

**Case Report of a 66-Year-Old Male with
Velo-Cardio-Facial Syndrome and Atypical Immune Deficits**

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Abstract

To date, only three cases older than fifty years of age with velo-cardio-facial syndrome (VCFS) have been published. We describe the fourth such case. Physical and laboratory findings are presented as a case report. The case described is a 66-year-old male with VCFS confirmed by fluorescence in-situ hybridization (FISH) who was referred by his psychiatrist for comprehensive care. He had a history of cleft palate and learning disabilities as a child with the onset of psychiatric illness in his late teens. Although there was no history of cardiac disease, the patient had agenesis of the left renal artery as well as other vascular anomalies, including hypoplasia of the left A1 segment of the anterior cerebral artery. Other findings included hypothyroidism, hypoparathyroidism, sensorineural hearing loss, and typical facies. He also suffered from chronic candidiasis. Immunologic laboratory studies revealed over a 2:1 ratio of CD8:CD4 T cells with a decreased CD4 percentage, markedly diminished B cell percentage, decreased T cell mitogen responses, and markedly decreased B cell mitogen responses. Nevertheless, total serum IgG and specific antibody responses remained normal, with a low serum IgM.

Conclusions: This patient meets the criteria for the diagnosis of VCFS and is only the fourth reported case diagnosed over the age of fifty. Though his immunologic findings may be consistent with his diagnosis, they may be due in some part to immunologic senescence given his age.

Introduction

The velo-cardio-facial syndrome (VCFS) was first described in 1978¹ with hundreds, perhaps even thousands of cases being described in the literature since. The population prevalence has been reported to be between 1:1600 and 1:2000 in medically sophisticated countries.^{2,3} A de novo deletion from chromosome 22 at the q11.2 band resulting in a haploinsufficiency of approximately 40 genes causes the syndrome. Once present, the inheritance pattern is autosomal dominant.⁴ Though its name suggests that patients with VCFS commonly present with a variety of genetic defects involving the soft palate (velum), the heart (cardiac) and the face (facies), patients can present with defects from an array of approximately 200 anomalies.⁵ Anomalies include tortuous blood vessels, delayed growth, cognitive impairment, psychiatric disorders, transient neonatal hypocalcemia, and sensorineural hearing deficits.⁶ Typically, developmental defects related to the third and fourth branchial pouches, leading to thymic aplasia or hypoplasia as well as hypoparathyroidism and hypocalcemia have been ascribed to cases of DiGeorge sequence (DGS). Because DGS is an etiologically heterogeneous developmental sequence, individuals with VCFS may present with immune disorders, including variable combinations and impairments of T cell production, T cell function, and humoral immunity.⁷ Most commonly, VCFS cases demonstrate lower T cell populations, but normal or slightly diminished T cell function and humoral immunity.⁸ As with hypocalcemia, immune defects are more pronounced in infancy and usually resolve with age. Unlike cases with DGS in whom there is complete thymic aplasia potentially requiring thymic or bone marrow transplants,^{9,10,11} similar therapies are not commonly used in VCFS.

The clinical spectrum of VCFS patients ranges from neonatal death from a complicated congenital heart defect to transient hypoparathyroidism to hypernasal speech. Series of published cases often reflect the authors' discipline and may show an ascertainment bias. Phenotypes in adults are less frequently reported. There have been few reports in adults over 18 years of age and only three cases over 50 years have been described in detail.^{12,13,14} We describe the phenotype and in particular the vascular and immunologic findings in a 66-year-old man.

Case Report

A 66 year-old man only recently diagnosed with VCFS was referred by his psychiatrist for comprehensive care. He was the 7 pound 8 ounce product of a full-term uneventful pregnancy delivered with the aid of forceps. The family history was not significant as far as is known and both of his parents were deceased. There were no reported neonatal problems. A cleft palate was repaired at 4 or 5 years of age. He did poorly at school and was enrolled in a vocational high school where he became a management problem. He was then kept at home until his first psychiatric hospitalization at 16 or 17 years of age. He had recurrent hospitalizations for his psychiatric illness

through adulthood, most recently in 1999. He demonstrated low-frequency sensorineural hearing loss and bilateral cataracts. There was no history of cardiac disease. He had left renal agenesis and recently had surgery for prostatic hypertrophy. He had a seizure disorder treated successfully with valproic acid. He was being treated for hypothyroidism and hypoparathyroidism. He had pancytopenia thought to be related to a myelodysplastic syndrome. He has thrombocytopenia without giant platelets or a bleeding diathesis. Imaging in the past revealed basal ganglia calcifications and he had chronic candidiasis, both of which conditions are associated with hypoparathyroidism. FISH was done at 64 years of age because of his facial appearance and his complex history and confirmed the presence of a deletion at 22q11.2 using the TUPLE1 probe.

His most recent psychiatric evaluation was done because of aggressive and abusive behaviors. He was referred from the group home in which he had lived since 1986 with four other developmentally delayed adults and where he attended a day treatment program. He was occasionally involved in fights with his roommates that escalated to the point where 911 had to be called to stabilize the situation. He was verbally abusive, suspicious, threatening and provocative. He was occasionally flirtatious with attractive women. Mostly, he appeared to be in a state of mild depression. His family reported that his overall level of functioning regressed many years ago when he started on antipsychotic drugs. During his mental status examination, he sat quietly. His affect was blunted and his mood was euthymic. His speech was a “word salad” of phrases that were hard to understand and more difficult to interpret. He did not seem preoccupied with internal stimuli and paranoia was not discernible. His psychotropic medications on referral were Seroquel, Depakote, and Cogentin. His psychiatric diagnosis was schizoaffective disorder and moderate cognitive impairment. He obtained a Verbal Scale IQ of 58, a performance scale IQ of 64 and a Full Scale IQ of 58 on the Wechsler Adult Intelligence Scale – Revised.

His physical examination revealed a bald adult male (photos could not be shown because of lack of consent). His weight was 66.7 kg and his height was 165 cm. The head circumference was 58 cm, the outer canthal distance was 10.5 cm and the inner 2.75 cm. The eyelids were hooded and the pinna were normally shaped and positioned. The nasal tip was broad and bulbous. He was edentulous and wore an upper dental plate. The palate was intact except for a bifid uvula. Bilateral carotid bruits were audible and he had extensive varicosities of both lower extremities extending from the ankle to the crura (Fig. 1). The digits were not tapered and there was no Raynaud’s phenomenon. His affect was dull, his speech mostly unintelligible and he wore a diaper. He had a shuffling gait and there were no focal sensorimotor deficits. His medications included levothyroid, dihydroxytachosterol and vitamin D.

Figure 1. Varicosities on the patient's leg



Laboratory studies revealed a TSH of 0.82 uU/mL (0.40-4.60), free T4 0.60 ng/dL, PTH (intact) 4.9 pg/ml. His platelet count was 94,000/uL. Venous duplex Doppler showed no evidence of deep or superficial vein thrombosis and spectral Doppler waveform analysis demonstrated a normal phasic venous flow pattern in the lower extremities. An echocardiogram was normal. An EEG was interpreted as abnormal because of slow background activity and an excess of diffuse irregular theta slow waves during wakefulness, indicative of diffuse cerebral dysfunction. A renal ultrasound showed no left kidney. An MRI of the brain showed more cerebral atrophy than expected for age, dilated ventricles, and possible mild underlying hydrocephalus. There was extensive periventricular and other white matter changes noted bilaterally in a pattern consistent with small vessel ischemic disease. Small cysts were noted in both basal ganglia as well as adjacent to the head of the left lateral ventricle and near both temporal horns. An MRA

of the head and neck showed hypoplasia of the left A1 segment of the anterior cerebral artery, approximately 60% stenosis of the right internal carotid artery, and a left dominant vertebral artery. The left carotid system was complex with possibly duplicated vessels.

Lymphocyte studies showed a reversed CD4/CD8 T cell ratio of 0.40 (0.13-4.49) with 450/22% CD4 T cells/uL (395-1495/34-57%) and 1134/69% CD8 T cells/uL (76-860), and B cells [CD3/CD19] 3% (7-26%). Serum immunoglobulins revealed IgG 1260 mg/dL (844-1912), IgA 159 mg/dL (68-423), and IgM 28 mg/dL (50-196). Specific antibody titers were all positive to measles, mumps, and rubella (MMR), and high titers were mounted to seven of twelve pneumococcal serotypes (> 4 ug/mL). Mitogen responses are reported in table 1.

Table 1. Mixed Lymphocyte Mitogen Responses

Primary Target Cells	Mitogens	Patient		Control		Normal Ranges	
		CPM	SI	CPM	SI	CPM	SI
	Background	243				57-274	-----
T cells	PHA	49,579	204	78,119	397	-----	118-354
T cells	CON A	21,368	88	102,479	520	-----	106-339
T + B	PWM	4,408	18	23,471	119	-----	21-100
B cells	STAPH A	5,518	23	26,855	136	-----	38-137

PHA = Phytohemagglutinin (red kidney bean), **CON A** = Concanavalin (Jack bean), **PWM** = Pokeweed mitgen (Pokeweed), **STAPH A** = Cowan Staph A+ (*Staphylococcus aureus* Cowan I, producing protein A), **CPM** = Counts per minute ³H thymidine uptake, **SI** = Stimulation index ([stimulated cells cpm] divided by [background unstimulated cells cpm]).

Discussion

Our patient meets the clinical criteria for VCFS first described by Shprintzen in 1978¹ and since noted for its variable phenotype and lack of genotype-phenotype correlation. Most phenotypic studies of VCFS to date have ascertained pediatric populations through cardiac or craniofacial programs. The largest attempt to publish a series of patients that would decrease this bias of ascertainment was the European collaborative study by Ryan et al., 1997.¹² The authors were able to include a total of 558 patients from participating centers. Of the 534 patients for which ages were given and after having excluded 10 fetuses, only 11% of patients were 18 years or over and the oldest patient was 51. Developmental data was available for 338 patients and indicated abnormal development in 68% of children and adults. Eleven of the 61 adults over 18 years had a psychiatric disorder. In general, the authors concluded that the adult group, primarily parents of VCFS children, had less severe cardiac and developmental problems. The oldest reported adult in the literature, age 52, was described by McDonald-McGinn et al.¹⁴ who emphasized the clinical variability of this disorder especially in their unselected cohort of patients. The authors identified 19 adults through an affected relative and found none had a congenital heart defect and useful facial features included hooded eyelids and bulbous nasal tip. Educational histories revealed that 67% graduated high school though many had learning difficulties. Occupational data indicated that most females were housewives and that most males worked in service industries. Additional studies of adults with the 22q11 deletion syndrome are necessary to delineate the adult phenotype and to better understand the natural history of the disease. The most comprehensive review of the subject to date¹³ reported on only a single adult over 50 years of age. The authors concluded that adults had lower rates of congenital heart defects (30% versus 75%), higher rates of palatal anomalies (88% versus 15%) and learning difficulties (94% versus 79%) and psychiatric conditions (36% versus 18%). The most common physical findings were minor facial anomalies. Bassett et al.¹⁵ attempted to delineate a schizophrenic subtype or phenotype in 22q11 adults with schizophrenia. Only additional signs such as temper outbursts, impulsivity, and physical aggression were noted. Some features, especially a bulbous nasal tip, may become more manifest with age while others may become less apparent.

Immunologically, our patient demonstrated an inverse ratio of CD4/CD8 T cells with a diminished CD4 population. It is important to note in the patient's history both his hypoparathyroidism and his chronic candidiasis. The former may be related with defects in the development of the 3rd and 4th branchial pouches, leading to a suspicion of altered thymic development and therefore diminished T cell populations and function. The latter may be a marker of decreased T cell function, and hence the inability to clear candidal infections. Both taken together speak towards decreased T cell functionality, which is somewhat confirmed by his decreased T cell mitogen responses, although one would expect worse results. One study compared the T cell populations of patients with DGS

and VCFS with matched controls and found both the DGS and VCFS patients were found to have significantly diminished total T cell populations (CD3) compared to controls, with no difference in CD4 T cell populations but decreased CD8 T cell populations compared with controls.¹⁵ This differs significantly from our patient who has an increased CD8 population and a decreased CD4 population. Since the variability of thymic defects and subsequently T cell abnormalities remains high in VCFS, this finding does not exclude the possibility that the T cell abnormality is related to VCFS.

The other striking feature of his immune workup is a marked reduction in his B cell population and mitogen responses. Given this, one would expect some combination of low serum immunoglobulins (namely IgG) and diminished or absent specific antibody responses. However, he demonstrated a normal quantity and specificity of antibodies. In diseases with thymic defects, B cell dysfunction generally reflects the inability of the T cell population to appropriately stimulate B cell maturation and development, particularly in the germinal centers of lymph nodes, as is the case in some familial DGS patients with selective polysaccharide antibody deficiency.¹⁷ Another study suggests that DGS (and VCFS) patients can generate specific antibody responses and have normal B cell populations with normal mitogen responses despite diminished T cell populations; their T cells function appropriately.¹⁸ Our patient differs from this paradigm with significantly low B cell numbers and mitogen responses but intact immunoglobulin levels and specific antibody responses. Regardless of the fact that the high variability of immune defects in VCFS prevents us from ruling out VCFS entirely as the cause, we believe that the unusual humoral immunity profile of our patient, as well as the disparity of his T cell findings compared to the study by Pierdominici et al.,¹⁷ may be better explained by immunologic senescence.

In conjunction with thymic involution, T cell proliferation declines with age, as demonstrated in vitro with mitogen responses, and in vivo with delayed-type hypersensitivity responses. It has been suggested that this is due to reduced IL-2 production as well as decreased expression of high-affinity IL-2 receptors after stimulation.¹⁹ A study of 11 healthy elderly subjects, 173 nursing-home residents, and 34 healthy young adults, found variability in memory B cell fractions of the older subjects similar to those of young patients with common variable immune deficiency (CVID).²⁰ Moreover, due to a lower population of naïve lymphocytes in older individuals, clonal expansion of existing memory T and B cells accounts for lymphocyte responses in the elderly.²¹ Of note, CD8 cells typically manifest such clonal expansion prior to CD4 cells,²² which may better explain the inverse ratio of CD4/CD8 T cell populations in our patient. With regard to B cell responses, one study suggests that aging patients produce more autoantibodies, in particular auto-anti-idiotypic antibodies (AAI).²³ These antibodies have been suggested to be the cause of poor vaccine responses in elderly subjects, as elevated levels of AAI antibodies have been found.²⁴ Our patient has not been challenged to make new vaccine responses.

Finally, the persistent specific antibody response provides the strongest piece of evidence in favor of immune senescence. Were his T cell defects, diminished B cell numbers and mitogen responses due to his VCFS, they would have been present throughout his life, likely preventing the formation of specific antibody responses to childhood immunizations such as MMR and therefore the formation of memory B cells to those responses. It is consequently more plausible that his decline in B cell function, as represented by low B cell populations and mitogen responses, is more likely due to immune senescence as described above, allowing our patient to retain the B cell memory he acquired during childhood.

Conclusions

This case resembles previously reported adults in that he lacks major cardiac anomalies and is mildly stigmatized. However, he has major psychiatric and developmental problems. Although he demonstrated immune deficits which may be consistent with VCFS, they are possibly related to immune senescence at least in part. His vascular changes including cerebral advanced atrophy, carotid bruit, carotid stenosis and severe varicosities have not been previously described in an adult. Similarly, there is little documentation of endocrine and immunological abnormalities in adult patients. A comprehensive phenotypic analysis of adults with the 22q11 deletion syndrome would help clarify differences in facial anomalies and the evolution of psychiatric, hematologic, endocrine and immune dysfunction and vascular abnormalities in adults.

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