

50. Protein S deficiency

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Q1: "What is protein S deficiency? Does everyone who has factor V Leiden have protein S deficiency?"

A1: Protein S deficiency is a rare clotting disorder. It has nothing to do with factor V Leiden other than that both can cause clots. Quite a few people who have been given a diagnosis of Protein S deficiency do not really have the disorder - their doctor misinterpreted the test results.

Q2: "I have factor V Leiden and am positive for deficits in proteins C and S. I am 30 years old and have never had any blood clotting problems. I have a healthy 2 year old son and am 5 months pregnant. Never had any problems with the first pregnancy, but had one miscarriage. That is when the doctor did these blood tests and all this came to light. I am currently on heparin injections and doing well. However, one doctor wants me on heparin injections for the rest of my life, while the other thinks that is too invasive and says I should just take a baby aspirin a day unless I have blood clots."

A2: To have protein C and S deficiency at the same time is extremely rare. Whenever I hear that a patient has been found to have such a combined "deficiency", I first suspect that (a) the patient was tested when he/she was on warfarin (warfarin makes protein C and S levels go down), or (b) the test is not valid because the blood draw was bad or a poor quality lab performed the test. If blood is tested at a time when the woman is taking birth control pills, is pregnant or postpartal, or is on hormone replacement therapy, protein S levels are often low; protein S deficiency should not be diagnosed in those situations, because protein S levels in most individuals return to normal once pregnancy is over or the pill and hormones have been stopped. So my first advice to the patient above is: question the diagnoses. Then, once one really knows what one is dealing with, one would need to assess the patient's other thrombophilia risk factors (overweight, smoking, previous surgeries, family history, etc) and come to a conclusion whether there is any indication for long-term blood thinners. That is only rarely done, if the patient has never had a blood clot.

Q3: "My hemo doc says that protein S deficiency has NOTHING to do with arterial clots.... But I have found several articles in professional journals at the university that say protein S deficiency DOES have to do with arterial clotting.... Anyone knows anything for sure?"

A3: Protein S deficiency mainly predisposes to clots in veins. A few cases of clots in arteries have also been reported, but whether these were coincidental or causatively related is not clear; a true association with arterial clots has not yet been clearly demonstrated.

Q4: "My husband has protein S deficiency and had a deep vein thrombosis at the age of 28. He's been on coumadin® for more than 10 years now and has done fine. Several of his brothers also have protein S deficiency and have had clots in their legs. However, his sister and his father, who is in his 70's, also have protein S deficiency, but have never had a clot. My 17-year-old son, who is healthy, has been found to have protein S deficiency as well. Should he be on coumadin?"

A4: Hardly ever does one put anybody who has never had a clot on coumadin, since long-term use of coumadin is associated with a substantial risk of bleeding. The family described above has only a moderate degree of clotting tendency - several family members have not clotted, in spite of the presence of protein S deficiency and advanced age. I would want to know whether the individuals who have had clots have tested positive for any other clotting disorders, such as factor V Leiden or the prothrombin 20210 mutation.

Biology and Lab Testing

Protein S is a protein in our blood that prevents us from clotting too much. It is a "police protein" that prevents criminal clotting activities. It is also called a "natural blood thinner" ("natural anticoagulant"). When blood clots (figure Ia), multiple clotting proteins act together to form the blood clot. One of these clotting proteins is factor V. To prevent us from clotting too much, protein S and protein C hook up to one another and then bind to factor V (figure Ib). The protein C/protein S complex then splits factor V into two pieces (figure Ic), thereby inactivating factor V. Blood then can not clot as easily. If a person is deficient in protein S or protein C, this police mechanism obviously does not work and the patient clots too easily. If a patient has a defective factor V at the site where the protein C/protein S complex

wants to split factor V, factor V can also not be inactivated; this factor V defect is called factor V Leiden.

Protein S was discovered in 1977; "S" stands for Seattle, where the discovery was made. When trying to understand the tests that doctors order when evaluating for protein S deficiency, one needs to know that protein S circulates in our blood in 2 forms (see figure II):

1. in a free, unbound form (active), and
2. bound to a transport protein (inactive).

It is the free form that is active and prevents us from clotting too much. The bound protein S can not be active, since it is blocked by the transport protein. There are 3 different protein S tests doctors can order that measure how much protein S we have:

1. protein S activity (= functional)
2. free protein S antigen (= free antigen)
3. total protein S (= total antigen)

How does protein S work? (fig. 1)

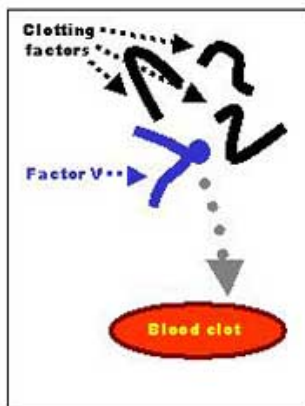


Figure 1a

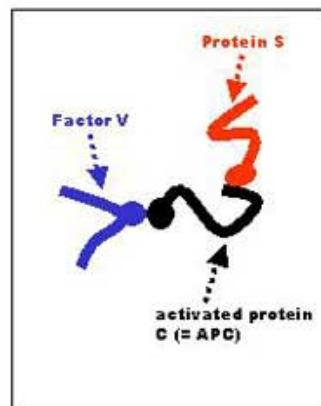


Figure 1b

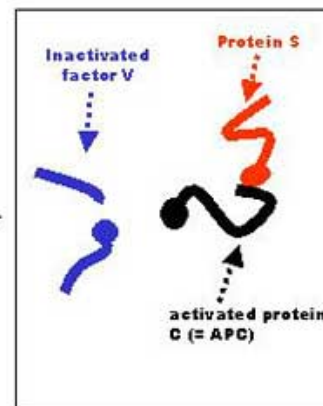
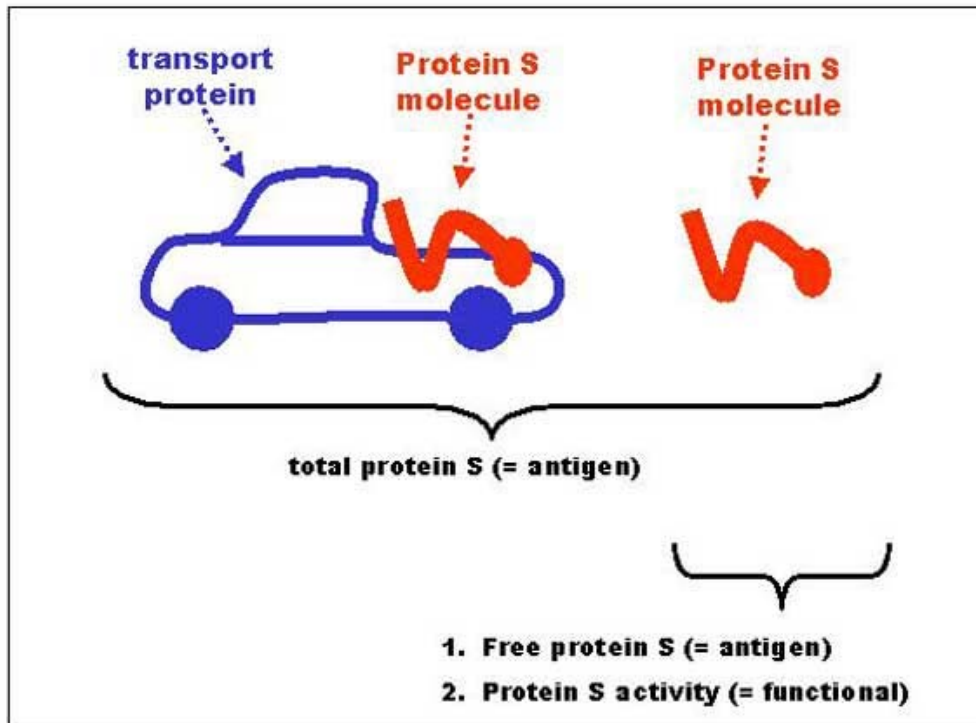


Figure 1c

Testing (fig. 2)



Patients with protein S deficiency always have low protein S activity. The antigen test measures how much of the protein is present, no matter whether the protein works (= is functional) or not. The activity measures, how much protein works correctly. The patient who has a normal amount of protein S (i.e. normal antigen), but a protein that does not work right (i.e. low activity), has protein S deficiency (= dysfunctional protein S). Thus, antigen levels are usually not helpful. If a patient's lab report only states "protein S normal", without indicating whether it was activity or antigen that was tested, the patient's doctor should clarify which of the two was performed. While optimally protein S activity test should always be performed, the protein S activity test is notoriously difficult to perform and not infrequently gives unreliable results. Many labs therefore do not perform protein S activity testing, but only antigen testing. In my practice I always repeat protein S tests, when values were found to be low at labs other than our university lab. I also obtain free and total protein S antigen levels. I do not base a diagnosis of protein S deficiency on values that were low once - I always repeat the tests after a few weeks.

Protein S deficiency

The observation that protein S deficiency causes thrombosis was first made in 1984. Protein S deficiency is an uncommon clotting disorder: approximately 1 per 500 to 1 per 3,000 people has inherited protein S deficiency. Since we all have 2 genes for every protein (one from mother and one from father), people can have 2 normal genes (healthy), one mutated protein S gene (heterozygous), or two mutated genes (homozygous). Individuals with protein S deficiency are typically heterozygous. Homozygous individuals have such a severe clotting problem, that they typically die immediately after birth because of clotting everywhere; this is termed "Purpura fulminans". Protein S deficiency can be caused by more than 100 different mutations in the protein S gene. This makes genetic testing for the defect very difficult, time-consuming, and expensive; it is therefore not done in routine clinical practice. Few academic institutions with a special interest in protein S deficiency perform genetic testing for research purposes.

Protein S levels are often low in the following situations ("acquired protein S deficiency"):

- in patients on warfarin (=coumadin),
- in patients on birth control pill,,
- in pregnant woman and in the first few weeks after delivery,

- in patients on hormone replacement;
- at the time of an acute blood clot.

A low level under these conditions does not mean that the patient has inherited protein S deficiency. A level needs to be re-checked once these underlying conditions have resolved. Many patient that I see in my practice who carry the diagnosis of "protein S deficiency" do not really have protein S deficiency - review of records often shows that they were on coumadin at the time of testing, were pregnant, or had been taking birth control pills. I question the diagnosis of "protein S deficiency" every time I come across it. I would advise patients who have been given a diagnosis of ""protein S deficiency" to also question the diagnosis; they should be seen by a thrombosis specialist in a thrombophilia center.

When protein S deficiency was first described in the 1980's it appeared that it was a strong risk factor for blood clots. Since then we have learned that some of those initial families had additional risk factors that made them clot, such as factor V Leiden or the prothrombin 20210 mutation. Protein S deficiency by itself may not be a very strong risk factor for clots. There has even been a publication that showed that protein S deficiency by itself is not a risk factor for blood clots [Koster T et al. Blood 1995;85:2756]. Clearly, the risk of clotting varies from family to family and from individual to individual, and we often do not understand why some families and individuals with protein S deficiency clot and others not. It is worthwhile to look for other clotting abnormalities in these families (see [Q/A 49](#)), such as factor V Leiden or the prothrombin 20210 mutation: it may be that individuals with 2 or more abnormalities clot, but the ones with only protein S deficiency do not.

No generalized recommendations on how patients with protein S deficiency should be treated are possible. Treatment recommendations for patients who have had a blood clot (DVT or PE) would be similar to the recommendations given to patients without protein S deficiency (see [Q/A 9](#) and [Q/A 10](#)). I would strongly advise against contraceptives or hormone replacement in the women with protein S deficiency. In the women who has protein S deficiency but who has never clotted, I would probably recommend postpartum warfarin or low molecular weight heparin for 6 weeks; if she has a strong family history of clots I may also recommend prophylactic low-dose heparin during pregnancy; if she does not have a positive family history of clots I may not recommend heparin during pregnancy.