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RESEARCH LETTER

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# Rosiglitazone-associated pseudotumour cerebri

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*To the Editor*: Several drugs may induce pseudotumour cerebri, which commonly presents with papilloedema, headache and/or transient visual disturbances. The diagnosis of pseudotumour cerebri should satisfy the following (Dandy's modified) criteria: (1) signs and symptoms of elevated intracranial pressure; (2) a normal neurological examination except for an abducens palsy; (3) cause of elevated intracranial pressure not evident from neuroimaging; and (4) normal cerebrospinal fluid examinations except for an increased opening pressure [1]. To the best of our knowledge, we report here the first case in the literature of a patient with rosiglitazone-associated pseudotumour cerebri.

A 61-year-old man with type 2 diabetes mellitus was admitted to our centre complaining of headache for the previous 3 weeks. Type 2 diabetes had been diagnosed during routine check-ups at another centre 3 months previously, and rosiglitazone (4 mg twice daily) had been prescribed as a first-line monotherapy. The patient had no history of diabetic micro- and/or macrovascular complications, but was known to have had hypertension for the last 7 years (treated by various ACE inhibitors, currently: quinaprile 20 mg/day). The physical (including neurological) examination was unremarkable except for hypertension (blood pressure: 155/90 mmHg), obesity (BMI: 31 kg/m$^2$) and bilateral papilloedema without any evidence of diabetic and/or hypertensive retinopathy. No peripheral oedema was observed. The laboratory evaluation revealed that fasting plasma glucose was 8.9 mmol/l, postprandial plasma glucose was 9.6 mmol/l, and $HbA_1c$ was 7.9 %; renal, hepatic and thyroid functions were normal, as were electrolytes. The possibility of a space-occupying lesion inside the central nervous system was excluded by normal cranial magnetic resonance imaging. Lumbar puncture revealed no cytological and/or biochemical abnormality except for an increased opening pressure of 41 cm $H_2O$.

Upon these findings, the patient was diagnosed with pseudotumour cerebri.

Despite lack of evidence regarding the salt and water retention effects of rosiglitazones, the patient's current antidiabetic medication was changed from rosiglitazone to metformin 850 mg taken orally twice a day. In addition, furosemide 40 mg/day was administered orally for 2 weeks. At the second week after discontinuation of rosiglitazone, the headache was resolved, but papilloedema was still present. By the tenth week, a follow-up examination revealed that the papilloedema had disappeared; and repeated lumbar puncture revealed completely normal cytological and biochemical findings, including normalised opening pressure of 16 cm $H_2O$. The patient has remained well, and has not developed any new neurological sign or symptom in the following 18 months while on metformin, salicylate, quinaprile and simvastatin therapies.

Glitazones have long been known to cause oedema, but isolated compartmental fluid retention as in pseudotumour cerebri is not one of the known complications of these agents [2]. Interestingly, Edwin Hurlbut Ryan reported in 2003, at the annual meeting of the American Academy of Ophthalmology, that glitazones could be linked to macular oedema in patients with diabetes [3]. But all of the cases presented retrospectively also had peripheral oedema at the same time as macular oedema [3]. On the other hand, glitazones have also been shown to decrease retinal neovascularisation in experimental models [4, 5].

Here we report on a type 2 diabetic patient who had pseudotumour cerebri that appeared and resolved in association with the onset and cessation of rosiglitazone therapy. Despite lack of further evidence, the temporal relationship between rosiglitazone initiation and neurological picture, as well as the lack of another aetiological risk factor for pseudotumour cerebri in our patient, makes a causal relation between rosiglitazone therapy and pseudotumour cerebri clearly conceivable.

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At present it is not known how rosiglitazone could contribute to the aetiopathogenesis of pseudotumour cerebri. Possible explanations may include: (1) central vasodilatation; (2) alterations in secretion–reabsorption rates of cerebrospinal fluid; and (3) changes in endothelial permeability. All of these possibilities warrant further confirmatory research.

We propose that physicians should be aware of the possible risk of pseudotumour cerebri in diabetic patients presenting with new-onset headache while on rosiglitazone therapy. In such cases, thorough and frequent funduscopic examinations for papilloedema seem to be the safest way to document pseudotumour cerebri. As our report gives no confirmatory data for the causal relationship between rosiglitazone and pseudotumour cerebri, further evidence should be sought.

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