sign：Long white arrow, Dot sign:Short red arrow.)