# Hereditary defect of cobalamin metabolism with adolescence onset resembling multiple sclerosis: 41-year follow up in two cases

**Jeremias Motte** (iD), **Janina Kneiphof, Katrin Straßburger-Krogias, Kalliopi Pitarokoili, Anna Lena Fisse** (iD), **Ludwig Kappos and Ralf Gold**

**Abstract:** The cblC defect is the most common inborn error of cobalamin (Cbl) metabolism. Clinical severity and presentation of the cblC defect ranges from death to mild disability. Only 71 cases of late-onset cblC defect have been described in the literature. We provide the 41-year follow up of two siblings with a late-onset cblC defect, first described after initial diagnosis in 1996. While one of the siblings showed initial symptoms resembling multiple sclerosis with a good response to corticosteroids, the other sister showed only subclinical signs of the disease. The course of the first case was characterized by a severe deterioration and intensive-care therapy after respiratory failure. After diagnoses and Cbl treatment, the patient survived and showed a pronounced improvement of the symptoms. Both sisters have an active life and gave birth to healthy children. The reason for the initial improvement after corticosteroids could not be explained by the classical metabolic pathways of Cbl. Recent studies have suggested that Cbl plays an important role as a regulator of the balance between neurotrophic and neurotoxic factors in the central and peripheral nervous system (CNS and PNS). This first long-term follow up revealed that ultra-high-dose intramuscular Hydroxocobalamin (OH-Cbl) treatment can effectively protect patients from disease progression. It underlines the importance of diagnostic vigilance and laboratory work up even in cases without typical hematologic signs of Cbl deficiency. Cbl-related diseases are often a chameleon and must always be considered in the differential of demyelinating diseases of the PNS and CNS. The case supports the theory that it is not only the classical biochemical pathways that play a key role in Cbl deficiency, especially with regard to neurological symptoms.

## Introduction

Vitamin B12 or cobalamin (Cbl) is an essential cofactor in humans. It is necessary for the integral function of two coenzymes, methylmalonyl coenzyme A mutase (MMC) and methionine synthase (MTR). Cbl exists in different conjugations of the molecule, where one of six binding sites of the cobalt ion differs. The two important forms of Cbl are adenosylcobalamin (AdoCbl) (essential for MMC in the mitochondria) and methylcobalamin (MeCbl) (essential for MTR in the cytoplasm), which serve as coenzymes.

Cbl deficiency in adults causes reversible megaloblastic anemia and often irreversible demyelinating neurologic disease, or both. Interestingly, the severity of megaloblastic anemia is inversely correlated with the degree of neurologic dysfunction, while the underlying pathomechanism of neurological manifestations remains unclear.[1]

In recent years, novel biochemical actions of Cbl were described in which cellular functions completely unrelated to the established metabolic biochemical actions of Cbl were shown.[2–4] It was

Correspondence to:
**Jeremias Motte**
Department of Neurology, Ruhr-University Bochum, St Josef- Hospital, Gudrunstrasse 56, Bochum 44791, Germany
**Jeremias.Motte@rub.de**

**Janina Kneiphof**
**Katrin Straßburger-Krogias**
**Kalliopi Pitarokoili**
**Anna Lena Fisse**
**Ralf Gold**
Department of Neurology, Ruhr-University Bochum, Bochum, Germany

**Ludwig Kappos**
Neurologic Clinic and Policlinic, University Hospital Basel, Basel, Switzerland

shown that Cbl plays an important immunoregulatory role and influences the production of cytokines and inflammatory factors (i.e. interleukine (IL)-6 and tumor necrosis factor alpha TNF-alpha) in the CNS and the PNS.[4,5] These new findings might help in understanding the often early, and maybe metabolically independent neurological manifestation of Cbl deficiency.

Cbl is synthesized by microorganisms and only food derived from animals contains enough Cbl for a sufficient supply. Cbl deficiency is caused mostly by inadequate intake or malabsorption. The nomenclature for hereditary disorders of intracellular Cbl metabolism defines Cbl groups A–J (cblA–cblJ) based on cellular complementation analysis. In infants, the cblC defect is the most common inborn error of Cbl metabolism and has been described in over 300 cases.[6–8] The methylmalonic aciduria and homocystinuria type C protein (MMACHC) was identified as the cause of cblC disease in 2005.[6] The clinical severity and presentation of the cblC defect ranges from death at an early age to late presenting disabilities.[9] In particular, infants with an early onset of symptoms often show a poor outcome with a mortality of more than 25%, whereas patients with a later onset (over 12 months of age) often survive with a better prognosis.[10,11] To date, there are only 71 reports of late-onset cblC defect (over 12 months) in the literature. A very late onset of the CblC defect in adolescence (10 years or over) has been described in only 42 cases,.[9–14] Late-onset cblC deficiency in siblings has been reported in 16 pairs.[14] Cognitive impairment, neuropathy, myelopathy, ataxia, dementia, delirium, or psychosis characterized the neurological findings of patients with late-onset cblC defect.[10,11]

In this report, we describe a 41-year, long-term follow up of two siblings with a very late-onset cblC defect. The first description of these cases was after initial diagnosis in 1996 in this journal.[15] The patients gave spoken and written consent prior to participation in the study. They provided written informed consent for publishing these case reports in an international medical journal.

## Case 1

In 1976, a female patient was admitted at the age of 12 years to the neurological department because of transient gait disorder, fatigue, and mild incontinence. Until then the developmental stages of childhood including cognitive and physiological development were normal. There was no family history of neurodegenerative disorders or consanguinity. The results of all the hematological laboratory tests (hemoglobin 141 g/L; mean corpuscular volume (MCV) 79 fl, normal 77–91 fl), as well as cell count and immunoglobulin levels in the cerebrospinal fluid (CSF), were normal. Cbl plasma level (680 ng/L, normal 160–970 ng/L) and Schilling test (24.1% absorption of Cbl, control 11–28%) were also normal. The diagnosis of juvenile-onset demyelinating disorder was suspected and supported by complete remission of symptoms following oral corticosteroid therapy.

Two years later in 1978, she was hospitalized again because of an acute onset of spastic-ataxic gait with hyperactive tendon reflexes of the lower limbs and a bilaterally positive Babinski sign. Vibration and position sense of the legs were also impaired. Again, the symptoms were reversed under treatment with oral prednisolone and multiple sclerosis (MS) was considered. Treatment with azathioprine was started.

Another 5 years later, the patient was stable under azathioprine treatment and had completed professional training with good results. The follow-up examinations revealed normal laboratory and electrophysiological conditions (hemoglobin 142 g/L, MCV slightly elevated at 97 fl). Again, CSF and visual-evoked potentials (VEPs) were normal (in CSF cell count, protein, blood–CSF barrier, and intrathecal IgG synthesis). As a result of stable conditions the patient decided to discontinue azathioprine treatment.

Four months later at the age of 19 years (in 1983), a new relapse occurred, this time with unequivocal signs of PNS involvement (i.e. bilateral flaccid weakness of the foot extensors and flexors, absent Achilles reflex, attenuated patellar reflex). Electrophysiology was compatible with axonopathy of the lower limbs. Ophthalmologic examinations did not reveal abnormalities of the retina or optic disc. Therapy with prednisolone and azathioprine was started again and complemented by an intrathecal injection of triamcinolone. This therapy resulted in a partial improvement of symptoms. Finally, she was able to walk about 3000 m.

Between 1986 and 1988, four relapses occurred with progressive residual deficits in accordance

with predominant peripheral nerve impairment; however, neuropsychiatric abnormalities were notable as well. Electrophysiological examinations confirmed progressive axonal nerve damage and a sural nerve biopsy revealed a predominantly axonal neuropathy. Cranial magnetic resonance imaging (MRI) examinations and CSF analyses remained normal. Walking distance was reduced to only 500 m due to paraparesis. Azathioprine was continued, and relapses were treated with systemic corticosteroids supplemented by intrathecal steroids.

In November 1988, the patient suffered a deep vein thrombosis (DVT) and further treatment with steroids was restricted. This led to a progressive deterioration over the following months. Finally, she was unable to walk unassisted for more than 20 m. Under the assumption of an immunological cause for the symptoms, with a relapsing-progressive, but to date steroid-responsive disease course, treatment with six cycles of plasmapheresis combined with steroids was performed. This attempt was unsuccessful, and she lost the ability to walk and to control the bladder in March 1989. Moreover, she developed a weakness and hyperreflexia of the upper limbs. Again, treatment with plasmapheresis and corticosteroids was started but progression was inexorable. Hemoglobin declined from 99 g/L to 86 g/L, further investigations revealed mucosal erosions in gastroscopy, and blood smear showed hypersegmented neutrophils and no macrocytosis of the red blood cells. Serum iron was low (5.4 μmol/L, normal 10.7–30.4 μmol/L), and a bone marrow biopsy showed a depletion of iron stores. Transferrin was measured only 4 weeks after starting iron substitution (19,890 mmol/L, normal 20,332–38,012 mmol/L). This was interpreted as iron deficiency anemia.

In mid-1989, she required intensive care including mechanical ventilation because of tetraparesis and respiratory failure followed by severe disturbance of electrolytes and metabolic alkalosis (pH 7.51, bicarbonate 34.0 mmol/L, base excess 10.9 mmol/L; hypokalemia 2.0 mmol/L, normal 3.5–5.0 mmol/L; hypophosphatemia 0.55 mmol/L, normal 0.8–1.5 mmol/L). A new extensive diagnostic work up including serum Cbl, transcobalamin, and serum folic acid was normal (serum Cbl 260 ng/L, normal 160–970 ng/L). Serum folic acid in was elevated (28.0 μg/L, normal 1.5–16.9 μg/L). Eventually, organic acid analysis revealed an increase of methylmalonic acid (MMA) in the urine (2900 mmol/mol creatinine, normal < 2 mmol/mol creatinine), elevated homocysteine in the plasma (174 μmol/L, normal < 15 μmol/L), and a low level of methionine (7 μmol/L, normal 13–28 μmol/L). These results indicated a disorder of Cbl metabolism and high-dose treatment with intravenous OH-Cbl combined with L-carnitine was started. Weaning from the respirator was possible after 13 days, and transfer to a normal ward 4 weeks later. After 9 months the patient was able to sit. The initial OH-Cbl treatment of 500 μg/day intravenously resulted in a distinct decrease in MMA excretion. Supplementation with oral cyanocobalamin (CNCbl) 300 μg/day or OH-Cbl 10 mg/day orally was insufficient and resulted in an increase in MMA excretion. Finally, weekly treatment with 10 mg OH-Cbl intramuscular (i.m.) lead to stable metabolic control. Metabolic studies with fibroblastic cell lines from the patient revealed that formation of both AdoCbl and MeCbl was deficient. Complementation studies with a fusion of the patient's fibroblast and well-known cell lines indicated that the patient suffered from a cblC defect.[15] An explanation for the long-standing successful therapy with corticosteroids could not be found in *in vitro* experiments. Hydrocortisone supplementation did not improve coenzyme synthesis *in vitro*.

Five years later in 1994, the weakness of the arms was completely absent, she was able to walk 20 m with assistance, but she was not able to control her bladder function. Weekly treatment with OH-Cbl i.m. was continued.

Another 23 years later in 2017, the 53-year-old patient presented for a follow up in our department. She reported a stable course of disease and no further relapses since the introduction of OH-Cbl treatment. Weekly treatment with OH-Cbl i.m. has been continued since 1989. Her husband supports her in everyday life and she is active in social volunteering. The control of bladder and sphincter function did not return.

The patient had six pregnancies and gave birth to three healthy children. In the most recent neurological examination she demonstrated with a spastic paraparesis. Babinski sign was negative on both legs. Vibration, temperature, and position sense of the legs were markedly impaired. Walking distance was 5 m with assistance. The upper limbs were not affected. An MRI examination of the
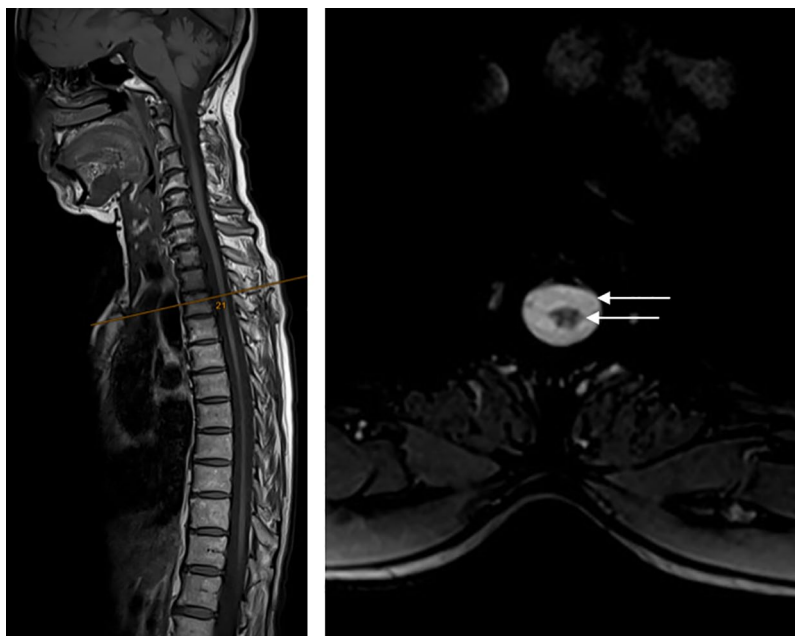
**Figure 1.** Left: sagittal plane of the entire spinal cord shows ubiquitous myelon atrophy; right: transverse plane of the spinal cord at Th3; the upper arrow shows the border of the dura, the lower arrow shows atrophic spinal cord.

cervical and thoracic spinal cord revealed a diffuse atrophy of the whole spinal cord without focal signal alterations (Figure 1). VEPs revealed normal P100 latencies and well-reproducible amplitudes (left 105.0 ms, right 113.0 ms, normal < 121 ms). Spectral domain optical coherence tomography (SD-OCT) was normal. Somatosensory evoked potentials of the tibial nerve were not recordable. Motor-evoked potentials of the musculus peroneus showed loss of central signal transduction to the legs, and peripheral signal transduction was only slightly prolonged in the right leg (central and total motor conduction time not available, peripheral motor conduction time right 18.8 ms, left 15.8 ms). The electrophysiological studies confirmed a remarkable axonal destruction without signs of acute denervation. Neuropsychiatric testing was normal. The laboratory analyses showed no signs of anemia (hemoglobin 134 g/L, normal 120–160 g/L; MCV 86 fl, normal 85–95 fl; mean corpuscular hemoglobin 28.9 pg, normal 27–33 pg). Cbl in the serum was massively elevated under therapy (> 2000 pg/ml; normal 197–866 pg/ml). Homocysteine (47.0 μmol/L, normal < 9.0 μmol/L), MMA in serum (11,386.6 nmol/L, normal 73–271 nmol/L), and MMA in urine (52.8 mg/g creatinine, normal < 3.8 mg/g creatinine) were elevated but stable in comparison with 1994.

## Case 2

Her sister was 4 years older than the patient described in case 1 and was first examined in 1983 at the age of 23 years, when the patient in case 1 suffered new relapses, including the PNS, and a hereditary disease was suspected. At this time, electrophysiological studies and neurological examination of this patient were normal (motor conduction velocity of peroneal nerve 58 m/s, normal > 43 m/s). In 1991, a follow up revealed decreased tibial nerve conduction velocity (41 m/s, normal > 43 m/s) and hypoactive reflexes of the legs. Metabolic screening revealed increased excretion of MMA in the urine (1550 mmol/mol creatinine, normal < 2 mmol/mol creatinine), increased homocysteine (79 μmol/L, normal 13–28 μmol/L), and decreased serum methionine (8 μmol/L, normal 13–28 μmol/L). A single i.m. dose of 2 mg OH-Cbl led to a 60% reduction in MMA excretion. At that time, she refused further investigations or further treatment. Both parents were also investigated with normal clinical, electrophysiological, and metabolic tests.

In 2017, the sister supplements oral CNCbl irregularly. She is married, has three healthy children, and has no subjective clinical complaints. She was

not available for a follow up with clinical and metabolic examination.

## Discussion

Spanning 41 years, this is the longest reported follow up of patients with late-onset cblC defect. The cases of the two sisters were initially described in 1996[15] and introduced a new variant of the clinical phenotype of cblC disorders. At that time, the cblC defect had been described in about 20 patients and a late-onset cblC defect in only two cases.[16,17] In the meantime, a total of 71 cases with late-onset cblC defect (onset > 12 months) have been published. A total of 42 cases, of which 16 pairs were siblings, had a symptom onset of 10 years or more.

Case 1 shows that highly dosed i.m. OH-Cbl treatment can not only effectively protect patients from further disease progression but can also lead to clinically relevant improvement. The lack of complete recovery underlines the necessity for increased vigilance in unclear neurological disorders for congenital Cbl defects even in elderly patients.

Both sisters were able to live an active life and have healthy children. Still, we recommended genetical testing of the children. However, the different disease course between the sisters and the late onset might be a result of an incomplete cblC defect and a residual activity of the affected enzymes. Furthermore, the late and different neurological impairment supports the thesis of further unknown Cbl effects.

The understanding of hereditary Cbl defects as well as other Cbl disorders has improved in recent years. Although the classical biochemical pathways of Cbl as a coenzyme are well known,[1,6,9,18,19] it remains elusive why neurologic changes often occur in the absence of hematologic abnormalities.[1] Prior theories supposed that the neurological symptoms were merely biochemical and based on the accumulation of different molecules because of enzymatic blockades caused by Cbl deficiency.[20]

However, new modes of action were shown and have been discussed in recent years.[2–5] These findings could be approaches to an explanation for the neurological manifestations of a Cbl deficiency.

In our case, the patient improved with immunosuppressive drugs (corticosteroids and azathioprine) over years. However, the metabolism of the patient's fibroblasts *in vitro* did not change after treatment with corticosteroids. A conclusive explanation of the therapeutic effect was not possible at that time[15] providing strong evidence for biochemical independent pathways of damage in Cbl deficiency.

A possible explanation of the initial response to steroids in our patient may be derived from findings of animal and human experiments. In rats and in humans, it was shown that Cbl plays an important role as a regulator of the balance between the production of neurotrophic factors (i.e. Epidermal-Growth-Factor (EGF) and IL-6) and neurotoxic factors (i.e. TNF-alpha) in the CNS.[4,5]

These studies could also show that Cbl deficiency induces an excess of normal cellular prion *via* excessive TNF-alpha in the rat spinal cord and PNS (both affected in our patient), as well as in human serum and CSF. In animal studies, this prion excess leads to myelin damage in the PNS and spinal cord with electrophysiological abnormalities an experimental neuropathy.[4] The beneficial effect of corticosteroids in our patient could be a result of corticosteroids inhibiting TNF-alpha, which is a well-known corticosteroid effect.[21–23]

Other ways that Cbl deficiency can influence the immune system are described in the literature: Cbl may serve as a donor for DNA methylation, Cbl may be bound by RNA receptors, and Cbl seems to have an impact on the HIV.[2,3] These functions of Cbl are not linked to the coenzyme functions of the vitamin and could also explain the initial corticosteroid response in our case. However, it is still unknown whether Cbl affects genetic or epigenetic mechanisms and how the exact mechanism works.

Recent SD-OCT studies in children with cblC defect showed extreme macular thinning with nearly complete loss of the outer nuclear layer and severe alterations in the outer and inner retinal layers.[24,25] Our patient did not show any ophthalmologic abnormalities neither in 1983 nor in 2017. VEPs were always normal and SD-OCT examination in 2017 was also normal. This highlights the difference between the infantile and later onset Cbl defects and may be a hint for a residual activity of Cbl processing in our patient.

Last, we want to point out the DVT in our patient. She received corticosteroids, which are a known risk factor for thrombotic events. With Cbl

deficiency and resulting hyperhomocysteinemia comprising additional risk factors for DVT,[26] increased vigilance for DVT is necessary in the case of elevated homocysteine levels.

### *Strengths and limitations of this study*

This was the longest follow up of patients with a late-onset cblC defect. These cases have helped to identify patients with a potentially fatal disease that mimics common neurological disorders like MS. The findings showed that ultra-high-dose i.m. Cbl treatment can effectively protect patients from further disease progression and lead to a clinically relevant improvement. The study also helped to understand the pathomechanism of Cbl disorders in general. However, due to the rarity of Cbl defects, there are no available systematic studies. For the same reason, this study is limited in its evidence.

### Conclusion

This first long-term follow up spanning more than 40 years revealed that high-dose i.m. OH-Cbl treatment can effectively protect patients from disease progression. The sustained clinically relevant but only partial benefits observed in one case and the mitigation of disease progression in the other sibling underlined the importance of diagnostic vigilance and thorough laboratory work up even in cases without typical hematologic signs of Cbl deficiency. Cbl-related diseases are often a chameleon and must always be considered in the differential of both central and peripheral demyelinating diseases of the nervous system. This long-term follow up also demonstrated the therapeutic value of long-term continuous Cbl supplementation. The cases supported the theory that not only the classical biochemical pathways play a key role in Cbl deficiency, especially in regard to neurological symptoms.

### Acknowledgments

### Funding

### Conflict of interest statement

### Ethical statement

All procedures performed in studies involving humans participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendment or comparable ethical standards.

### ORCID iDs

Jeremias Motte https://orcid.org/0000-0002-6624-8565

Anna Lena Fisse https://orcid.org/0000-0003-0493-8656

## References

1. Stabler SP. Vitamin B12 deficiency. *N Engl J Med* 2013; 368: 149–160.

2. Solomon LR. Disorders of cobalamin (vitamin B12) metabolism: emerging concepts in pathophysiology, diagnosis and treatment. *Blood Rev* 2007; 21: 113–130.

3. Hathout L and El-Saden S. Nitrous oxide-induced B12 deficiency myelopathy: perspectives on the clinical biochemistry of vitamin B12. *J Neurol Sci* 2011; 301: 1–8.

4. Scalabrino G and Veber D. Myelin damage due to local quantitative abnormalities in normal prion levels: evidence from subacute combined degeneration and multiple sclerosis. *J Neurol* 2013; 261: 1451–1460.

5. Scalabrino G, Buccellato FR, Veber D, *et al.* New basis of the neurotrophic action of vitamin B12. *Clin Chem Lab Med* 2003; 41: 52.

6. Lerner-Ellis JP, Tirone JC, Pawelek PD, *et al.* Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. *Nat Genet* 2005; 38: 93–100.

7. Lerner-Ellis JP, Anastasio N, Liu J, *et al.* Spectrum of mutations in MMACHC, allelic expression, and evidence for genotype-phenotype correlations. *Hum Mutat* 2009; 30: 1072–1081.

8. Nogueira C, Aiello C, Cerone R, *et al.* Spectrum of MMACHC mutations in Italian and Portuguese patients with combined methylmalonic aciduria and homocystinuria, cblC type. *Mol Genet Metab* 2008; 93: 475–480.

9. Fischer S, Huemer M, Baumgartner M, *et al.* Clinical presentation and outcome in a series of 88 patients with the cblC defect. *J Inherit Metab Dis* 2014; 37: 831–840.

10. Rosenblatt DS, Aspler AL, Shevell MI, *et al.* Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC). *J Inherit Metab Dis* 1997; 20: 528–538.

11. Huemer M, Scholl-Bürgi S, Hadaya K, *et al.* Three new cases of late-onset cblC defect and review of the literature illustrating when to consider inborn errors of metabolism beyond infancy. *Orphanet J Rare Dis* 2014; 9: 1–12.

12. Ardissino G, Perrone M, Tel F, *et al.* Case report late onset cobalamin disorder and hemolytic uremic syndrome: a rare cause of nephrotic syndrome. *Case Rep Pediatr* 2017: 1–4.

13. Petropoulos TE, Ramirez ME, Granton J, *et al.* Renal thrombotic microangiopathy and pulmonary arterial hypertension in a patient with late-onset cobalamin C deficiency. *Clin Kidney J* 2017; 11: 310–314.

14. Wang SJ, Yan CZ, Liu YM, *et al.* Late-onset cobalamin C deficiency Chinese sibling patients with neuropsychiatric presentations 2018: 1–7.

15. Gold R, Bogdahn U, Kappos L, *et al.* Hereditary defect of cobalamin metabolism (homocystinuria and methylmalonic aciduria) of juvenile onset. *J Neurol Neurosurg Psychiatry* 1996; 60: 107–108.

16. Shinnar S and Singer HS. Cobalamin C mutation (methylmalonic aciduria and homocystinuria) in adolescence. *N Engl J Med* 1984; 311: 451–454.

17. Carmel R, Watkins D, Goodman SI, *et al.* Hereditary defect of cobalamin metabolism (cblG mutation) presenting as a neurologic disorder in adulthood. *N Engl J Med* 1988; 318: 1738–1741.

18. Hunt A, Harrington D and Robinson S. Vitamin B12 deficiency. *BMJ* 2014; 349: g5226.

19. Quadros EV. Advances in the understanding of cobalamin assimilation and metabolism. *Br J Haematol* 2010; 148: 195–204.

20. Scalabrino G. Cobalamin (vitamin B12) in subacute combined degeneration and beyond: traditional interpretations and novel theories. *Exp Neurol* 2005; 192: 463–479.

21. Baranowski M, Muc-Wierzgon M, Madej K, *et al.* The estimation of endogenous tumor necrosis factor alpha and cortisol levels in serum in advanced neoplasm. *J Exp Clin Cancer Res* 1999; 18: 241–245.

22. Schuld A, Birkmann S, Beitinger P, *et al.* Low doses of dexamethasone affect immune parameters in the absence of immunological stimulation. *Exp Clin Endocrinol Diabetes* 2006; 114: 322–328.

23. van der Poll T, Barber AE, Coyle SM, *et al.* Hypercortisolemia increases plasma interleukin-10 concentrations during human endotoxemia – a clinical research center study. *J Clin Endocrinol Metab* 1996; 81: 3604–3616.

24. Brooks BP, Thompson AH, Sloan JL, *et al.* Ophthalmic manifestations and long-term visual outcomes in patients with cobalamin C deficiency. *Ophthalmology* 2016; 123: 571–582.

25. Bacci GM, Donati MA, Pasquini E, *et al.* Optical coherence tomography morphology and evolution in cblC disease-related maculopathy in a case series of very young patients. *Acta Ophthalmol* 2017; 95: e776–e782.

26. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005; 352: 1791–1798.

Visit SAGE journals online
journals.sagepub.com/home/tan

SAGE journals