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Early onset steroid induced posterior subcapsular cataract in a patient with common variable immunodeficiency: case reports and review of literature

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Summary

Purpose. To report early onset steroid induced posterior subcapsular cataract in a case of common variable immunodeficiency. **Methods.** Case report. **Results.** Here we report a 14-year-old male of steroid induced bilateral posterior subcapsular cataract in a common variable immunodeficiency patient with damaging mutations in Glutathione reductase gene, leading to hypersensitivity of patient to glucocorticoid (GC) products. **Conclusions.** In order to reduce the ocular side effects of the GCs there are some advisements, including a complete history, regular examination, GC should be prescribed in minimal dosage and minimal course, and as possible GC-sparing drugs should always be considered.

Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency disease (1-3). CVID is characterized by reduced serum immunoglobulin levels and increased susceptibility to recurrent bacterial infections, autoimmunity and malignancies (4-6). CVID may present at any age but the peaks of presentation are in childhood and early adulthood (1,7-9). The range of clinical manifestations is broad. Recurrent bacterial infections are most in respiratory and gastrointestinal tracts (3). Most frequent autoimmune disorders are idiopathic thrombocytopenia and autoimmune hemolytic anemia, and most common malignancies are gastric adenocarcinoma or lymphoma (3,10). Ocular manifestations in CVID

patients are due to infections and usually present with conjunctivitis (11). There are a few unusual reports in the literatures, which are unilateral diffuse placoid choroidopathy (12), uveitis (13-16), optic disc neovascularization (16), retinitis (17), loss of retinal function (18), retinal vasculitis (19), unilateral peri-orbital redness, pain, proptosis and restriction of ocular movements (20), corneal perforation (21), bilateral optic neuritis (22), choroidal granulomas (23). Age independent cataract has not been reported as an ocular manifestation in a CVID patient so far. Our report is the first case report of bilateral posterior subcapsular cataract in a CVID patient with heterozygous mutations in glutathione reductase (GSR) gene leading to hypersensitivity to glucocorticoid (GC).

Case presentation

The patient is a 14-year-old male with a history of omphalitis at 12 days of age and recurrent post vaccination fever as his first complaints. He is a child from related parents (first cousin), with no family history of immunodeficiency. He experienced recurrent episodes of infectious diarrhea and upper and lower respiratory tract infections such as pneumonia, otitis media and sinusitis, which required recurrent hospitalization. He had scalp and scrotum abscess at 9 and 15 months of age. At the age of 1.5 years he was diagnosed with CVID based on panhypogammaglobulinemia, defective specific antibody production and normal B cells (**table 1**). He received regular intravenous immunoglobulin (IVIG), which resulted in serum immunoglobulin levels increase and improvement of clinical condition. At the age of 5 y, he presented with elevated liver enzymes. Viral hepatitis was excluded by negative results of HBS antigen, HCV antigen, PCR HCV and HBS antibody level of 76 IU/L. Liver biopsy was performed and chronic autoimmune hepatitis was diagnosed, and required prednisolone administration. During GC therapy, the patient suffered from progressive visual impairment and finally bilateral lens opacity was diagnosed at age 12 y in routine ophthalmic examinations. Visual acuity

was diminished to 6/10 for both eyes, and his eye examination revealed abnormal Bruckner test (red eye reflex). He had no leukocoria, photophobia, abnormal extraocular movements, strabismus or nystagmus. Relative afferent pupillary defect (marcus gunn pupil) was negative for both eyes. Intraocular pressure was 16 mmHg in both eyes, with its normal range from 10 to 21 mmHg. Lids, conjunctives, corneas, anterior chambers and irises were all normal in examination. His drug history included IVIG 2.5-15 mg monthly since 12 years before (following diagnosis of CVID), prednisolone 10-50 mg daily since 8 years before (following diagnosis of autoimmune hepatitis), azathioprine, ursobil, colchicine, inderal and zinc plus. Our patient was candidate for cataract surgery and it was done successfully. To investigate the genetic cause of hyper sensitive response of patient to steroid therapy, the next generation sequencing was performed using the method previously described, and the data obtained were filtered out for synonymous mutations and eliminated common variants, then prioritized the results for following genes: GILZ (GC-induced leucine zipper), SERPINE family (Serpin peptidase inhibitor), Cadherin family (cadherin-associated protein and E-cadherin), FGF2 (Fibroblast growth factor 2), IGF1 (Insulin-like growth factor 1), IGFBP family (Insulin-like growth factor binding protein) MAPK1,3 (Mitogen-activated protein kinase 1 and 3), CTRF (Cystic fibrosis transmembrane conductance regulator), PIK3 family (Phosphatidylinositol-4,5-bisphosphate 3-kinase), AKT family (akt murine thymoma viral oncogene), PTK2B (Protein tyrosine kinase 2 beta), ABC family (ATP-binding cassette), NFKB family (Nuclear factor of kappa light polypeptide gene enhancer in B-cells), REL family (v-rel avian reticuloendotheliosis viral oncogene), GSK family (Glycogen synthase kinase), IRS family (Insulin receptor substrate), RAS family (rat sarcoma viral oncogene), MAPK family (Mitogene activated protein kinase), GPX family (Glutathione peroxidase), FOXO family (Forkhead box) and WNT family (Wingless type MMTV integration site). We subsequently found 2 novel, heterozygote mutations in the *GSR* (Glutathione reductase) gene (**table 2**). This mutation was confirmed by means of sanger sequencing (**figure 1**). The mRNA accession number was NM_000637.3. The primers used were AGGAAGGGAGATC-CAGAGGTT (ex10-F) and CCCTCACCAAGAAGGGAAGA (ex10-R), giving a product of 221 bp, as well as TGAAACTGT-CAGAACTAGGGC (ex11-F) and GGGGAAAGAGGAAG-GAAACCA (ex11-R), giving a product of 294 bp.

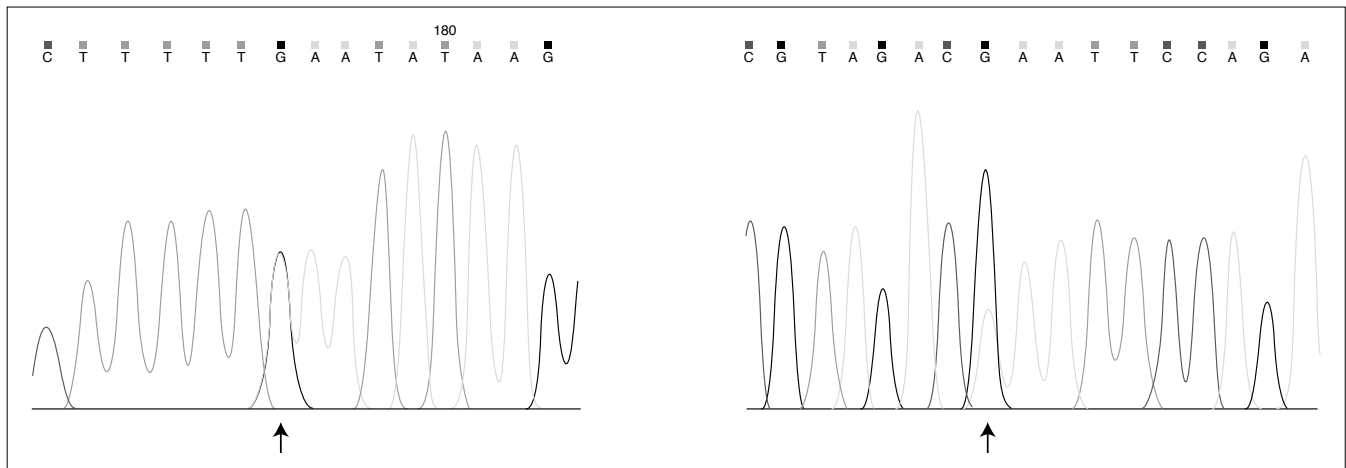
Table 1 - Laboratory Data of the Patient with Steroid Induced Posterior Subcapsular Cataract at the Time of Diagnosis.

Parameters	Patient	Normal Range
IgG (mg/dl)	150	650 - 1410
IgM (mg/dl)	18	55 - 210
IgA (mg/dl)	25	83 - 255
Anti-tetanus (IU/ml)	< 0.01	Upper than 0.1
Anti-diphtheria (IU/ml)	< 0.01	Upper than 0.1
White blood cell count (cells/ μ L)	4500	4500 - 13000
Lymphocytes (cells/ μ l)	1350	900 - 7800
CD3+ (cells/ μ l)	1160	495 - 2106
CD4+ (cells/ μ l)	669	243 - 4134
CD8+ (cells/ μ l)	445	171 - 2652
CD19+ (cells/ μ l)	94	36 - 2418

Table 2 - Glutathione reductase gene mutation analysis of the CVID patient with steroid induced posterior subcapsular cataract.

Gene	Nucleotide change	Protein change	Allele frequency	SIFT prediction	Type of mutation
<i>GSR</i>	c.G1081>A	p.E361K	Not reported	Damaging	Heterozygous
<i>GSR</i>	c.G1195>A	p.E399K	Not reported	Damaging	Heterozygous

Figure 1 - Mutation analysis of GSR gene in a CVID patients presenting with early onset steroid induced posterior subcapsular cataract.



Discussion

The range of CVID clinical spectrum is broad, but there are a few reports of ocular manifestations (as mentioned before) and no reports of cataract. Here we describe a CVID patient with bilateral cataract. Cataract is one of the major curable causes of blindness in children (24). Children cataract has a lot of etiologies, which are categorized in several major groups including ocular trauma, hereditary, disease-associated, ionizing radiation and glucocorticoids (25-29). Our patient had no ocular trauma and no ionizing radiation in his history. He was born with normal vision until 1 year before, so hereditary causes were excluded too. Numerous diseases are associated with cataract (29), but none of them was diagnosed in this patient, and the only systemic disease in our patient was CVID. CVID itself has not been reported as a cause of cataract so far. Our patient had a long history of receiving various drugs but the only drug that could cause his cataract was GC. In treatment of CVID, the GCs are mostly used to treat polyclonal lymphocytic infiltration, autoimmune disorders such as autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura, gastrointestinal problems for example enteropathy (3). Also, it has been used as the first line treatment for autoimmune cytopenia in these patients (30). Our patient had a lot of episodes of cytopenia plus autoimmune hepatitis, which led to administration of GCs. Long term use of systemic GCs can cause various ophthalmic side effects including ocular hypertension, serous chorioretinopathy and cataract (26,31-33). Steroid-induced cataract follows this pattern: 1) It is posterior subcapsular, 2) Mostly affects both eyes and progresses slowly, 3) Children are more affected than adult (34), which are all compatible with our patient. Prednisone and prednisolone are the most common GCs used. This is

because of higher GC effects comparing to mineralocorticoids (35). Our patient has been receiving systemic corticosteroid (prednisolone) 10-50 mg daily since 8 years before. Many broad retrospective studies had shown the usage of GCs for a long period, whether in low doses, is an independent factor to predict happening of the many GC side effects (36,37). In one study on patients taking low doses of GC (prednisone 7.5 mg daily), long term using (more than 90 days) was associated forming of bruising, acne, weight gain and cataract (38). Posterior subcapsular cataract is really affecting the vision of patient and needs more rapid surgical intervention comparing to other subgroups of cataract. Susceptibility of patients for cataract after long term treatment with GCs is different. The patient should use at least for 1 year more than 10 mg daily oral prednisone (or the same dose of other GC) (35,39). The patient presented above, received at least more than 10 mg prednisolone daily for 8 years. Although there is not yet a real safe dosage of GC to prevent cataract, in 2 clinical trials which were done for 2 years on low dose administration of systemic GC, (prednisone 7.5 mg daily), 4 of 273 cases got glaucoma. This rate in the control group was 0, but the appearance of cataract did not differ (40). The results of these studies cannot be generalized because of limited course of GC administration and dosage. Unfortunately, early cataract may not have any symptoms up to the late levels.

Oxidation of lens proteins is one of mechanisms which causes cataract, especially age related cataract. There are a few papers showing this mechanism responsible for steroid-induced cataract (41,42). Steroids affect cellular processes by steroid response elements (GRE) in the promoter region of specific genes (43,44) including glutathione reductase gene. Glutathione is oxidized (forming GSSG) as a key substrate in the intracellular antioxidant systems, such as glutathione peroxidase / reductase.

This system detoxifies H₂O₂ to water in lens epithelial cells. When glutathione is decreased, this system oxidizes other cell proteins which leads to cataract formation. There are several mechanisms causes GSH level diminish (45-48), among which is defect in glutathione reductase activity (49-51). GSR reduces oxidized glutathione (GSSG) to regenerate GSH. When GSR impair glutathione is decreased, and glutathione peroxidase / reductase system oxidizes other cell proteins. Our study revealed compound heterozygous mutations in *GSR* gene following steroid administration which subsequently leads to GSR activity impairment and cataract formation.

In order to reduce the ocular side effects of the GCs there are some advisements: most importantly a complete history and physical examination should be taken, to identify the risk factors of getting the side effects of GC. Second, regular examination of the eyes is recommended to be done more frequently. Third, GC should be prescribed in minimal dosage and minimal course. Forth, as possible GC-sparing drugs should always be considered e.g. using anti immunoglobulin E monoclonal antibody can reduce the exacerbation of asthma which needs systemic GC and improve quality life of the patients (35).

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