

The 25th Annual

Waltham/OSU Symposium

Small Animal Ophthalmology

October 27 – 28, 2001

Clinical Syndromes In Canine And Feline Uveitis

Brian C. Gilger, DVM, MS, Dipl. American College of Veterinary Ophthalmologists

Associate Professor, Ophthalmology

Department of Clinical Sciences

North Carolina State University

Raleigh, North Carolina

Introduction

Uveitis is inflammation of the uveal tract – Anterior uveitis is inflammation of the the iris and ciliary body, while posterior uveitis is inflammation of the choroids. Panuveitis is inflammation of the entire uveal tract. Panuveitis is the most common type of uveitis in small animals.

Clinical signs of uveitis, in general, includes: miosis, flare (protein +/- cells in the anterior chamber as a result of a breakdown in the blood-aqueous barrier), redness or hyperemia of the episcleral/scleral blood vessels, photophobia (extreme sensitivity to light), pain (blepharospasm, squinting, photophobia, and rubbing the eye), and keratic precipitates (accumulations of protein and mononuclear cells on the corneal endothelium).

There are two general etiologic categories for uveitis: ocular and systemic. **Ocular causes** include corneal ulceration, which can result in a neurogenic reflex anterior uveitis, lens-induced (a hypermature cataract can result in uveitis as a result of the leakage of lens protein), ocular trauma, and primary neoplasia. **Systemic causes** include bacteremia, viremia, or septicemia (see syndromes below).

Uveitis workup and diagnostic tests:

A complete medical **history** is essential. Questioning about other physical changes such as weight loss, anorexia, vomiting, diarrhea and the animal's environment (does this animal have exposure to other animals, to mycotic organisms etc., exposure to endemic areas?)

Physical examination - a complete physical examination must be performed on all animals with uveitis. Carefully evaluate the lymph nodes, liver, spleen, auscultate the chest, take the temperature, etc.

Blood work includes a complete blood count / biochemical profile, and appropriate serology of diseases suspected through the history and physical examination (or even after initial CBC and profile is back. Common **Serology** includes Blasto, Histo, Crypto, FeLV, FIV and Toxo - request IgG, IgM, and Toxo antigen tests (see more information below).

Radiology-thoracic radiographs looking for neoplasia, mycotic involvement.

Treatment of Uveitis

Treatment of uveitis includes **specific therapy** (that directed towards the inciting cause (i.e., blasto, histo, crypto, etc.)) and **non-specific therapy**. Specific therapy requires that you to correctly diagnose the etiology and, if possible, eliminate it

Non-Specific therapy includes topical and systemic medications. The two main goals of therapy is to reduce discomfort, which is achieved through mydriatic-cycloplegics (Atropine) and to decrease inflammation (corticosteroids and non-steroidal anti-inflammatory medications). Topical **Atropine 1%** is generally given to effect and then continued as required to maintain pupil dilation, usually once a day. Topical corticosteroids are most commonly used to decrease

inflammation. **Prednisolone acetate** has the best ocular penetration and frequency of therapy varies according to the severity of the disease (1-6x/day). Topical corticosteroids have side effects, including the ability to potentiate infections, potentiate collagenase (melting of the cornea), delay healing of corneal ulcers, and can be absorbed systemically. Topical non-steroidal anti-inflammatory medications (NSAIDs - **Ocufen®** - 0.03% flurbiprofen, **Profenal®** - 0.1% suprofen) can also be used as a topical anti-inflammatory. Their main advantages are that they can be administered to **diabetic** patients without fear of the systemic effects associated with topical corticosteroids.

Systemic antiinflammatories are also used in non-specific therapy of uveitis. They are initiated if the **posterior uvea** (retina & choroid) is involved, if there is a **corneal ulcer** that precludes the use of topical corticosteroids, or if the anterior uveitis fails to respond adequately to topical therapy. **Prednisolone** is usually the corticosteroid of choice (Anti-inflammatory dose: 0.5 mg/kg BID; Immunosuppressive dose: 1.0 mg/kg BID). Oral NSAIDs can also be effective in the control of less severe uveitis. They have an added advantage in that they can be administered to **diabetic** patients and to patients with **infectious** disease. New NSAIDs such as Rimadyl and Ectodesic are effective as mild to moderate ocular antiinflammatories at the dose recommended for osteoarthritis.

Oral Cyclosporine A Therapy Protocol - Uveitis

- Pre-therapy CBC/Serum chemistry profile - avoid CsA if renal or hepatic insufficiency
- Starter dose: 5 mg/Kg/ day for approximately 30 days (once dog clinical responds well to treatment)
- Then reduce to either 5 mg/kg po every other day OR 2.5 mg every 24 hours.
- Typical total treatment time is approximately 75-90 days (or longer if needed)
- Monitor CBC/profile @ 2, 6 and 10 weeks into treatment - if no changes no further bloodwork required

Occasionally more potent immunosuppressive agents such as azathioprine (Imuran®), cyclophosphamide (Cytosan®), or cyclosporin (Neoral) are required. Low doses of oral cyclosporine (CsA) is especially effective in the control of immune mediated uveitis.

Clinical Syndromes In Canine Uveitis

Bacterial

Leptosporosis - caused by a spirochete; *Leptospira interrogans*, *L. canicola* and *L. icterohaemorrhagiae* are the most common serovars found in the dog. Infection is multisystemic with hepatic, renal and pulmonary involvement. Ocular findings include icterus and petechia of the sclera and conjunctiva, nonspecific conjunctivitis and anterior uveitis. Anterior uveitis is a result of both direct bacterial infection and hypersensitivity reaction.

Brucellosis - caused by the gram-negative coccobacillus *Brucella canis*. Infection is multisystemic and involves urogenital infection, abortion and infertility. Ocular signs include recurrent nongranulomatous uveitis, endophthalmitis, corneal opacification, retinitis, optic neuritis, and retinal detachment. Organisms may be cultured from aqueous and vitreal humor in affected cases. Brucellosis is a zoonotic disease.

Lyme Disease - caused by the spirochete *Borellia burgdorferi* that is transmitted by the *Ixodes dammini* tick. There have been **no** documented cases in the dog; proven infection in the horse and man produce conjunctivitis, iritis, periorbital edema and optic neuropathy.

Bacteremia/Sepsis - Any systemic bacterial infection has the potential for induction of uveitis. Direct colonization of the uveal tract, damage due to bacterial toxins and/or immunologic responses may all play a role in uveal inflammation. Bacterial diseases in locations other than the eye associated with uveitis in dogs include dental disease, endocarditis, pancreatitis, prostatitis, sacculitis and pyometra.

Fungal

Blastomycosis - caused by *Blastomyces dermatidis*; endemic to the Ohio River Valley and Mid-Atlantic States. Infection is through inhalation with spread to skin bones, lungs, lymph nodes, gonads, and eyes. Anterior uveitis is the most common ocular sign, however the posterior segment is affected first and lesions are more severe. Affecting all tunics of the eye, disease is centered on the choriocapillaries of the nontapetal choroid. Retinal separations and choroiditis are common sequela to ocular disease.

Cryptococcosis - etiology is *Cryptococcus neoformans* which is found commonly in soil. Disease is common in cats, less common in dogs. The CNS and eye are most commonly affected, with blindness and optic neuritis resulting from meningoencephalitis. Other ocular signs include granulomatous chorioretinitis, retinal separation and occasionally, exophthalmos. Examination of the fundus reveals single or multiple raised, gray, whitish exudative lesions which may have a "bull's-eye" appearance.

Coccidiomycosis - caused by *Coccidioides immitis*, which is endemic to western and southwestern United States. Infection is via inhalation of spores with hematogenous spread from lungs to the eyes. Ocular findings include keratitis, endophthalmitis, chorioretinitis with retinal detachment, granulomatous panuveitis and orbital cellulitis. As with Blastomycosis, anterior segment lesions are an extension of posterior segment involvement. A possible breed predilection exists in the Boxer and Doberman.

Histoplasmosis - caused by *Histoplasma capsulatum* found in soil and endemic to the Mississippi River Valley. Clinical signs typically involve the liver and gastrointestinal tract; ocular involvement is reportedly rare. Ocular signs include optic neuritis, uveitis and chorioretinitis. Some believe idiopathic chorioretinitis is actually nonfulminating ocular histoplasmosis.

Algal

Protothecosis - caused by the colorless, saprophytic, ubiquitous, opportunistic alga *Prototheca zopfii* and *P. wickerhamii*. Infection is via GI tract with subsequent hematogenous and/or lymphogenous spread to other organs. Clinical signs are multisystemic involving all major organ systems. Granulomatous panuveitis, endophthalmitis, chorioretinitis and retinal separation are the most common ocular signs. Blindness has been reported in over one-half of infected dogs.

Viral

Distemper - Most common viral disease of dogs. Infection results in neurologic, GI, respiratory and ophthalmic signs. Common ocular findings include conjunctivitis, chorioretinitis and acute keratoconjunctivitis sicca. The characteristic neurotropism of CDV results in optic neuritis and optic tract or cortical lesions which occasionally leads to blindness. KCS-related corneal ulceration may lead to reflex anterior uveitis, however primary anterior uveitis resulting from CDV is rare.

Infectious Canine Hepatitis - etiology is canine *adenovirus type-1*. Infection is most common in unvaccinated dogs less than one year of age. Clinical signs are attributable to organs in which virus replicates (reticuloendothelial system, hepatic parenchyma, vascular endothelial cells). Approximately 20% of naturally infected dogs recovering from ICH develop anterior uveitis and corneal edema. Secondary problems associated with keratouveitis include persistent corneal edema, secondary glaucoma and phthisis bulbi. The pathogenesis of ICH keratouveitis is related to immune complex deposition (Arthus-type reaction). Approximately 0.4% of dogs vaccinated with CAV-1 vaccine develop keratouveitis (this vaccine is no longer in use). Afghan hounds may be more susceptible to this post vaccination keratouveitis than other breeds.

Miscellaneous - other viruses may produce uveal inflammation secondary to systemic involvement, as seen with bacterial causes. This is especially true of neurotropic viruses such as Herpes and Rabies.

Protozoal

Toxoplasmosis - caused by the obligate intracellular parasite *Toxoplasma gondii*. The cat is the only definitive host. Dogs are infected via ingestion of sporulated oocysts and infection is subclinical in the majority of cases. Concurrent infection with canine distemper virus is thought to predispose dogs to clinical toxoplasmosis. This disease may infect any system of the body with a predilection for neuromuscular, respiratory, GI and ocular tissues. Ocular lesions include anterior and posterior segment inflammation (anterior uveitis, choroiditis) and are more common with chronic infection. Optic neuritis and extraocular myositis are less common findings. Even though anterior uveitis is common with ocular infection, organisms (tachyzoites) are more commonly seen in the retina than the uveal tract.

Leishmaniasis - caused by a flagellated organism, *Leishmania donovani*. Cases in the United States are seen predominantly in dogs who originated in endemic areas of Greece, Spain or Portugal. The organism is found in cells of the reticuloendothelial system, with resultant clinical signs seen in these organs (spleen, liver, lymph nodes). Ocular findings include blepharitis, retinitis, keratoconjunctivitis, uveitis and endophthalmitis. Anterior segment involvement is usually more pronounced than posterior involvement.

Rickettsial

Ehrlichiosis - results from infection with *Ehrlichia canis* (and less commonly from *Ehrlichia platys*), an intracellular organism transmitted via ticks. The disease occurs in both an acute and chronic form. Clinical signs are many and include fever, anemia, leukopenia, thrombocytopenia, mono or polyclonal gammopathy, neurologic dysfunction and bleeding disorders. Ocular abnormalities are more common in the chronic form and include anterior uveitis (with and without hyphema), conjunctivitis, corneal edema, conjunctival and/or scleral petechiation, diffuse retinitis and/or vasculitis, papilledema, retinal detachment, optic neuritis and photophobia. The most common histologic finding is mononuclear cell infiltrate of the uveal tract.

Rocky Mountain Spotted Fever - unlike Ehrlichiosis, RMSF occurs almost exclusively in the acute form; the etiology is *Rickettsia rickettsii*, transmitted by ticks. Clinical signs are similar to Ehrlichial infection, with vasculitis the primary and most severe lesion. Ocular signs include anterior uveitis, iris stromal petechiation, subconjunctival hemorrhage and hyphema anteriorly; retinitis (with characteristic perivasculitis), petechiation and focal areas of edema occur posteriorly. These signs are more mild in clinical settings when compared to experimental infection. RMSF is differentiated from canine Ehrlichiosis histologically; the most characteristic lesion of RMSF is necrotizing vasculitis with perivascular accumulations of polynuclear and lymphoreticular cells.

Immune Mediated

Lens-Induced Uveitis - During embryological development, lens proteins are normally sequestered from the immune system. As a result, immunotolerance does not develop and when encountered, both humoral and cell-mediated responses act against lens protein antigens. Two of the most antigenic lens proteins are insoluble albuminoid and soluble chrySTALLIN. Exposure to these antigens following trauma, cataract extraction or spontaneous lens resorption will result in varying degrees of uveitis. Two major types of LIU occur in dogs: phacolytic and phacoclastic. Phacolytic uveitis occurs when soluble lens proteins leak through an intact lens capsule (i.e. fast developing or hypermature cataracts). This has also been referred to as nongranulomatous LIU. A second form of phacolytic uveitis, known as granulomatous LIU occurs in older animals with rapidly progressing or long-standing cataracts. The most prominent feature of this form is the deposition of fat-like keratic precipitates. The granulomatous form holds a less favorable response to treatment than the nongranulomatous form. The other major type of LIU is phacoclastic uveitis, which occurs following rupture of the lens capsule. Phacoclastic uveitis occurs most commonly secondary to trauma.

Immune-Mediated Vasculitis - may occur as a primary process or secondary to other autoimmune or infectious diseases. Due to the vascular nature of the uveal tract, immune-mediated vascular disorders commonly result in ocular involvement. Inflammation and necrosis results from vascular deposition of immune complexes and subsequent activation of complement. Typical clinical signs include episcleritis, enlarged retinal vessels and retinal edema. An immunogenetic predisposition to sulfonimide antibiotics is said to occur in Dobermans resulting in a reversible "patchy" retinitis.

Immune-Mediated Thrombocytopenia - as with immune-mediated vasculitis, the vascular nature of the uveal tract predisposes the eye to bleeding disorders associated with platelet inactivation, destruction or consumption.

Uveodermatologic Syndrome - referred to as Vogt-Koyanagi-Harada (VKH) syndrome (extrapolated from man). VKH is a disease of the pigmented areas of both the eyes and skin and is characterized by both anterior and posterior segment abnormalities, vitiligo, and meningitis. The disease is thought to be an immune-mediated disorder whereby melanocytes are targeted by cytotoxic T-lymphocytes. Ocular findings usually precede dermatological manifestations and are characterized by bilateral anterior uveitis or panuveitis, uveal depigmentation, retinal detachment, and in advanced cases, blindness. VKH primarily affects young dogs with a mean age of 2.8 years. A suspected immunologic predisposition exists in the Akita, Samoyed, Siberian Husky and Shetland Sheepdog. Clinical neurologic disease is seen in man but absent in the dog.

Metabolic

Diabetes Mellitus - the main ocular lesion is lens-induced uveitis secondary to rapidly progressive cataract formation. As a result of osmotic changes within the lens, glucose is converted to sorbitol via aldose reductase, an intralenticular enzyme. Sorbitol is not eliminated from the lens as efficiently as glucose. As a result of the osmotic difference between the intra and extralenticular microenvironments, imbibition, swelling and cataract formation occurs at a rapid rate. LIU (phacolytic) occurs as a result of rapid cataract progression.

Hyperlipidemia - certain conditions (i.e. lipemia retinalis, corneal lipidosis) are associated with hyperlipidemia and result in lipid engorgement of the retinal vessels and/or lipid infiltration of the perilimbal cornea. Lipid laden aqueous humor occasionally occurs as a secondary manifestation of anterior uveitis.

Neoplastic Disorders

Intraocular neoplasms are uncommon in dogs. As with any organ, both primary and secondary neoplasia may occur.

Primary Intraocular Tumors

Melanocytic Neoplasia - most common primary intraocular tumor in dogs. The vast majority of canine melanomas arise from the anterior uvea. The incidence of metastatic disease with this tumor type is low. Uveal melanoma occurs most commonly in older dogs, eight to ten years of age. Highly pigmented breeds such as German Shepherds and Boxers have a higher incidence of disease.

Ciliary Body Neoplasia - second most common primary intraocular tumor in dogs. Adenomas and adenocarcinomas arise from differentiated cell types in middle aged to older dogs. The majority of these tumors arise from the nonpigmented epithelium of the ciliary body. The incidence of benign ciliary body tumors (adenoma) is about equal to that of the malignant form (adenocarcinoma). The rate of metastasis is believed to be low, occurring most often late in the disease process.

Medulloepithelioma - a rare tumor of dogs arising from undifferentiated cells (primitive neuroectoderm) during early neonatal life. It appears as a gray-white mass in the pupil extending through the iris of young dogs.

Secondary Intraocular Tumors

Hematogenous spread accounts for the majority of secondary intraocular neoplasia. In the dog, intraocular **lymphosarcoma** is the most common secondary neoplasm. As opposed to primary intraocular tumors where unilateral involvement is more common, bilateral involvement is more characteristic of secondary intraocular neoplasia. Systemic involvement may be apparent, however, the patient may present only with problems associated with the eye. Ocular signs may show more anterior segment than choroidal involvement. Retinal findings include perivascular infiltrates; in severe cases, the retina may be completely effaced by neoplastic cells. Ocular signs may also show evidence of systemic disease such as anemia, thrombocytopenia and DIC.

Additional metastatic neoplasms aside from LSA include hemangiosarcoma, oral and cutaneous melanoma, fibrosarcoma and various forms of adenocarcinoma. Intraocular tumors of the secondary nature may also occur as a result of direct invasion from associated adnexal tissues or adjacent structures such as the orbit, paranasal/nasal sinuses and brain.

Pseudoneoplastic and Paraneoplastic Disorders

Granulomatous Meningoencephalitis - inflammatory condition of the CNS of unknown cause. Three forms exist: diffuse, focal and ocular. Clinical signs associated with the ocular form consist of optic neuritis, peripapillary retinitis, scleritis and retinal separation. Secondary glaucoma may also occur. Ocular lesions precede CNS signs and are often bilateral. In its initial stages, ocular lymphosarcoma is similar in clinical appearance to GME.

Hyperviscosity Syndrome - occurs secondary to monoclonal gammopathies which occur secondary to lymphoproliferative disorders. In dogs, the condition is associated with elevated levels of IgM, IgG and IgA. Ophthalmic abnormalities seen in the anterior chamber include corneal edema, hyphema, and secondary glaucoma resulting from anterior uveitis. Posterior segment abnormalities are more severe and include dilation and tortuosity of the retinal vessels, retinal hemorrhage, papilledema and retinal detachment.

Miscellaneous

Trauma - Ocular trauma resulting in anterior uveal contusion results in uveitis and may include epibulbar hyperemia, corneal edema, miosis and hypopyon. Trauma may also result in additional ocular abnormalities such as hemorrhage within the anterior chamber, uveal stroma (with associated hyphema) and posterior segment (retinal hemorrhage). Ocular trauma may also lead to disruption of the fibrous tunic surrounding the eye.

Systemic Hypertension - secondary hypertension resulting from renal failure is the most common cause. Other etiologies include Cushing's Disease, pheochromocytoma and neoplasia of the brain. The most common ocular manifestations of systemic hypertension in dogs are retinal detachment and hemorrhage. Anterior uveitis, hyphema and secondary glaucoma are occasionally seen.

Etiologies And Syndromes Associated With Feline Uveitis

Viral

Feline Infectious Peritonitis (FIP) - This disease is caused by a coronavirus that more often affects young animals. The ocular lesion that it causes is pyogranulomatous inflammation of the uveal tract with necrotizing vasculitis. Both the anterior and posterior uvea may be affected, but the anterior lesions are more visible, clinically. Signs seen are aqueous flare, hypopyon, fibrin, and keratic precipitates. Corneal edema may also be seen, which is proportionate to the degree of inflammation. Posteriorly, there is pyogranulomatous chorioretinitis and retinal vasculitis, manifesting as retinal detachment due to choroidal exudation, as well as optic neuritis and perivascular exudates. Histologically, there may be lymphocytes, plasma cells, monocytes, leukocytes and macrophages in varying numbers.

Feline Immunodeficiency virus (FIV) - FIV is a lentivirus, causing a persistent immunodeficiency. Ocular lesions seen most commonly with FIV infection are aqueous flare, iridal hyperemia, posterior synechiae, and cataracts. Also, white punctate, cellular infiltrates may be seen in the anterior vitreous. Histologically, there may be a lymphocytic-plasmacytic perivascular uveal infiltrate.

Fungal

Histoplasmosis - The organism responsible is *Histoplasma capsulatum* which is indigenous to the midwestern and southern US. The organism gains access to the body via the respiratory tract, causing nonclinical infections. The organism then gets into the systemic circulation, crossing the blood-ocular barrier. Ocular lesions noted are aqueous flare and inflammatory cells in the aqueous humor, granulomatous chorioretinitis and optic neuritis. Histologically, inflammatory infiltrates consist of lymphocytes, plasma cells, and macrophages.

Blastomycosis - This is a very rare condition in cats, as compared to dogs. It occurs mainly in the eastern US by the organism, *B. dermatitidis*. Like *Histoplasma*, it gains entry into the body via the respiratory tract, and then, eventually, entering the systemic circulation, and crossing the blood-ocular barrier. The main lesion is a granulomatous chorioretinitis. Histologically, there is pyogranulomatous inflammation with large numbers of organisms in the choroid and subretinal space, consisting of macrophages, neutrophils, and lymphocytes.

Cryptococcosis - This is the most common infectious mycoses of cats, although it is still rather rare. Again, it enters the body through the respiratory system. The choroid is mainly affected, but the anterior segment may become inflamed as well. Clinical signs of the anterior chamber include hyphema, fibrin, and posterior synechiae formation. Organisms are rarely seen in the anterior chamber. Posterior signs include choroidal inflammation with secondary exudative retinal detachment and subretinal granuloma formation. Histologic evaluations show lymphocytic-plasmacytic infiltrates in the uveal tissue with Cryptococcal organisms in the choroid, subretinal spaces and vitreous cavity.

Coccidioidomycosis - This is the least common intraocular fungal infection of cats. Clinical signs include fibrin in the anterior chamber, iridal swelling, posterior synechiae and small, cotton-like masses located in the anterior chamber. Histology shows diffuse granulomatous inflammation of the anterior and posterior uvea, with organisms possibly seen in the inflammatory tissue.

Candidiasis - *Candida albicans* is the organism that causes infection in cats. Ocular lesions consist of conjunctival hyperemia and chemosis, fibrin and flocculent material in all ocular chambers, and small nodular lesions in the fundus. There are free and phagocytized organisms in the vitreal and retinal exudates, histologically.

Protozoal

Toxoplasmosis - This is caused by the protozoa *Toxoplasma gondii*. Ocular infection occurs via hematologic spread of sporozoites that are released from ingested cysts or sporulated oocysts. Ocular lesions are retinitis, visualized by focal dark spots in the tapetal fundus and white to gray lesions in the nontapetal area. Histologically, the retinas may be necrotic, have cellular degeneration, and organisms may be present. Inflammatory cells present in the retina are mainly plasma cells and some epithelioid cells.

Miscellaneous

Ophthalmomyiasis - This is due to parasite migrations in and around the sensory retina. Such parasites include *Cuterebra* larvae. Clinical signs include ocular pain, aqueous flare, and corneal edema. Other parasites known to do this include *Metastrongylus*.

Chediak-Higashi Syndrome - This syndrome is characterized by partial oculocutaneous albinism, a tendency to bleed, and increased susceptibility to infection. Ocular abnormalities include lightly colored irides, fundic hypopigmentation, and congenital cataracts. Histologically, enlarged cytoplasmic granules, including lysosomes and melanosomes may be present.

Periarteritis Nodosa - this is a rare disease of cats where medium and small arteries undergo fibrinoid necrosis. The anterior chambers contained large amounts of proteinaceous exudate. The ciliary body is infiltrated with lymphocytes and plasma cells, with foci of necrosis. Also there is a cyclic membrane, choroidal thickening by cellular infiltrates, and exudative retinal detachment.

Copyright © 2001

Waltham USA, Inc.

All rights including that of translation into other languages, reserved. Photomechanical reproduction (photocopy, microcopy) of this publication or parts thereof without written permission from Waltham USA, Inc. is prohibited.

The opinions expressed in these proceedings are those of the authors and not necessarily those of Waltham.

Additional copies can be obtained from Waltham USA, Inc. The proceedings may also be found online at the WALTHAM® web site at <http://www.walthamusa.com> or the VIN web site at <http://www.vin.com/OSUWaltham/2001/>.

Designed and published by Veterinary Information Network (VIN).