Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Roth spots in pyridoxine dependent epilepsy

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Summary

Pyridoxine dependent epilepsy (PDE) is a rare metabolic defect in the degradation of lysine. The authors report a patient with metabolic and DNA confirmed PDE, on the fifth day of life ophthalmoscopy showed bilateral multiple white centred retinal haemorrhages, so called Roth spots. Roth spots are non-specific haemorrhagic signs that occur in a variety of conditions of acute systemic insults in homeostasis – most often infections- which relate to retinal capillary damage and the ensuing reparative process. No biochemical or microbiological signs of infection were present in blood and liquor. MRI of the brain showed an abnormal diffusion signal with increased apparent diffusion coefficient and little blood around the tentorium.

The knowledge of the pathogenesis of PDE is still limited. The presence of Roth spots is suggestive for a pathogenic mechanism of vasogenic damage in PDE.

BACKGROUND

In this paper we report for the first time a patient with metabolic confirmed pyridoxine dependent epilepsy (PDE) and Roth spots. PDE is a rare metabolic¹ defect in the degradation of lysine. This metabolic defect leads to the accumulation of α -amino adipic semialdehyde (α -AASA) and indirectly to an inactivation of pyridoxal-5-phosphate, the active metabolite of pyridoxine (vitamin B6). The most striking symptoms of PDE are seizures which do not respond to conventional antiepileptic drugs but respond to pyridoxine. Knowledge of the clinical spectrum and associated abnormalities of PDE is rapidly expanding since the detection of the underlying metabolic defect and its genetic basis.²⁻⁴ Although squint is seen in 30%⁵⁻⁷ and optic nerve hypoplasia is reported in two patients,⁷ other true ophthalmologic abnormalities are rarely reported. Roth spots are suggestive for vasogenic damage, and they might be a clue for a pathologic pathway in PDE. Therefore we believe our data could be of important additional value.

CASE PRESENTATION

A male newborn, born after an uneventful pregnancy and delivery, was admitted with generalised seizures 12 h after birth. The convulsions were unresponsive to anticonvulsants but subsided with 100 mg pyridoxine intravenously. As can be expected in PDE, the first dose of pyridoxine led to severe respiratory depression, necessitating mechanical ventilation during a short period. The boy was clinically diagnosed with PDE on the second day of life. This diagnosis was confirmed by demonstration of highly elevated α -AASA levels in the urine (37 mmol/mol creat; N < 2 mmol/mol creat) and a homozygous 1195 G>C antequitin

mutation (figure 1). Ophthalmoscopy on the fifth day of life showed multiple white centred retinal haemorrhages, so called Roth spots, in both retinas. On follow-up these Roth spots gradually disappeared within a few months. No biochemical or microbiological signs of infection were present in blood and liquor, bacterial cultures and viral antigens (toxoplasmosis, rubella, cytomegalovirus, herpes and HIV) remained negative. Brain MRI showed some blood on the tentorium and on the falx cerebri and an abnormal diffuse signal with increased apparent diffusion coefficient.

DISCUSSION

The observed Roth spots are rare ophthalmologic abnormalities, different from more common neonatal intraretinal haemorrhages which are flame shaped and/or dot blot haemorrhages often related to the delivery.⁸ These common postnatal retinal haemorrhages resolve usually within days.⁹ Retinal haemorrhages occasionally described in metabolic diseases,¹⁰⁻¹⁷ are not reported as Roth spots.

Roth spots are non-specific haemorrhagic signs that occur following a variety of conditions. These conditions have in common an acute disturbance of the homeostasis contributing to retinal capillary damage and the ensuing reparative process.^{18 19} Usually and most often, Roth spots are seen in patients with subacute bacterial endocarditis. They may also occur in several other conditions such as other infectious diseases and perinatal hypoxic encephalopathy. These were excluded in this patient.^{18 20}

Whether the observed Roth spots are coincidentally found in this patient with PDE, or are directly related to PDE is not clear. We can only speculate whether there is an association of Roth spots with PDE. Roth spots or

Figure 1 Fundusphoto of the nasal side of the right eye, in the peripheral retina is multiple Roth spots (white centered retinal dot haemorrhages).

retinal haemorrhages have never been reported in patients with PDE (with pyridoxal 5'-phosphate inactivation and α -AASA accumulation) or in other patients with pyridoxine responsiveness, example hyperprolinemia type II or hypofosfataemia. A direct relation of the Roth spots with the seizures or the antiepileptic drugs, including pyridoxine, also remains speculative.

Learning points

- Ophthalmoscopy should be done in PDE patients.

Competing interests None.

Patient consent Obtained.

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