TEST

Cytochrome b5 reductase

A blood test that measures an enzyme helping red blood cells keep haemoglobin able to carry oxygen.

WHAT IT MEASURES
Red-cell cytochrome b5 reductase enzyme activity

SAMPLE
Whole blood from a vein

FASTING NEEDED?
No

HOW LONG IT TAKES
Less than 10 minutes for the blood draw

RESULTS IN
Several days; timing differs among laboratories

USED FOR
Diagnosis of inherited cytochrome b5 reductase deficiency

MAIN LIMITATION
Transfusion or young red cells can mask low activity

Overview

Cytochrome b5 reductase is an enzyme found in red blood cells and other tissues. In red blood cells, it helps keep haemoglobin in a form that can carry oxygen.

Haemoglobin is the protein that transports oxygen in your blood. A small amount naturally changes into methemoglobin, which cannot carry oxygen effectively. Cytochrome b5 reductase helps change it back into working haemoglobin.

This test measures the enzyme's activity in your red blood cells. It is mainly used when an inherited enzyme deficiency is suspected. That deficiency can cause persistent methemoglobinemia, meaning that more haemoglobin than usual is in the methemoglobin form.

The enzyme test is different from a methemoglobin level. A methemoglobin level, usually measured by co-oximetry, shows how much methemoglobin is present now. The cytochrome b5 reductase test looks for one possible reason it is elevated.

Why the test is ordered

The test may be ordered after another blood test finds an unexplained, persistent increase in methemoglobin. It can help distinguish an inherited enzyme deficiency from acquired methemoglobinemia caused by a medicine, chemical or illness.

Reasons for ordering it may include:

This is not usually the first test used during sudden symptoms. Co-oximetry can measure the current methemoglobin level more quickly and is more useful for immediate treatment decisions.

- Bluish or grey skin or lips that cannot be explained by heart or lung findings
- Repeated high methemoglobin measurements
- Methemoglobinemia beginning in infancy or childhood
- A relative with a confirmed cytochrome b5 reductase deficiency
- A need to clarify whether methemoglobinemia is inherited or acquired

Who should have the test

This test is not used for routine population screening. It is generally reserved for people whose history and earlier test results suggest an inherited problem affecting methemoglobin.

It may be considered for a baby, child or adult with persistent methemoglobinemia, especially when there is no clear medicine or chemical exposure. Relatives may also be tested after a specific inherited deficiency has been identified in a family.

A raised methemoglobin level does not automatically mean this enzyme is deficient. Medicines, local anaesthetics, nitrates and other oxidising substances can increase methemoglobin even when cytochrome b5 reductase activity is normal.

How to prepare

You do not usually need to fast. You can normally eat, drink and take your regular medicines before the blood draw.

Tell the healthcare professional arranging the test about:

Do not stop a prescribed medicine simply to prepare for this test. Medicine information is useful because some drugs raise methemoglobin without causing an enzyme deficiency.

The laboratory may have special instructions about when and where the sample must be collected. Enzyme activity can be affected by transport and storage, so some collection centres cannot send this test routinely.

- Any blood transfusion in recent months
- Recent major bleeding or destruction of red blood cells
- Medicines and supplements
- Exposure to chemicals that may affect haemoglobin
- A known blood disorder or haemoglobin variant

What happens during the test

A healthcare professional cleans an area of skin, usually inside your elbow, and inserts a small needle into a vein. Blood is collected into a tube containing an anticoagulant like warfarin or apixaban , which prevents clotting.

The blood draw usually takes less than 10 minutes. You may feel a brief scratch or sting. The sample is then sent to a specialist laboratory, where enzyme activity in the red blood cells is measured.

This is different from genetic testing. Genetic testing looks for changes in the CYB5R3 gene, while the enzyme test measures how well the enzyme is working.

Understanding your results

Your report will compare your enzyme activity with the reference interval used by that laboratory. Reference ranges and interpretation vary by laboratory, age, sex, pregnancy status, medicines and clinical context.

A clearly low result can support a diagnosis of cytochrome b5 reductase deficiency, particularly when methemoglobin is persistently elevated. The result still needs to be considered alongside symptoms, family history, transfusion history and other blood tests.

A result within the laboratory's range makes a major red-cell enzyme deficiency less likely. It does not rule out other causes of methemoglobinemia, such as medicine or chemical exposure, haemoglobin M variants, or another uncommon red-cell condition.

Higher activity is not usually interpreted as an enzyme disorder. It can occur when the blood contains many young red cells, which often have more enzyme activity than older cells.

The enzyme result alone usually cannot establish whether a confirmed inherited deficiency is limited to red blood cells or affects other tissues. Clinical assessment and CYB5R3 genetic testing may be needed to clarify the type.

What affects the results

A recent blood transfusion is one of the most important influences. Normal donor red cells can raise the measured activity and temporarily hide a deficiency in your own cells. The effect can persist while those donor cells remain in circulation.

Altered red-cell turnover can also be misleading. After bleeding or haemolysis, which is premature red-cell destruction, the body releases more young red cells called reticulocytes. Their higher enzyme activity may produce a reassuring result despite an underlying deficiency.

Other relevant influences include:

Meals, coffee and ordinary exercise do not usually have a meaningful direct effect on this enzyme test. Kidney function, pregnancy and sex are not generally major causes of an incorrect result, but they may affect the wider clinical interpretation or other blood findings.

- Age: Newborn enzyme activity may differ from adult activity, so age-appropriate interpretation matters
- Sample handling: Delayed transport, incorrect temperature or a clotted sample can affect testing or require another sample
- Medicines and chemicals: Dapsone, benzocaine, nitrates and other oxidising substances may increase methemoglobin while enzyme activity remains normal
- Blood disorders: Conditions that change the mixture of young and old red cells can alter measured activity

Accuracy and limitations

A markedly reduced activity result, obtained from a properly handled sample without recent transfusion, is useful evidence of enzyme deficiency. However, laboratories use different methods and reporting units, so results should not be compared directly across laboratories.

The test can miss a deficiency when normal donor cells or unusually large numbers of young red cells raise the measured activity. Borderline results may also be difficult to classify, particularly in someone carrying one altered gene copy.

The test may appear low when the sample has deteriorated during transport or storage.

Repeating the test with carefully handled blood can help distinguish a true low result from a sample problem.

No single enzyme result explains every case of methemoglobinemia. Co-oximetry is the better test for measuring the current methemoglobin level. Genetic testing may be better for confirming the underlying CYB5R3 change, clarifying an uncertain enzyme result or testing relatives.

Neither test is perfect. Genetic testing may not find every disease-causing change, and it can occasionally identify a change whose meaning is uncertain.

Risks and complications

The risks are those of an ordinary blood draw. You may have brief discomfort, a small bruise or light-headedness; serious complications are uncommon.

What happens next

A low result is usually reviewed with your methemoglobin level, blood count, transfusion history and family history. The test may be repeated if the result is borderline or the sample may have been affected by handling, transfusion or increased red-cell production.

Genetic testing may be offered to confirm an inherited cause. If enzyme activity is normal, further assessment may focus on medicines, chemical exposures, haemoglobin variants or other explanations for an elevated methemoglobin level.

These are usually routine follow-up steps. Seek emergency care for sudden blue or grey skin accompanied by trouble breathing, chest pain, severe weakness, confusion, fainting or a seizure. Do not wait for an enzyme test result if serious symptoms are present.

Common questions

Can I drink coffee before the test?

Yes. Coffee does not usually affect cytochrome b5 reductase activity, and fasting is not normally required.

Does the time of day matter?

Usually not. Collection timing is more likely to be set by the laboratory's transport and storage requirements than by changes in your body during the day.

Can I exercise beforehand?

Ordinary activity is unlikely to change the result. Tell the healthcare professional about unusually strenuous exercise if it was associated with illness, bleeding or suspected red-cell breakdown.

Should I stop my medicines?

No, not unless the clinician who prescribed them tells you to. Bring an accurate medicine list because some medicines can raise methemoglobin even when enzyme activity is normal.

How long after a transfusion should I wait?

There is no single waiting period suitable for everyone. Donor red cells can remain in the circulation for weeks to months, so the testing laboratory should be told the date and type of transfusion.

Is this the same as a genetic test?

No. This test measures enzyme activity in red cells. A genetic test looks for changes in the CYB5R3 gene and may be used to confirm or clarify the result.

Sources

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